UROLOGICAL CANCERS

PROSTATE CANCER

Review question:
What is the risk of prostate cancer in patients presenting in primary care with symptom(s)?

Results

Literature search

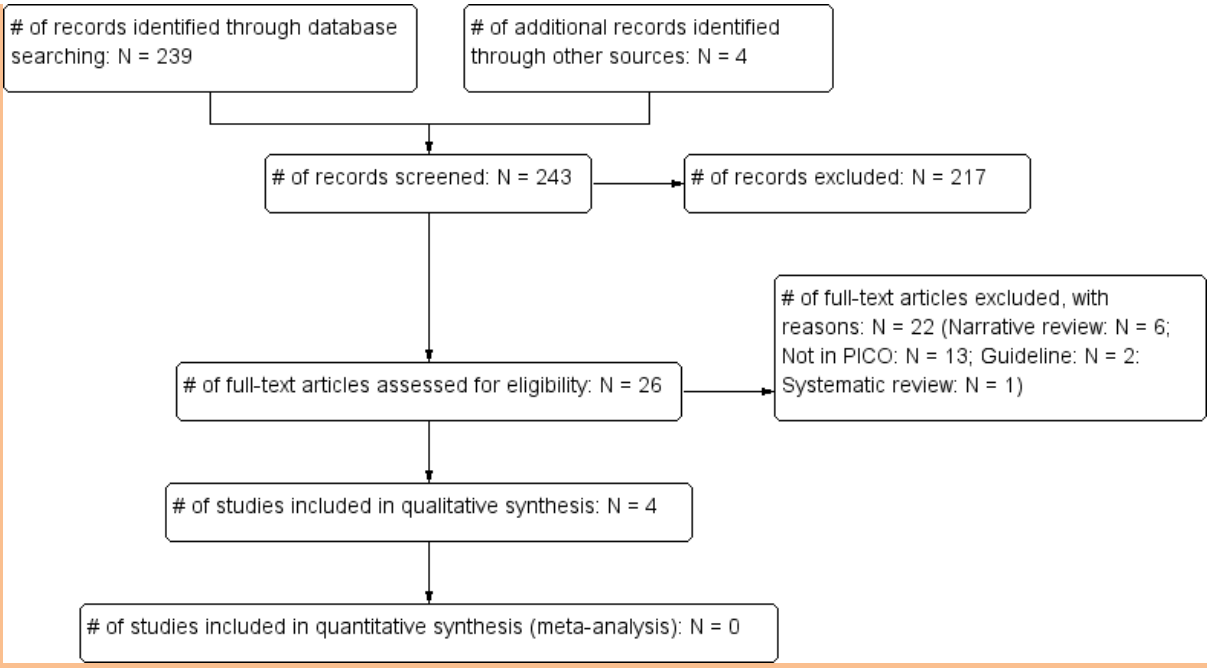
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2012	858	103	27/11/2012
Premedline	All-2012	33	3	27/11/2012
Embase	All-2012	2023	82	28/11/2012
Cochrane Library	All-2012	134	0	28/11/2012
Psychinfo	All-2012	33	4	27/11/2012
Web of Science (SCI & SSCI) and ISI Proceedings	All-2012	540	66	28/11/2012
Biomed Central	All-2012	29	4	28/11/2012

Total References retrieved (after de-duplication): 215

Update Search

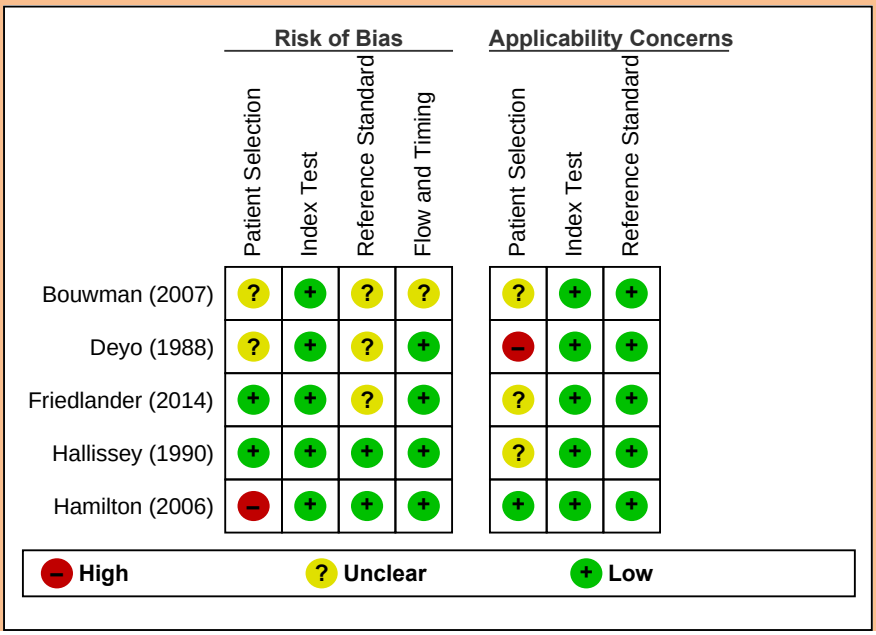
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	11/2012-26/08/2014	115	11	26/08/2014
Premedline	11/2012-26/08/2014	57	1	26/08/2014
Embase	11/2012-26/08/2014	289	10	26/08/2014
Cochrane Library	11/2012-26/08/2014	77	0	26/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	11/2012-26/08/2014	160	5	26/08/2014

Total References retrieved (after de-duplication): 24



Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issue to note is that 4/5 studies employed samples of patients that are not directly representative of an unselected symptomatic population of patients presenting to the UK-based GP and the 5th study employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence. Three of the studies also employed reference standards that are subject to an unclear risk of bias; all of which must be born in mind when evaluating the evidence contributed by these studies.



Study results

Table 1: Prostate cancer: Single symptoms

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)%
Bouwman (2007)	Urinary symptoms	Males aged ≥ 50 years	7.37 (5-10.7) 26/353
Deyo (1988)	Back pain	Male patients	0. 13 (0.007-0.9) 1/750
Friedlander (2014)	Haematuria	All included patients	0.61 (0.36-1.03) 15/2455
Hamilton (2006)	Haematuria	All included patients	1 (0.57-1.8)
Hamilton (2006)	Haematuria (reported twice)	All included patients	1.6 (0.8-3.2)
Hamilton (2006)	Loss of weight	All included patients	0.75 (0.38-1.4)
Hamilton (2006)	Loss of weight (reported twice)	All included patients	2.1 (NR)
Hamilton (2006)	Nocturia	All included patients	2.2 (1.2-3.6)
		Patients 40-69 years	1.1 (NR)
		Patients ≥ 70 years	5.9 (NR)
Hamilton (2006)	Nocturia (reported twice)	All included patients	3.3 (NR)
Hamilton (2006)	Hesitancy	All included patients	3 (1.5-5.5)
Hamilton (2006)	Hesitancy (reported twice)	All included patients	2 (NR)
Hamilton (2006)	Rectal exam: Benign	All included patients	2.8 (1.6-4.6)
		Patients 40-69 years	0.85 (NR)
		Patients ≥ 70 years	8.7 (NR)
Hamilton (2006)	Rectal exam: Malignant	All included patients	12 (5-37)
Hamilton (2006)	Frequency/urgency	All included patients	2.2 (1.1-3.5)
Hamilton (2006)	Frequency/urgency (reported twice)	All included patients	3.1 (1.9-5.5)
Hamilton (2006)	Frequency	Patients 40-69 years	0.61 (NR)
		Patients ≥ 70 years	7.4 (NR)
Hamilton (2006)	Retention	All included patients	3.1 (1.5-6)
		* excluding 39 patients with unsuspected cancer	1.6 (NR)
Hamilton (2006)	Impotence	All included patients	3 (1.7-4.9)
		Patients 40-69 years	1.1 (NR)
		Patients ≥ 70 years	8.4 (NR)
Hamilton (2006)	When PSA was added to a small multivariate analysis (N = 208; N = 137 patients and N = 71 controls) with the following otherwise significant variables: urinary retention, second presentation with loss of weight, impotence, frequency, hesitancy, nocturia, haematuria, and rectal examination, these variables ceased to be significant predictors of prostate cancer while PSA > 4 ng/ml was significant (OR = 29, 95% CI 3.9-220; p = .001).		

Hallissey (1990)	Dyspepsia	All patients	0.08 (0.01-0.3) 2/2585

CI = Confidence interval. *The authors report that a sub-analysis excluding the 39 patients who had previously unsuspected cancer identified at prostatectomy, showed that the PPVs of symptoms were little changed, other than for retention.

Table 2: Prostate cancer: Symptom combinations

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)%
Hamilton (2006)	Haematuria + nocturia	All included patients	1.9 (NR)
Hamilton (2006)	Haematuria + benign rectal exam	All included patients	3.3 (NR)
Hamilton (2006)	Haematuria + malignant rectal exam	All included patients	3.9 (NR)
Hamilton (2006)	Haematuria + frequency/urgency	All included patients	1.8 (0.9-3.9)
Hamilton (2006)	Loss of weight + nocturia	All included patients	12 (NR)
Hamilton (2006)	Loss of weight + benign rectal exam	All included patients	9.4 (NR)
Hamilton (2006)	Loss of weight + frequency/urgency	All included patients	1.8 (NR)
Hamilton (2006)	Nocturia + hesitancy	All included patients	2.8 (NR)
Hamilton (2006)	Nocturia + benign rectal exam	All included patients	3.9 (2.1-7.8)
Hamilton (2006)	Nocturia + malignant rectal exam	All included patients	15 (NR)
Hamilton (2006)	Nocturia + frequency/urgency	All included patients	3.2 (1.9-6)
Hamilton (2006)	Hesitancy + benign rectal exam	All included patients	3.3 (NR)
Hamilton (2006)	Hesitancy + malignant rectal exam	All included patients	10 (NR)
Hamilton (2006)	Hesitancy + frequency/urgency	All included patients	4.7 (NR)
Hamilton (2006)	Benign rectal exam + frequency/urgency	All included patients	4 (2.3-7.4)
Hamilton (2006)	Malignant rectal exam + frequency/urgency	All included patients	13 (NR)

CI = Confidence interval.

Evidence statement(s):

The positive predictive values for prostate cancer of single symptoms presenting in a primary care setting ranged from 0.08% (for dyspepsia) to 12% (for malignant rectal exam; 5 studies, N = 7440). The studies were associated with 1-4 bias or applicability concerns (see also Table 1).

The positive predictive values for prostate cancer of symptom pairs presenting in a primary care setting ranged from 1.8% (for haematuria + frequency/urgency) to 15% (for nocturia + malignant rectal exam; 1 study, N = 1297). This study was a case-control study (i.e, high risk of bias for patient selection; see also Table 2).

Evidence tables

Bouwman (2007)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Database study using data from the Registration Network Groningen (RNG) from 2003 and 2004, which is a database registering continuous automatic recorded data from, on average, 17 GPs working in practices in Groningen, Hoogeveen and Hoogezand-Sappemeer (population of approximately 30000 people) in the Netherlands.
Was a consecutive or random sample of patients enrolled?	**Unclear**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes (probably)**
Could the selection of patients have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Patient characteristics and setting	In the whole sample there were 4422 men aged ≥ 50 years in the period 2003 to 2004. Of these 353 men consulted the GP for urinary symptoms. *No further details reported.* Inclusion criteria: Male patients aged ≥ 50 years in the period 2003 to 2004 who visited participating practices because of urinary symptoms (see "Index test" for further details) for the first time. Exclusion criteria: None listed Clinical setting: Primary care in the Netherlands.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	The following ICPC codes were used: U01 (painful urination), U02 (increased urinary frequency / urgency), U04 (urinary incontinence), other micturition U05) and Y06 (symptoms / complaints prostate) and some minor codes: U07 (other symptoms / complaints urine) and U13 (other symptoms / complaints bladder). The code Y85 for BPH / LUTS was not included in this selection because the RNG agreements apply to the use of the different parts of the ICPC. This agreement is that a health problem is initially registered as a symptom or complaint until by advancing knowledge and further research a diagnosis code may be added to the records.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	The reference standard consisted checking the database to see if a BHP diagnosis (ICPC code Y85) or prostate carcinoma diagnosis (ICPC code Y77)

	had been registered by 2005.
Is the reference standard likely to correctly classify the target condition?	**Unclear**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No (but all patients had a positive index test)**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	There is very little information about the included patients and the patient pool from which they were drawn. It is therefore not possible to ascertain whether all patients are accounted for.
Was there an appropriate interval between index test and reference standard?	**Yes (probably)**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Unclear**
Could the patient flow have introduced bias?	**Unclear risk**
NOTES	Original paper is published in Dutch

Deyo (1988)

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Prospective consecutive? patient series	
Was a consecutive or random sample of patients enrolled?		**Unclear**
Was a case-control design avoided?		**Yes**
Did the study avoid inappropriate exclusions?		**Yes (probably)**
Could the selection of patients have introduced bias?		**Unclear risk**
B. Concerns regarding applicability		
Patient characteristics and setting	N = 1975, mean (SD; range) age = 39.5 (15.4; 15-86) years, 62% females. 54% of the patients were seeking medical care for back pain for the first time and 76% of the patients had had back pain for < 3 months. 3% had a history of back pain surgery. Maximal back pain in the low back (84%) or in the upper back (16%). Inclusion criteria: Patients who sought treatment between March 1982 and September 1984 in the walk-in clinic of a public hospital where virtually all patients are self-referred. In each case back pain was part of the chief complaint. Exclusion criteria: Neck pain. Clinical setting: Walk-in clinic of a public hospital; this clinic is a source of primary care for indigent persons in a county in the USA with a population of approximately 1 million.	
Are there concerns that the included patients and setting do not match the review question?		**High concern**

INDEX TEST		
A. Risk of bias		
Index test	Back pain; not further specified.	
Were the index test results interpreted without knowledge of the results of the reference standard?		**Yes**
Could the conduct or interpretation of the index test have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		**Low concern**
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	The reference standard consisted of a search on each patient name in the institutional tumour registry ≥ 6 months after the index visit. The registry included every patient with a histological diagnosis of cancer made in the authors' hospital system regardless of site of care. The authors point out that "while this method might fail to identify cancer patients who sought care elsewhere, it is likely that most patients sought follow-up for a particular illness at the same facility.	
Is the reference standard likely to correctly classify the target condition?		**Unclear**
Were the reference standard results interpreted without knowledge of the results of the index tests?		**No (but all patients had a positive index test)**
Could the reference standard, its conduct, or its interpretation have introduced bias?		**Unclear risk**
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		**Low concern**
FLOW AND TIMING		
A. risk of bias		
Flow and timing	All the patients are accounted for in the results.	
Was there an appropriate interval between index test and reference standard?		**Yes (probably)**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**Yes**
Could the patient flow have introduced bias?		**Low risk**
NOTES	It is a concern that some patients with cancer might have been missed due to the choice of reference standard because this would result in an underestimation of the positive predictive value. 38/1975 patients were found in the tumour registry. Of those 38, 13 patients had tumours that were probable causes of back pain, and 4 of these 13 patients already had a diagnosis of cancer at presentation. The 9/1975 patients who had undiagnosed cancer that the back pain could be attributed to had: Lymphoma (NOS; 2), cancer of unknown primary (1), prostate cancer (1), retroperitoneal liposarcoma (1), lung cancer (1), renal cell (1), multiple myeloma (1), mucinous adenocarcinoma (of gallbladder?; 1)	

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1 **Friedlander (2014)**

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Retrospective cohort study, using claims data and laboratory values from the Vanderbilt University Medical Centre's (VUMC) Research Derivative, which is a "data repository that contains administrative and clinical information, including a complete record of visits and admissions, laboratory data, and diagnosis and procedure codes, on every patient treated in the Vanderbilt health system" (p 634) located in Tennessee in the USA.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes (probably)**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 2455 patients, 724 males / 1731 females, median (inter-quartile range) age = 58 (49-68) years; smoking history: current smoker (N = 406), former smoker (N = 473), non-smoker (N = 1514). Inclusion criteria: "Patients aged ≥ 40 years with a first diagnosis of hematuria" "between 2004 and 2012 by urinalysis (>3 red blood counts per high power field) or International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes for hematuria (599.7, 599.70, 599.71 or 599.72) at one of the VUMC's 19 primary care clinics. To be included in the study, patients must have had records for 1 year before the date of hematuria diagnosis." Exclusion criteria: "Patients were excluded if they had a urinary tract infection (defined as a urinalysis positive for both leukocyte esterase and urine nitrites, or a positive urine culture) within 4 weeks before or 1 week after the index hematuria episode (n = 590, 9.0%) or had a prior explanatory diagnoses and procedures that would preclude the need for a hematuria evaluation (according to a convened panel of content experts; prostate/renal/bladder/other cancer, benign prostate/renal/bladder/other mass, prostate dysplasia, cystitis, urethritis, epididymitis/orchitis, prostatitis, pyelonephritis, urolithiasis, prostatic enlargement, trauma, medical renal disease, haematologic/thrombotic diease?, anatomic abnormality, prostatectomy, prostate biopsy, transurethral incision of prostate, resection of prostate, cystoscopy, cystectomy, ureteroscopy, nephrectomy, pyeloplasty, ureteral reimplantation)." We then used Physicians Current Procedural Terminology Coding System, 4th Edition and ICD-9 codes to exclude patients with an explanatory diagnosis or procedure within 180 days preceding their hematuria diagnosis (n = 3540, 53.8%)." Clinical setting: Primary care, USA.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	First diagnosis of hematuria" "by urinalysis (>3 red blood counts per high power field) or International Classification of Diseases, Ninth Revision (ICD-9)

	diagnosis codes for hematuria (599.7, 599.70, 599.71 or 599.72)".
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	The reference standard consisted checking the database for diagnoses of genitourinary neoplasms within 180 days after haematuria diagnosis, as determined by ICD-9 codes.
Is the reference standard likely to correctly classify the target condition?	**Unclear (is 180 days enough time to get a diagnosis of all cancers?)**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear (but all patients had a positive index test)**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	There were 66 patients with cancer: Bladder (N = 33), renal cell (N = 16), prostate (N = 15). The types of cancer for the remaining two cases were not reported.

Hallissey (1990)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Propective consecutive patient series from a group of 10 general practices in England.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and	N = 2585 aged > 40 years. No other information reported. The patient group was equally divided between new patients with dyspepsia, old patients with

setting	uninvestigated dyspepsia, and and old patients with investigated dyspepsia. Inclusion criteria: All patients over 40 years making their first attendance during the study period (4 years and 9 months) with any degree of dyspepsia Exclusion criteria: None listed. Clinical setting: Primary care, England.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Dyspepsia of any degree
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Upper gastrointestinal endoscopy within 4 weeks and follow up.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	2659 patients were seen and 2585 attended for investigation
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	Malignancy was detected in 115 patients: Gastric adenocarcinoma (57), gastric lymphoma (1; added to the gastric adenocarcinoma data in the PPV), oesophageal cancer (15), colorectal (14), pancreatic (6), bronchial (8), prostatic (2), duodenal (1, also added to the gastric carcinoma data in the PPV), liver (1), gall bladder (1), carcinoid (1), uterine (1), leukaemia (1), circinomatosis of unknown primary (7).

Hamilton (2006)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Population-based case-control study, involving all 21 general practices in Exeter, Devon, UK.
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: 217 male patients; age at diagnosis: < 60 years: N = 15 (7%); 60-69 years: N = 51 (24%); 70-79 years: N = 100 (46%): ≥ 80 years: N = 51 (24%); median number of consultations in the 2 years preceding diagnosis = 14 (IQR = 10-21). Controls: 1080 male patients; age at diagnosis: < 60 years: N = 79 (7%); 60-69 years: N = 253 (23%); 70-79 years: N = 494 (46%): ≥ 80 years: N = 254 (24%); median number of consultations in the 2 years preceding diagnosis = 14 (IQR = 10-21). Inclusion criteria: Cases: All patients aged 40 years or over with prostate cancer, diagnosed from 1998 to 2002 inclusive, were identified from the cancer registry at the Royal Devon and Exeter Hospital (the only hospital offering urological services to Exeter patients). Computerised searches at every practice identified any cases missing from the register. Cases without positive histology were included if the records contained a consultant urologist diagnosis of cancer based on strong clinical evidence. Controls: Five male controls were matched to each case on general practice and on age (to 1-year bands if possible, increased in 1-year multiples to a maximum of 5 years). Controls were eligible if they were alive at the time of diagnosis of their case. Exclusion criteria: Unobtainable records; no consultations in the 2 years before diagnosis; previous prostate cancer; or residence outside Exeter at the time of diagnosis. Clinical setting: Primary care, UK
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	All entries into the primary care records for 2 years before diagnosis were coded, blinded to case/control status, using the International Classification of Primary Care-2. Only variables occurring in >2.5% of cases or

	controls were analysed.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Prostate cancer code, from 1998 to 2002 inclusive, in the cancer registry at the Royal Devon and Exeter Hospital or the general practice records
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	

References

Included studies

Bouwman, I., Van Der Heide, W. K., Van Der Veen, W. J., and Van Der Meer, K. GPs and patients still think that lower urinary tract symptoms are an indication of prostate cancer. [Dutch]. Huisarts en Wetenschap 50[7], 321-325. 2007.

Deyo, R. A. and Diehl, A. K. Cancer as a cause of back pain: Frequency, clinical presentation, and diagnostic strategies. Journal of General Internal Medicine 3, 230-238. 1-11-1988.

Friedlander, D.F., Resnick, M.J., You, C., Bassett, J., Yarlagadda V., Penson, D.F., Barocas D.A. Variation in the intensity of hematuria evaluation: A target for primary care quality improvement. American Journal of Medicine, 127, 633-640. 2014.

Hallissey, M.T., Allum, W.H., Jewkes, A.J., Ellis, A.J., Fielding, J.W.L. Early detection of gastric cancer. British Medical Journal 301, 513-515. 1990.

Hamilton, W., Sharp, D. J., Peters, T. J., and Round, A. P. Clinical features of prostate cancer before diagnosis: a population-based, case-control study. British Journal of General Practice 56[531], 756-762. 2006.

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Not in PICO

Afifi, A. H. A. A., Etaby, A. N., Ahmad, M. A. Y. & Farghaly, Y. T. (2013) Value of diffusion weighted magnetic resonance imaging in the prediction of cancer prostate. *Alexandria Journal of Medicine,* 49: 57-66.
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Ahaghotu, C., Baffoe-Bonnie, A., Kittles, R., Pettaway, C., Powell, I., Royal, C., Wang, H., Vijayakumar, S., Bennett, J., Hoke, G., Mason, T., Bailey-Wilson, J., Boykin, W., Berg, K., Carpten, J., Weinrich, S., Trent, J., Dunston, G. & Collins, F. (2004) Clinical characteristics of African-American men with hereditary prostate cancer: the AAHPC study. *Prostate Cancer and Prostatic Diseases,* 7: 165-169.
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Allen, D., Popert, R. & O'Brien, T. (2004) The two-week-wait cancer initiative in urology: useful modernization? *Journal of the Royal Society of Medicine,* 97: 279-281.
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Allgar, V. L., Neal, R. D., Ali, N., Leese, B., Heywood, P., Proctor, G. & Evans, J. (2006) Urgent GP referrals for suspected lung, colorectal, prostate and ovarian cancer. *British Journal of General Practice,* 56: 355-362.
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Anast, J. W., Andriole, G. L. & Grubb, R. L. (2007) Managing the local complications of locally advanced prostate cancer. [Review] [24 refs]. *Current Urology Reports,* 8: 211-216.
Narrative review

Antunes, A. A., Srougi, M., Dall'oglio, M. F., Vicentini, F., Paranhos, M. & Freire, G. C. (2008) The role of BPH, lower urinary tract symptoms, and PSA levels on erectile function of Brazilian men who undergo prostate cancer screening. *Journal of Sexual Medicine,* 5: 1702-1707.
Not in PICO

Arumainayagam, N., Ahmed, H. U., Moore, C. M., Freeman, A., Allen, C., Sohaib, S. A., Kirkham, A., van der Meulen, J. & Emberton, M. (2013) Multiparametric MR imaging for detection of clinically significant prostate cancer: a validation cohort study with transperineal template prostate mapping as the reference standard. *Radiology,* 268: 761-769.
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Review question:
Which investigations of symptoms of suspected prostate cancer should be done with clinical responsibility retained by primary care?

Results

Literature search

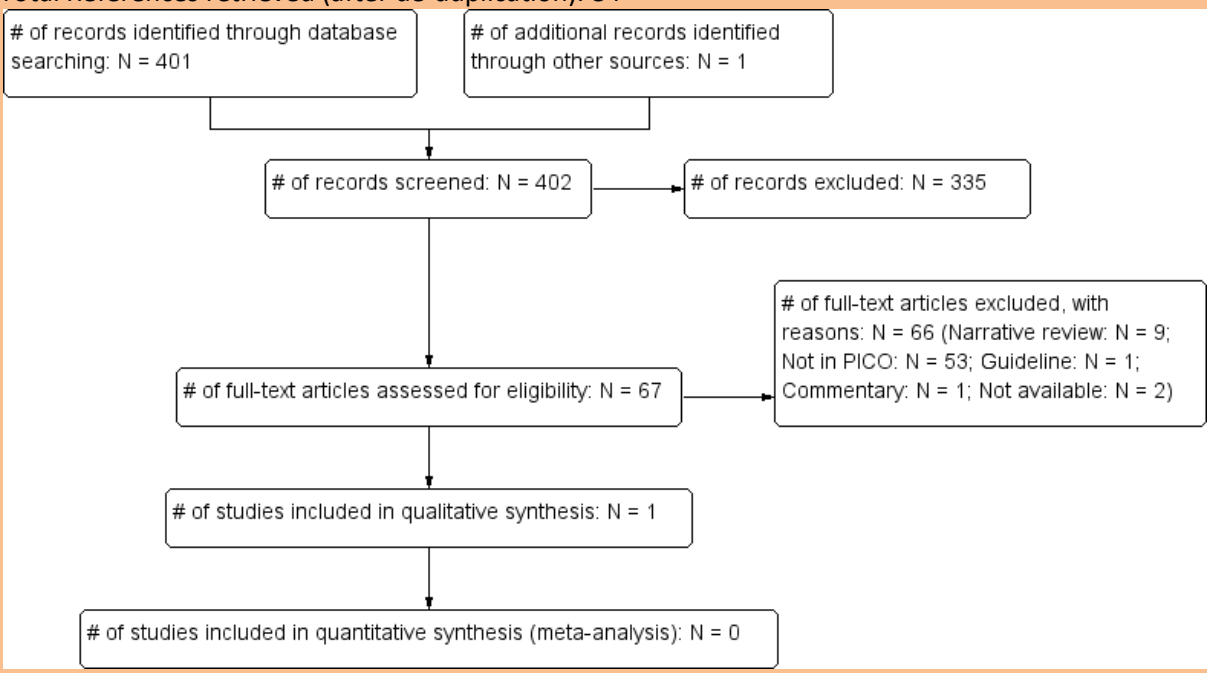
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-2013	3732	59	04/02/2013
Premedline	1980-2013	179	22	04/02/2013
Embase	1980-2013	1695	122	04/02/2013
Cochrane Library	1980-2013	139	15	31/01/2013
Psychinfo	1980-2013	73	3	04/02/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2013	491	99	31/01/2013
Biomed Central	1980-2013	695	2	31/01/2013

Total References retrieved (after de-duplication): 317

Update Search

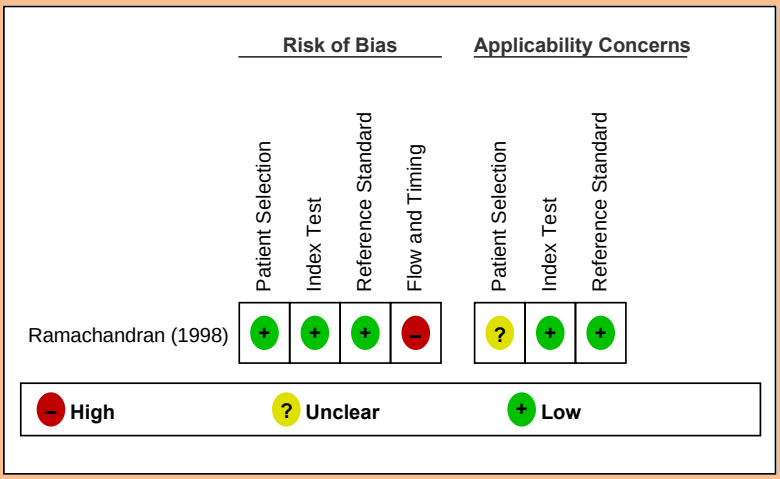
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2013-26/08/2014	189	21	26/08/2014
Premedline	2013-26/08/2014	196	43	26/08/2014
Embase	2013-26/08/2014	179	42	26/08/2014
Cochrane Library	2013-26/08/2014	38	0	26/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	2013-26/08/2014	76	14	26/08/2014

Total References retrieved (after de-duplication): 84



Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included study in the figure below. The main risk of bias in this study pertains to the ca 20% of missing data in this study. It is not possible to ascertain whether these data are missing in a systematic manner and whether they are likely to substantially influence the test accuracy estimates provided by this study. The only applicability concern identified for this study concerns the underspecification of the patients, that is, it is not clear from, the study whether all the patients were symptomatic patients presenting to primary care, and to the extent they are not from this patient group, the applicability to the current guideline is limited.



Study results

Table 1: Prostate cancer: PSA

Study	Test	Prevalence	Sensi-tivity (95% CI)	Speci-ficity (95% CI)	Other results
Ramachandran (1998)	PSA 4 ng/ml	54/582	88.9% (NR)	70% (NR)	False negativity rate = 11.1%
	PSA 5 ng/ml		88.9% (NR)	78% (NR)	False negativity rate = 11.1%
	PSA 6 ng/ml		87% (NR)	82.6% (NR)	False negativity rate = 13%
	PSA 7 ng/ml		83.3% (NR)	86% (NR)	False negativity rate = 16.7%
	PSA 8 ng/ml		83.3% (NR)	88.3% (NR)	False negativity rate = 16.7%
	PSA 9 ng/ml		83.3% (NR)	89% (NR)	False negativity rate = 16.7%
	PSA 10 ng/ml		77.8% (NR)	90.2% (NR)	False negativity rate = 22.2%

No evidence was found for MRI.

Evidence statement(s):

PSA testing (1 study, N = 582) conducted in patients presenting in a primary/hospital care setting is associated with sensitivities that ranged from 77.8-88.9%, specificities that ranged from 70-90.2% and false negativity rates that ranged from 11.1-22.2% for prostate cancer. The study was associated with one bias and one applicability concern (see also Table 1).

Evidence tables

Ramachandran (1998)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Audit of laboratory database, England.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 582. *No further detail reported.* Inclusion criteria: All patients who had a prediagnostic PSA estimation between August 1991 and December 1992 in the laboratory "Telepath" database. *Unclear if they are all symptomatic and if they are all from primary care.* Exclusion criteria: None listed. Clinical setting: Primary/hospital (?) care, England.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	PSA
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Follow up for min 18 months using GP, Family Services Health Authority, hospice and hospital records
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**

B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		**Low concern**
FLOW AND TIMING		
A. risk of bias		
Flow and timing	A total of 721 patients met the inclusion criteria. However, complete data were only available for 582 patients.	
Was there an appropriate interval between index test and reference standard?		**Yes**
Did all patients receive the same reference standard?		**Unclear**
Were all patients included in the analysis?		**No**
Could the patient flow have introduced bias?		**High risk**
NOTES	2-by-2 tables cannot be extracted	

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Narrative review

BLADDER CANCER

Review question:
What is the risk of bladder cancer in patients presenting in primary care with symptom(s)?

Results

Literature search

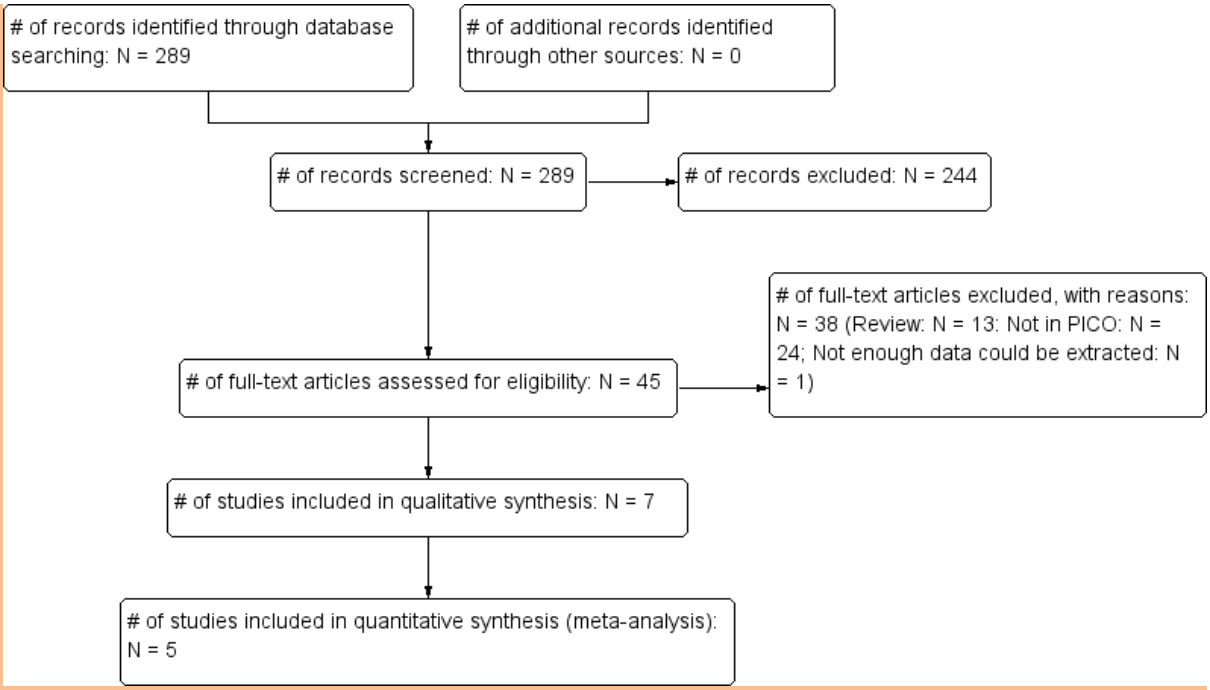
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All - 2012	1070	189	03/09/2012
Premedline	All - 2012	17	5	03/09/2012
Embase	All - 2012	2103	111	30/08/2012
Cochrane Library	All - 2012	126	1	03/09/2012
Psychinfo	All - 2012	2	0	03/09/2012
Web of Science (SCI & SSCI) and ISI Proceedings	All - 2012	163	28	03/09/2012
Biomed Central	All - 2012	158	3	12/09/2012

Total References retrieved (after de-duplication): 263

Update Search

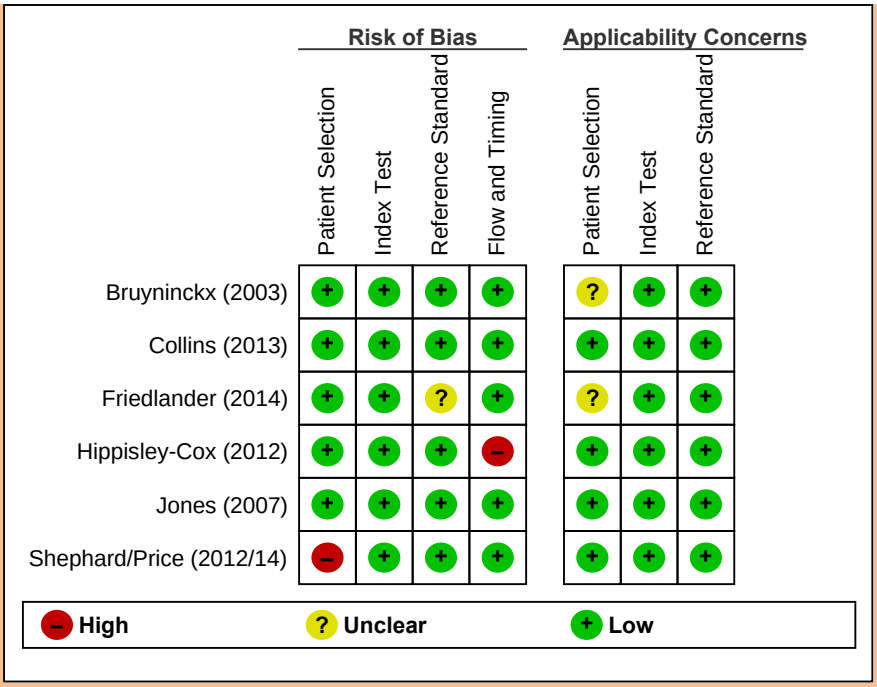
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2013-11/08/2014	64	7	11/08/2014
Premedline	2013-11/08/2014	48	11	11/08/2014
Embase	2013-11/08/2014	283	18	11/08/2014
Cochrane Library	2013-11/08/2014	65	0	11/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	2013-11/08/2014	68	3	11/08/2014

Total References retrieved (after de-duplication): 26



Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main bias and validity issues to note are that one study was conducted in a Belgian primary care population (Bruyninckx, 2003) and another in US primary care setting (Friedlander, 2014) and these studies are therefore only applicable to the extent that the populations are comparable to a UK GP population, another study (Hippisley-Cox 2012) only presented data for 967681 out of 1240722 eligible patients and it is unclear why, a third study (Jones, 2007) report the results for both 6 months and 3 years after first symptom presentation and it is unclear whether 3 years is too long an interval to be confident that the symptom is a result of underlying cancer, similarly, Friedlander (2014) only followed up the included patients for 180 days, which may be too short a time period. The final study (Shephard, 2012) employed a case-control design which has been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection.



Study results

Table 1: Bladder cancer: Meta-analyses

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

Please note that the data from Shephard (2012) are not included in these meta-analyses due to the case-control design of the study. These data are instead reported in the table below.

Table 2: Bladder cancer: Individual positive predictive values from the meta-analyses

Studies included	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Bruyninckx (2003)	Haematuria	All patients (N = 409)	10.27 (7.6-13.7)
Collins (2013)	Haematuria	All patients (N = 37810)	4.35 (4.1-4.6)
Friedlander (2014)	Haematuria	All included patients (N = 2455)	1.34 (0.94-1.91) 33/2455
Hippisley-Cox (2012)	Haematuria	All patients (N = 18548)	6.48 (6.1-6.8)
Jones (2007, at 6 months),	Haematuria	All patients (N = 11108)	4.2 (3.8-4.6)

Jones (2007, at 3 years),	Haematuria	All patients (N = 11108)	5.7 (5.3-6.2)

Table 3: Bladder cancer: Additional results reported by the individual papers

Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Bruyninckx (2003)	Macroscopic haematuria	Men (all ages)	14.2 (10.1-19.5)
Collins (2013)	Haematuria	Men (all ages)	5.5 (5.2-5.8)
Jones (2007)	Haematuria	Men (all ages) at 6 months	5.47 (4.9-6.1)
Bruyninckx (2003)	Macroscopic haematuria	Men < 40 years	0 (0-12)
Jones (2007)	Haematuria	Men < 45 years at 3 years	0.99 (0.53-1.69)
Bruyninckx (2003)	Macroscopic haematuria	Men 40-59 years	3.6 (.6-13.4)
Jones (2007)	Haematuria	Men 45-54 years at 3 years	4.35 (3.11-5.9)
Jones (2007)	Haematuria	Men 55-64 years at 3 years	8.51 (6.94-10.32)
Bruyninckx (2003)	Macroscopic haematuria	Men > 59 years	22.1 (15.8-30.1)
Jones (2007)	Haematuria	Men 65-74 years at 3 years	11.21 (9.66-12.9)
Jones (2007)	Haematuria	Men 75-84 years at 3 years	10.27 (8.61-12.13)
Jones (2007)	Haematuria	Men ≥ 85 years at 3 years	9.22 (6.43-12.7)
Bruyninckx (2003)	Macroscopic haematuria	Women (all ages)	5.1 (2.5-9.8)
Collins (2013)	Haematuria	Women (all ages)	2.6 (2.3-2.8)
Jones (2007)	Haematuria	Women (all ages) at 6 months	2.48 (2.1-3)
Bruyninckx (2003)	Macroscopic haematuria	Women < 40 years	0 (NR)
Jones (2007)	Haematuria	Women < 45 years at 3 years	0.22 (0.05-0.64)
Bruyninckx (2003)	Macroscopic haematuria	Women 40-59 years	6.4 (1.7-18.6)
Jones (2007)	Haematuria	Women 45-54 years at 3 years	1.34 (0.65-2.45)
Jones (2007)	Haematuria	Women 55-64 years at 3 years	3.42 (2.26-4.93)
Bruyninckx (2003)	Macroscopic haematuria	Women > 59 years	8.3 (3.4-17.9)
Jones (2007)	Haematuria	Women 65-74 years at 3 years	5.91 (4.42-7.72)
Jones (2007)	Haematuria	Women 75-84 years at 3 years	6.83 (5.06-8.98)
Jones (2007)	Haematuria	Women ≥ 85 years at 3 years	8.53 (5.6-12.3)
Bruyninckx (2003)	Macroscopic haematuria	All patients < 60 years	2.6 (.9-6.2)
Shephard (2012)	Visible haematuria (coded data only)	All patients 40-59 years	3.1 (1-9.8)
Price (2014)	Visible haematuria (coded and uncoded	All patients 40-59 years	1.2 (0.64-2.3)

	data)		
Shephard (2012)	Visible haematuria (coded data only)	All patients ≥ 60 years	3.9 (3.5-4.6)
Price (2014)	Visible haematuria (coded and uncoded data)	All patients ≥ 60 years	2.8 (2.5-3.1)
Shephard (2012)	*Visible haematuria*	*All patients*	*Cases: 2595/4915 Controls: 196/21718*
Shephard (2012)	Visible haematuria (second attendance)	All patients ≥ 60 years	6.1 (5.1-8.2)
Price (2014)	Non-visible haematuria (coded and uncoded data)	Patients 40-59 years	0.79 (0.11-5.6)
Price (2014)	Non-visible haematuria (coded and uncoded data)	All patients ≥ 60 years	1.6 (1.2-2.1)
Bruyninckx (2003)	Macroscopic haematuria + pain	All patients	5.3 (2.7-9.8)
Bruyninckx (2003)	Macroscopic haematuria + pain	Men > 60 years	17.8 (8.5-32.6)
Shephard (2012)	Visible haematuria + abdominal pain (coded data only)	All patients ≥ 60 years	3.2 (1.9-5.8)
Price (2014)	Visible haematuria + abdominal pain (coded and uncoded data)	All patients ≥ 60 years	2.3 (1.5-3.5)
Price (2014)	Non-visible haematuria + abdominal pain (coded and uncoded data)	All patients ≥ 60 years	1.7 (0.6-4.2)
Bruyninckx (2003)	Macroscopic haematuria without pain	All patients	10.9 (7.3-16)
Bruyninckx (2003)	Macroscopic haematuria without pain	Men > 60 years	18.9 (11.9-28.6)
Bruyninckx (2003)	Macroscopic haematuria + increased frequency of micturition	All patients	7.2 (3.8-12.8)
Bruyninckx (2003)	Macroscopic haematuria + increased frequency of micturition	Men > 60 years	22.6 (10.3-41.5)
Bruyninckx (2003)	Macroscopic haematuria without increased frequency of micturition	All patients	13.4 (9.4-18.7)
Bruyninckx (2003)	Macroscopic haematuria without increased frequency of micturition	Men > 60 years	22 (14.9-31.2)
Bruyninckx (2003)	Macroscopic haematuria + dysuria	All patients	5.6 (2.6-11)
Bruyninckx (2003)	Macroscopic haematuria + dysuria	Men > 60 years	24.1 (11-43.9)
Shephard (2012)	Visible haematuria + dysuria (coded data	All patients ≥ 60 years	6.4 (NR as N < 10)

	only)		
Price (2014)	Visible haematuria + dysuria (coded and uncoded data)	All patients ≥ 60 years	4.1 (2.6-6.3)
Price (2014)	Non-visible haematuria + dysuria (coded and uncoded data)	All patients ≥ 60 years	4.5 (NR)
Bruyninckx (2003)	Macroscopic haematuria without dysuria	All patients	23.6 (17.1-31.5)
Bruyninckx (2003)	Macroscopic haematuria without dysuria	Men > 60 years	21.6 (14.6-30.6)
Bruyninckx (2003)	Macroscopic haematuria + nocturia	All patients	6.3 (2.4-14.8)
Bruyninckx (2003)	Macroscopic haematuria + nocturia	Men > 60 years	12.5 (3.3-33.5)
Bruyninckx (2003)	Macroscopic haematuria without nocturia	All patients	11.2 (8.1-15.2)
Bruyninckx (2003)	Macroscopic haematuria without nocturia	Men > 60 years	23.3 (16.3-32.1)
Bruyninckx (2003)	Macroscopic haematuria + weight loss	All patients	10 (.5-45.9)
Bruyninckx (2003)	Macroscopic haematuria + weight loss	Men > 60 years	33.3 (1.8-87.5)
Bruyninckx (2003)	Macroscopic haematuria without weight loss	All patients	8.3 (5.8-11.5)
Bruyninckx (2003)	Macroscopic haematuria without weight loss	Men > 60 years	18.2 (12.4-26)
Bruyninckx (2003)	Macroscopic haematuria + fatigue	All patients	20.8 (11-35.4)
Bruyninckx (2003)	Macroscopic haematuria + fatigue	Men > 60 years	30 (12.8-54.3)
Bruyninckx (2003)	Macroscopic haematuria without fatigue	All patients	8.9 (6.2-12.4)
Bruyninckx (2003)	Macroscopic haematuria without fatigue	Men > 60 years	20.8 (14.2-29.4)
Bruyninckx (2003)	Macroscopic haematuria with other symptoms	All patients	6.4 (4.3-9.3)
Bruyninckx (2003)	Macroscopic haematuria without other symptoms	All patients	3.9 (2.3-6.4)
Shephard (2012)	Visible haematuria + constipation (coded data only)	All patients ≥ 60 years	2.7 (1.6-4.5)
Price (2014)	Visible haematuria + constipation (coded and uncoded data)	All patients ≥ 60 years	2.2 (1.5-3.4)
Price (2014)	Non-visible haematuria + constipation (coded and uncoded data)	All patients ≥ 60 years	2 (NR)
Shephard (2012)	Visible haematuria + urinary tract infection (coded data only)	All patients ≥ 60 years	4.1 (3-6.2)

Price (2014)	Visible haematuria + urinary tract infection (coded and uncoded data)	All patients ≥ 60 years	2.2 (1.8-2.8)
Price (2014)	Non-visible haematuria + urinary tract infection (coded and uncoded data)	All patients ≥ 60 years	1.4 (0.8-2.4)
Shephard (2012)	Visible haematuria + raised inflammatory markers (coded data only)	All patients ≥ 60 years	5.6 (NR as N < 10)
Price (2014)	Visible haematuria + raised inflammatory markers (coded and uncoded data)	All patients ≥ 60 years	3.3 (2-5.4)
Price (2014)	Non-visible haematuria + raised inflammatory markers (coded and uncoded data)	All patients ≥ 60 years	1.25 (NR)
Shephard (2012)	Visible haematuria + raised creatinine (coded data only)	All patients ≥ 60 years	5.1 (3.4-8.4)
Price (2014)	Visible haematuria + raised creatinine (coded and uncoded data)	All patients ≥ 60 years	2.9 (2.1-3.9)
Price (2014)	Non-visible haematuria + raised creatinine (coded and uncoded data)	All patients ≥ 60 years	1.1 (0.6-2.2)
Shephard (2012)	Visible haematuria + raised white blood cell count (coded data only)	All patients ≥ 60 years	8.8 (NR as N < 10)
Price (2014)	Visible haematuria + raised white blood cell count (coded and uncoded data)	All patients ≥ 60 years	3.7 (2.1-6.3)
Price (2014)	Non-visible haematuria + raised white blood cell count (coded and uncoded data)	All patients ≥ 60 years	3.9 (NR)
Collins (2013)	Abdominal pain	All patients	0.11 (0.1-0.13)
		Men	0.2 (0.2-0.21)
		Women	0.1 (0.1-0.1)
Hippisley-Cox (2012)	Abdominal pain	All patients	0.2 (0.2-0.2)
Shephard (2012)	Abdominal pain	All patients ≥ 60	0.2 (0.1-0.2)
Shephard (2012)	*Abdominal pain*	*All patients*	*Cases: 358/4915 Controls: 787/21718*
Shephard (2012)	Abdominal pain (second attendance)	All patients ≥ 60	0.2 (0.1-0.2)
Shephard (2012)	Abdominal pain +	All patients ≥ 60	0.4 (0.3-0.7)

	dysuria		
Shephard (2012)	Abdominal pain + constipation	All patients ≥ 60	0.2 (0.1-0.3)
Shephard (2012)	Abdominal pain + urinary tract infection	All patients ≥ 60	0.4 (0.3-0.6)
Shephard (2012)	Abdominal pain + raised inflammatory markers	All patients ≥ 60	0.2 (0.1-0.3)
Shephard (2012)	Abdominal pain + raised creatinine	All patients ≥ 60	0.3 (0.2-0.4)
Shephard (2012)	Abdominal pain + raised white blood cell count	All patients ≥ 60	0.2 (0.1-0.3)
Shephard (2012)	Dysuria	All patients ≥ 60	0.7 (0.6-0.8)
Shephard (2012)	*Dysuria*	*All patients*	*Cases: 444/4915 Controls: 209/21718*
Shephard (2012)	Dysuria (second attendance)	All patients ≥ 60	1 (0.7-1.5)
Shephard (2012)	Dysuria + constipation	All patients ≥ 60	0.5 (0.3-0.9)
Shephard (2012)	Dysuria + urinary tract infection	All patients ≥ 60	0.7 (0.4-1.1)
Shephard (2012)	Dysuria + raised inflammatory markers	All patients ≥ 60	0.9 (0.5-1.7)
Shephard (2012)	Dysuria + raised creatinine	All patients ≥ 60	0.6 (0.4-1)
Shephard (2012)	Dysuria + raised white blood cell count	All patients ≥ 60	0.9 (0.5-1.9)
Shephard (2012)	Constipation	All patients ≥ 60	0.1 (0.1-0.2)
Shephard (2012)	*Constipation*	*All patients*	*Cases: 286/4915 Controls: 708/21718*
Shephard (2012)	Constipation (second attendance)	All patients ≥ 60	0.1 (0.1-0.2)
Shephard (2012)	Constipation + urinary tract infection	All patients ≥ 60	0.5 (0.3-0.7)
Shephard (2012)	Constipation + raised inflammatory markers	All patients ≥ 60	0.2 (0.1-0.2)
Shephard (2012)	Constipation + raised creatinine	All patients ≥ 60	0.2 (0.2-0.3)
Shephard (2012)	Constipation + raised white blood cell count	All patients ≥ 60	0.3 (0.2-0.5)
Shephard (2012)	Urinary tract infection	All patients ≥ 60	0.4 (0.3-0.4)
Shephard (2012)	*Urinary tract infection*	*All patients*	*Cases: 835/4915 Controls: 705/21718*
Shephard (2012)	Urinary tract infection (second attendance)	All patients ≥ 60	0.5 (0.4-1.6)
Shephard (2012)	Urinary tract infection + raised inflammatory markers	All patients ≥ 60	0.4 (0.3-0.7)
Shephard (2012)	Urinary tract infection + raised creatinine	All patients ≥ 60	0.5 (0.3-0.6)
Shephard (2012)	Urinary tract infection + raised white blood cell	All patients ≥ 60	0.6 (0.4-0.9)

	count		
Shephard (2012)	Raised inflammatory markers	All patients ≥ 60	0.1 (0.1-0.2)
Shephard (2012)	*Raised inflammatory markers*	*All patients*	*Cases: 293/4915 Controls: 717/21718*
Shephard (2012)	Raised inflammatory markers + raised creatinine	All patients ≥ 60	0.3 (0.2-0.3)
Shephard (2012)	Raised inflammatory markers + raised white blood cell count	All patients ≥ 60	0.2 (0.1-0.3)
Shephard (2012)	Raised creatinine	All patients ≥ 60	0.1 (0.12-0.14) *As reported, but PPV or CI not reported correctly*
Shephard (2012)	*Raised creatinine*	*All patients*	*Cases: 660/4915 Controls: 1668/21718*
Shephard (2012)	Raised creatinine + raised white blood cell count	All patients ≥ 60	0.3 (0.2-0.4)
Shephard (2012)	Raised white blood cell count	All patients ≥ 60	0.2 (0.17-0.23)
Shephard (2012)	*Raised white blood cell count*	*All patients*	*Cases: 250/4915 Controls: 401/21718*
Collins (2013)	Appetite loss	Women	0.1 (0.04-0.3)
Hippisley-Cox (2012)	Appetite loss	All patients	0.18 (0.07-0.4)
Collins (2013)	Weight loss	Women	0.1 (0.1-0.2)
Hippisley-Cox (2012)	Weight loss	All patients	0.41 (0.3-0.6)
Collins (2013)	Anaemia	All patients	0.6 (0.5-0.7)
		Men	1.4 (1.1-1.9)
		Women	0.3 (0.3-0.5)
Hippisley-Cox (2012)	Anaemia	All patients	0.69 (0.5-0.9)

NR = Not reported. Please note the calculations of the positive predictive values differ between the studies with Bruyninckx (2003), Hippisley-Cox (2012) and Jones (2007) using (TP)/(TP+FP) and Shephard (2012) using Bayesian statistics due to the case-control design of this study.

Evidence statement(s):

Haematuria (6 studies, N = 89345) presenting in a primary care setting is associated with overall positive predictive values ranging from 1.34%-10.27% for bladder cancer, which tended to be higher in men (5.47%-14.2%) than in women (2.48%-5.1%; 3 studies, total N = 49327) and to increase with age in men (up 22.1%; 2 studies, total N = 11517) and much less so in women (up to 8.53%; 2 studies, total N = 11517). All the studies were associated with 0-2 bias or applicability concern (see also Tables 1-3).

Haematuria in combination with other symptoms presenting in a primary care setting was associated with positive predictive values ranging from 1.1% (non-visible with raised creatinine in patients ≥ 60 years; 1 study, total N = 26633) to 33.3% (with weight loss in men > 60 years old; 1 study, total N = 409) for bladder cancer. Both studies were associated with 1 bias or applicability concern (see also Table 3).

Other symptoms (than haematuria) presenting alone or in combination with each other (but not haematuria) in a primary care setting were all associated with positive predictive values ≤ 1.5% for bladder cancer (3 studies, total N = 1284137). All the studies were associated with 0-1 bias or applicability concern (see also Table 3).

Evidence tables

Bruyninckx (2003)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective consecutive patient series using a register populated by GPs in Belgium. This register is based on the voluntary and constant registration of epidemiological data by GPs and is spread equally over the country. At the time of the study data (1993-1994) this GP network covered ca 1% of the Belgian population. GP participation rate was ca 90% (N = 83).
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 83890 patient-years were registered. Patients with macroscopic haematuria: N = 409 (232 males/176 females/ 1 of unknown sex); mean (SD) age of patients with macroscopic haematuria but not cancer = 57 (20) years. Inclusion criteria: All patients complaining to their GP of macroscopic haematuria in 1993-1994 were included. Patients complaining repeatedly of haematuria were included only once. Exclusion criteria: None reported. Clinical setting: Primary care, Belgium.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Haematuria was registered if a patient complained to the GP of any blood of urological origin that had not necessarily been checked by the GP during the study period, irrespective of the duration of the complaint and irrespective of the existence or absence of other signs or symptoms. Registered associated signs and symptoms were fatigue, weight loss, pain, nocturia, dysuria or frequency of micturition.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**

REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Diagnosis of urological cancer during a clinical follow-up of ≥ 18 months was registered as the reference standard. Urological cancer was defined as any malignancy of the urological tract that was confirmed histologically or by cystoscopy, intravenous pyelogram, or ultrasound scan. Recall letters were sent to the practices every six months, to check the included cases again upon the emergence of a diagnosis of any urological cancer. To ensure that all cases of urological cancer diagnosed within the follow-up period were identified, at the end of the period each of the GPs was sent a list of all their patients with macroscopic haematuria who were included in the study, in order to check for any 'hidden' urological cancer diagnosis.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No (but all patients had a positive index test)**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients are accounted for in the results but the number of true negatives and false negatives could not be ascertained from the reported results.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	Type of urological cancer found in the 409 haematuria patients: Bladder: N = 34, other urological cancer: N = 8. All these cancers were included in the meta-analysis.

Collins (2013)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Retrospective patient series using the THIN database.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 2145133 patients (1063355 men, 1081778 women) were identified from 364 practices. Symptoms:

	Haemoglobin < 11 g/dl recorded in the last year (N = 16961; 3969 men, 12992 women), abdominal pain (N = 253344; 105247 men, 148097 women), appetite loss (N = 6097; 2616 men, 3481 women), weight loss (N = 29369; 13332 men, 16037 women), haematuria (N = 37810; 22810 men, 15000 women), previous diagnosis of cancer apart from renal tract cancer at study entry (N = 49303; 18130 men, 31173 women). Incident cases of renal tract cancer during the 2-year follow up period: N = 2283 (1685 men, 598 women). Inclusion criteria: Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (e.g., haematuria, abdominal pain, weight loss, appetite loss, and anaemia), the date of the first recorded onset within the study period. Exclusion criteria: Patients with a prior diagnosis of renal tract cancer, registered less than 12 months with the general practice, had invalid dates, < 30 years old or ≥ 85 years old. Clinical setting: Primary care, UK
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms were defined as symptoms that might alarm the patient and also indicate the presence of renal tract cancer; that is, symptoms of haematuria, loss of appetite, weight loss, or abdominal pain.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Renal tract cancer, which was defined as incident diagnosis of cancer of the bladder, kidney, ureter, or urethra during the 2 years after study entry, recorded either on the patient's GP record using the relevant UK diagnostic Read Codes. Patients without the outcome were censored at the earliest of the date of death, date of leaving the practice study of 2 years of follow up.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**

FLOW AND TIMING		
A. risk of bias		
Flow and timing	All patients seem to be accounted for	
Was there an appropriate interval between index test and reference standard?		**Yes**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**Yes**
Could the patient flow have introduced bias?		**Low risk**
NOTES	It is unclear why no data has been presented for men for the symptoms of appetite loss and weight loss.	

Friedlander (2014)

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Retrospective cohort study, using claims data and laboratory values from the Vanderbilt University Medical Centre's (VUMC) Research Derivative, which is a "data repository that contains administrative and clinical information, including a complete record of visits and admissions, laboratory data, and diagnosis and procedure codes, on every patient treated in the Vanderbilt health system" (p 634) located in Tennessee in the USA.	
Was a consecutive or random sample of patients enrolled?		**Yes**
Was a case-control design avoided?		**Yes**
Did the study avoid inappropriate exclusions?		**Yes (probably)**
Could the selection of patients have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Patient characteristics and setting	N = 2455 patients, 724 males / 1731 females, median (inter-quartile range) age = 58 (49-68) years; smoking history: current smoker (N = 406), former smoker (N = 473), non-smoker (N = 1514). Inclusion criteria: "Patients aged ≥ 40 years with a first diagnosis of hematuria" "between 2004 and 2012 by urinalysis (>3 red blood counts per high power field) or International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes for hematuria (599.7, 599.70, 599.71 or 599.72) at one of the VUMC's 19 primary care clinics. To be included in the study, patients must have had records for 1 year before the date of hematuria diagnosis." Exclusion criteria: "Patients were excluded if they had a urinary tract infection (defined as a urinalysis positive for both leukocyte esterase and urine nitrites, or a positive urine culture) within 4 weeks before or 1 week after the index hematuria episode (n = 590, 9.0%) or had a prior explanatory diagnoses and procedures that would preclude the need for a hematuria evaluation (according to a convened panel of content experts; prostate/renal/bladder/other cancer, benign prostate/renal/bladder/other mass, prostate dysplasia, cystitis, urethritis, epididymitis/orchitis, prostatitis, pyelonephritis, urolithiasis, prostatic enlargement, trauma, medical renal disease, haematologic/thrombotic diease?, anatomic abnormality, prostatectomy, prostate biopsy, transurethral incision of prostate, resection of prostate, cystoscopy, cystectomy, ureteroscopy, nephrectomy,	

	pyeloplasty, ureteral reimplantation)." We then used Physicians Current Procedural Terminology Coding System, 4th Edition and ICD-9 codes to exclude patients with an explanatory diagnosis or procedure within 180 days preceding their hematuria diagnosis (n = 3540, 53.8%)." Clinical setting: Primary care, USA.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	First diagnosis of hematuria" "by urinalysis (>3 red blood counts per high power field) or International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes for hematuria (599.7, 599.70, 599.71 or 599.72)".
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	The reference standard consisted checking the database for diagnoses of genitourinary neoplasms within 180 days after haematuria diagnosis, as determined by ICD-9 codes.
Is the reference standard likely to correctly classify the target condition?	**Unclear (is 180 days enough time to get a diagnosis of all cancers?)**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear (but all patients had a positive index test)**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	There were 66 patients with cancer: Bladder (N = 33), renal cell (N = 16), prostate (N = 15). The types of cancer for the remaining two cases were not reported.

Hippisley-Cox (2012)

PATIENT SELECTION	

A. risk of bias	
Patient sampling	Prospective patient series using patients in the QResearch database (version 30).
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 1240722 patients were identified from 189 practices (622166 males, 618556 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6). Current symptoms and symptoms in the preceding year: Current haematuria (N = 25553), current abdominal pain (N = 128721), current appetite loss (N = 5531), current weight loss (N = 14464), constipation in the last year (N = 8472), diarrhoea in the last year (N = 12171), tiredness in the last year (N = 12669), haemoglobin recoded in the last year (N = 216201), haemoglobin < 11 g/dl in the last year (N = 16169). Incident cases of renal tract cancer during the 2-year follow up period: N = 1622; mean age at diagnosis = 70 years, 1187 males/ 435 females; **Type of cancer: Bladder: N = 1292; Kidney: N = 307; Ureter: N = 21; Urethra: N = 2.** Inclusion criteria: All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000) and 12 months after the patient registered with the practice, ensuring that all patients had ≥ 12 months' registration prior to study entry. For patients with incident haematuria, appetite loss, weight loss, or abdominal pain, the entry date was the date of the first consultation with the symptom within the study period. *The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.* Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of renal tract cancer at baseline, and patients with a recorded 'red-flag' (see "Definition of symptom" below) symptom in the 12 months prior to the study entry date. Clinical setting: Primary care
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms were defined as symptoms that might alarm the patient and also indicate the presence of renal tract cancer; that is, symptoms of haematuria, loss of appetite, weight loss, or abdominal pain.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**

Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Renal tract cancer, which was defined as incident diagnosis of cancer of the bladder, kidney, ureter, or urethra during the 2 years after study entry, recorded either on the patient's GP record using the relevant UK diagnostic Read Codes, or their linked Office for National Statistics cause-of-death record, using the relevant ICD-9 codes (188 or 189) or ICD-10 diagnostic codes (C64–67).
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	A total of 1342329 patients were initially identified of whom 101607 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of renal tract cancer (N = 1506), and ≥ one 'red flag' symptom recorded in the 12 months prior to study entry (N = 29254), leaving 1240722 patients. However, data is presented for 967681 / 1240722 patients. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**No**
Could the patient flow have introduced bias?	**High risk**
NOTES	Please note, the included cancer cases were for renal tract cancer, not just bladder cancer.

Jones (2007)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Retrospective consecutive patient series using patients in the UK's General Practice Research Database.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**

Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 923605 patients were identified, of whom 762325 were aged ≥ 15 years. Number of first occurrences in patients with no previous diagnosis of cancer: Haematuria: N = 11138, mean (SD) age at first symptom = 58.5 (18.9) years. Patients excluded due to incomplete dates for their first symptom: N = 30. Sex (of final sample): 6385 males, 4723 females. Haemoptysis: N = 4822, mean (SD) age at first symptom = 61.6 (18) years. Patients excluded due to incomplete dates for their first symptom: N = 10. Sex (of final sample): 2930 males, 1882 females. Dysphagia: N = 6003, mean (SD) age at first symptom = 54.5 (19.4) years. Patients excluded due to incomplete dates for their first symptom: N = 4. Sex (of final sample): 2628 males, 3371 females. Rectal bleeding: N = 15314, mean (SD) age at first symptom = 52.5 (18.8) years. Patients excluded due to incomplete dates for their first symptom: N = 25. Sex (of final sample): 7523 males, 7766 females. Inclusion criteria: All patients from 128 general practices that provided data of a sufficient standard from 1 January 1994 to 31 December 2000 and which provided exclusively Read coded data, who were aged between 15 and 100 years, whose first ever recorded occurrence of each alarm symptom (haematuria, haemoptysis, dysphagia, or rectal bleeding) was after 31 December 1994 and who had not previously been diagnosed as having any cancer. Exclusion criteria: Patients whose date of first symptom or first relevant diagnosis of cancer was before 1 January 1995 and patients with a diagnosis of any other cancer than the ones of interest before the date of the first recorded symptom or before the index cancer diagnosis date if the related symptom was not recorded. Clinical setting: Primary care
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	Identification of all patients who ever had symptoms recorded for haematuria, haemoptysis, dysphagia, or rectal bleeding.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Cancer code in the UK's General Practice Research Database: Haematuria: Urinary tract neoplasms, including neoplasms of the urethra, bladder, ureter, and kidney but excluding neoplasms of the prostate and

	other reproductive organs. Haemoptysis: Respiratory tract neoplasms. Dysphagia: Oesophageal neoplasms. Rectal bleeding: Colorectal neoplasms.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear (but all patients had a positive index test)**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients are accounted for in the results
Was there an appropriate interval between index test and reference standard?	**Unclear**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	Diagnoses of cancer were most often made in the first three months after the onset of alarm symptoms; very few diagnoses of cancer were made later than three years after symptom onset. In the 4th and 5th years of study, the small number of observed occurrences of cancer was similar to the number expected from background incidence rates. Secondary analyses evaluating whether the incidence of neoplasms other than those prespecified was increased after the occurrence of alarm symptoms showed for: Haematuria: Inclusion of cancers of the reproductive organs yielded 21 additional cancers in women and 158 cancers in men, mostly cancers of the prostate. Inclusion of these cancers in the analysis would give a positive predictive value of 3.9% in women and 9.9% in men. Dysphagia: Inclusion of gastric cancers yielded 17 additional cancer diagnoses in women and 30 in men. Inclusion of these cancers gave positive predictive values of 5.2% in women and 6.9% in men. *Estimates based on the pre-specified cancers may be thus conservative for these symptoms.* Haemoptysis: Extension of the diagnostic criteria yielded 6 additional cancers. Rectal bleeding: Extension of the diagnostic criteria yielded 2 additional cancers.

Shephard (2012)/Price (2014)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Matched case-control study using patients in the UK's General Practice Research Database.

Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: Males: 3563 patients, median age at diagnosis = 73 (IQR = 65-80) years, median number of consultations = 14 (IQR = 9-22), UK. Females: 1352 patients, median age at diagnosis = 75 (IQR = 67-82) years, median number of consultations = 15 (IQR = 10-23), UK. Controls: Males: 15452 patients, median age at diagnosis = 73 (IQR = 66-79) years, median number of consultations = 8 (IQR = 4-15), UK. Females: 6266 patients, median age at diagnosis = 75 (IQR = 67-82) years, median number of consultations = 9 (IQR = 4-15), UK. Inclusion criteria: Cases: Patients with a first record of bladder cancer between January 2000 and December 2009 inclusive, aged ≥ 40 years, with min. 1 year of data before diagnosis. The first instance of a bladder cancer code was assigned the data of diagnosis/index date. Controls: Up to 5 controls were matched on sex, general practice, and to 1 year of age of the case. The index date was the index date of the matched case. Exclusion criteria: Metastatic cancer of the bladder from a non-bladder primary, diagnosis before 2000, or no consultations in the year before diagnosis. Clinical setting: Primary care
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	A list of symptoms, signs and investigations (features) potentially associated with bladder cancer was compiled from the authors' literature search, augmented by viewing material from bladder cancer support organisations and online chat rooms. Internet search terms included 'bladder cancer', 'bladder symptoms', and 'early signs/indications'. Visible and non-visible haematuria were studied separately. Only codes specifying the word 'microscopic' were assigned to the latter group, so generic codes such as the single word 'haematuria' were assumed to be visible haematuria. For each feature a list of relevant medical codes from the GPRD's master list of over 100,000 codes was assembled. Occurrences of these in the year before the index date were identified. Repeated consultations for the same complaint were also identified along with all codes for fractures as a test for any

	recording bias between cases and controls (making the assumption that the fracture rate would be approximately equal). Variables were retained only if they occurred in at least 5% of either cases or controls (this was always cases). Investigation results were deemed to be abnormal if they fell outside their local laboratory's normal range: for analysis, patients with a normal laboratory result were grouped with those who had not been tested.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Bladder cancer code in the UK's General Practice Research Database.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	A total of 29033 patients were identified, 24098 controls and 4935 cases. Of the controls the following exclusions were applied: bladder cancer post-2000 (N = 134), bladder control [?] pre-2000 (N = 125), metastatic cancer (N = 35), and no data in year pre-index date (N = 2086). Of the cases the following exclusions were applied: No controls (N = 13), metastatic cancer (N = 7).
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	43 symptoms and 104 abnormal test results were considered initially. 6 symptoms and 7 abnormal test variables were present in ≥ 5% of cases. The proportion of patients with a recorded fracture did not differ between cases (1.45%) and controls (1.46%). The authors have published extra analyses of the same data in an additional paper (Price, 2014) wherein the data analysis is extended to the uncoded

	data in the CPRD, namely 'free text' notes added by GPs to augment a coded entry in a patient's record. In particular, the authors "sought to identify whether there were sufficient additional non-visible haematuria entries to allow reliable estimates of its association with bladder cancer."

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Excl reason: Narrative review

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Review question:
Which investigations of symptoms of suspected bladder cancer should be done with clinical responsibility retained by primary care?

Results

Literature search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-2013	796	91	16/01/2013
Premedline	1980-2013	30	5	16/01/2013
Embase	1980-2013	358	40	17/01/2013
Cochrane Library	1980-2013	40	1	17/01/2013
Psychinfo	1980-2013	1	0	16/01/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2013	46	9	17/01/2013
Biomed Central	1980-2013	114	2	17/01/2013

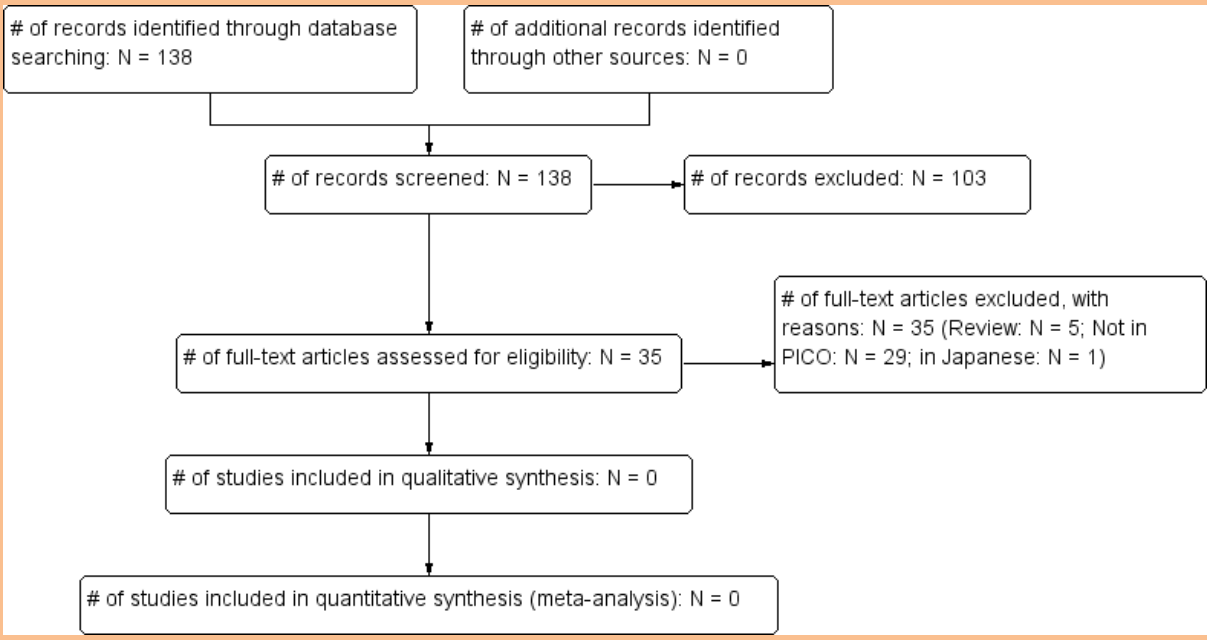
Total number of references retrieved after de-duplication: 104

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2013-11/08/2014	37	14	11/08/2014
Premedline	2013-11/08/2014	52	10	11/08/2014
Embase	2013-11/08/2014	53	19	11/08/2014
Cochrane Library	2013-	25	0	11/08/2014

	11/08/2014			
Web of Science (SCI & SSCI) and ISI Proceedings	2013-11/08/2014	10	1	11/08/2014

Total References retrieved (after de-duplication): 34



Study results

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

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None

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RENAL CANCER

Review question:
What is the risk of renal cancer in patients presenting in primary care with symptom(s)?

Results

Literature search

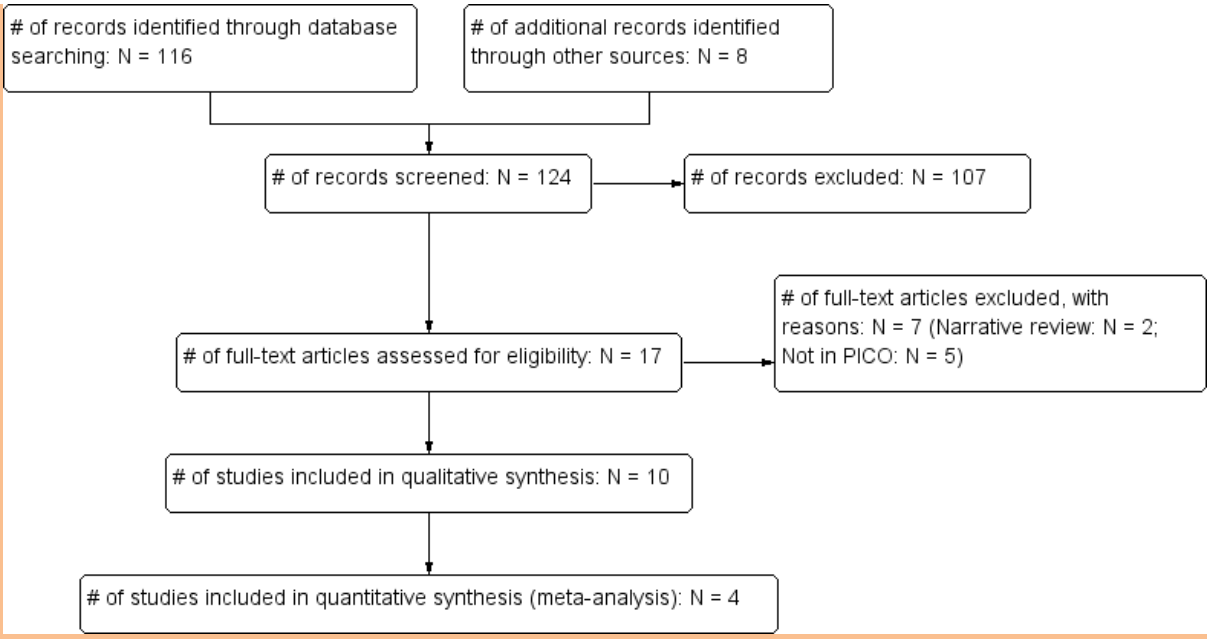
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2012	718	72	10/12/2012
Premedline	All-2012	29	2	10/12/2012
Embase	All-2012	662	57	10/12/2012
Cochrane Library	All-2012	289	0	11/12/2012
Psychinfo	All-2012	1	0	10/12/2012
Web of Science (SCI & SSCI) and ISI Proceedings	All-2012	283	5	11/12/2012
Biomed Central	All-2012	18	0	11/12/2012

Total References retrieved (after de-duplication): 94

Update Search

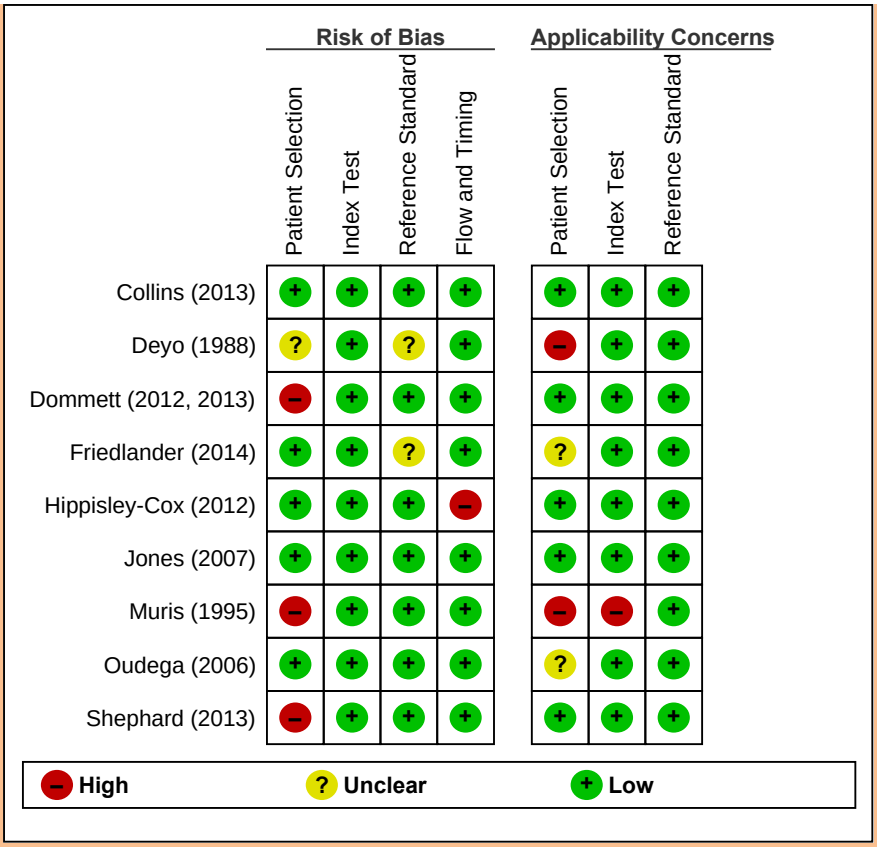
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2013-18/08/2014	49	8	18/08/2014
Premedline	2013-18/08/2014	67	7	18/08/2014
Embase	2013-18/08/2014	140	8	18/08/2014
Cochrane Library	2013-18/08/2014	207	0	18/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	2013-18/08/2014	67	5	18/08/2014

Total References retrieved (after de-duplication): 22



Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issue to note is that patient selection is associated with a number of bias or applicability concerns in most of the included studies, with some studies employing non-consecutive or non-random selection of patients and with some studies being employed in settings that are not clearly directly representative of UK-based primary care. Other areas of concern include missing data, compromised reference standards and underspecified presenting symptoms. These issues should all be born in mind when evaluating the evidence along with the fact that a large number of the included cancers were not renal cancers.



Study results

Table 1: Renal cancer: Meta-analyses

Studies included	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Collins (2013), Friedlander (2014), Hippisley-Cox (2012), Jones (2007, at 6 months)	Haematuria	All patients (N = 69921)	3.05 (1.3-7.01)
Collins (2013), Friedlander (2014), Hippisley-Cox (2012), Jones (2007, at 3 years)	Haematuria	All patients (N = 69921)	3.3 (1.35-7.84)

Please note that the data from Shephard (2012) are not included in these meta-analyses due to the case-control design of the study. These data are instead reported in the table below.

Table 2: Renal cancer: Individual positive predictive values from the meta-analyses

Studies included	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Collins (2013)	Haematuria	All patients (N = 37810)	4.35 (4.1-4.6)
Friedlander (2014)	Haematuria	All included patients (N = 2455)	0.65 (0.39-1.83) 16/2455
Hippisley-Cox (2012)	Haematuria	All patients (N = 18548)	6.48 (6.1-6.8)
Jones (2007, at 6	Haematuria	All patients (N = 11108)	4.2 (3.8-4.6)

months),			
Jones (2007, at 3 years),	Haematuria	All patients (N = 11108)	5.7 (5.3-6.2)

Table 3: Renal cancer: Patients aged > 14 years: Single symptoms

Study	Symptom(s)	Patient group	Positive predictive value % (95% CI)
Collins (2013)	Abdominal pain	All patients	0.11 (0.1-0.13)
		Men	0.2 (0.2-0.21)
		Women	0.1 (0.1-0.1)
Hippisley-Cox (2012)	Abdominal pain	All patients	0.2 (0.2-0.2)
Muris (1995)	Non-acute abdominal complaints	All patients	0.11 (0.01-0.7) 1/933
Shephard (2013)	Abdominal pain	Patients ≥ 60 years	0.1 (0.1-0.2) Cases: 350/3149 Controls: 514/14091
Shephard (2013)	Abdominal pain: 2 presentations	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2013)	Constipation	Patients ≥ 60 years	0.1 (0.08-0.11) Cases: 194/3149 Controls: 420/14091
Shephard (2013)	Constipation: 2 presentations	Patients ≥ 60 years	0.1 (0.06-0.12)
Shephard (2013)	Lower urinary tract infection	Patients ≥ 60 years	0.1 (0.09-0.12) Cases: 339/3149 Controls: 608/14091
Shephard (2013)	Lower urinary tract infection: 2 presentations	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2013)	Fatigue	Patients ≥ 60 years	0.1 (0.09-0.13) Cases: 210/3149 Controls: 405/14091
Shephard (2013)	Fatigue: 2 presentations	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2013)	Nausea	Patients ≥ 60 years	0.1 (0.1-0.2) Cases: 171/3149 Controls: 263/14091
Shephard (2013)	Nausea: 2 presentations	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2013)	Raised inflammatory markers	Patients ≥ 60 years	0.2 (0.1-0.2) Cases: 738/3149 Controls: 993/14091
Shephard (2013)	Thrombocytosis	Patients ≥ 60 years	0.3 (0.2-0.3) Cases: 348/3149 Controls: 251/14091
Shephard (2013)	Microcytosis	Patients ≥ 60 years	0.3 (0.2-0.4) Cases: 233/3149 Controls: 158/14091
Deyo (1988)	Back pain	All included patients	0.05 (0.002-0.3) TP = 1, FP = 1974 N = 8 had other

			types of cancer
Shephard (2013)	Back pain	Patients ≥ 60 years	0.1 (0.07-0.12) Cases: 341/3149 Controls: 901/14091
Shephard (2013)	Back pain: 2 presentations	Patients ≥ 60 years	0.1 (0.07-0.12)
Collins (2013)	Anaemia	All patients	0.6 (0.5-0.7)
		Men	1.4 (1.1-1.9)
		Women	0.3 (0.3-0.5)
Hippisley-Cox (2012)	Anaemia	All patients	.69 (0.5-0.9)
Collins (2013)	Appetite loss	Women	0.1 (0.04-0.3)
Hippisley-Cox (2012)	Appetite loss	All patients	0.18 (0.07-0.4)
Oudega (2006)	Deep vein thrombosis	All patients	1.16 (0.4-2.9) 5/430
Collins (2013)	Weight loss	Women	0.1 (0.1-0.2)
Hippisley-Cox (2012)	Weight loss	All patients	0.41 (0.3-0.6)
Collins (2013)	Haematuria	Men	5.5 (5.2-5.8)
		Women	2.6 (2.3-2.8)
Shephard (2013)	Visible haematuria	Patients 40-59 years	0.7 (0.4-1.3)
Shephard (2013)	Visible haematuria	Patients ≥ 60 years	1 (0.08-1.3) Cases: 558/3149 Controls: 97/14091
Shephard (2013)	Visible haematuria: 2 presentations	Patients ≥ 60 years	1.2 (0.9-1.8)
Jones (2007)	Haematuria	Men (all ages) at 6 months	5.47 (4.9-6.1)
Jones (2007)	Haematuria	Men < 45 years at 3 years	0.99 (0.53-1.69)
Jones (2007)	Haematuria	Men 45-54 years at 3 years	4.35 (3.11-5.9)
Jones (2007)	Haematuria	Men 55-64 years at 3 years	8.51 (6.94-10.32)
Jones (2007)	Haematuria	Men 65-74 years at 3 years	11.21 (9.66-12.9)
Jones (2007)	Haematuria	Men 75-84 years at 3 years	10.27 (8.61-12.13)
Jones (2007)	Haematuria	Men ≥ 85 years at 3 years	9.22 (6.43-12.7)
Jones (2007)	Haematuria	Women (all ages) at 6 months	2.48 (2.1-3)
Jones (2007)	Haematuria	Women < 45 years at 3 years	0.22 (0.05-0.64)
Jones (2007)	Haematuria	Women 45-54 years at 3 years	1.34 (0.65-2.45)
Jones (2007)	Haematuria	Women 55-64 years at 3 years	3.42 (2.26-4.93)
Jones (2007)	Haematuria	Women 65-74 years at 3 years	5.91 (4.42-7.72)
Jones (2007)	Haematuria	Women 75-84 years at 3 years	6.83 (5.06-8.98)

Jones (2007)	Haematuria	Women ≥ 85 years at 3 years	8.53 (5.6-12.3)

TP = True positives, FP = False positives. Shephard (2013) calculated the positive predictive values using Bayesian statistics.

Table 4: Renal cancer: Patients aged ≥ 60 years: Symptom combinations

Study	Symptom(s)	Patient group	Positive predictive value % (95% CI)
Shephard (2013)	Abdominal pain and back pain	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2013)	Abdominal pain and constipation	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2013)	Abdominal pain and lower urinary tract infections	Patients ≥ 60 years	0.3 (0.2-0.4)
Shephard (2013)	Abdominal pain and fatigue	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2013)	Abdominal pain and nausea	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2013)	Abdominal pain and raised inflammatory markers	Patients ≥ 60 years	0.2 (0.2-0.3)
Shephard (2013)	Abdominal pain and thrombocytosis	Patients ≥ 60 years	0.5 (0.3-1)
Shephard (2013)	Abdominal pain and microcytosis	Patients ≥ 60 years	> 5 (NR)
Shephard (2013)	Abdominal pain and visible haematuria	Patients ≥ 60 years	2.8 (NR)
Shephard (2013)	Visible haematuria and back pain	Patients ≥ 60 years	0.7 (0.4-1.3)
Shephard (2013)	Visible haematuria and constipation	Patients ≥ 60 years	1 (NR)
Shephard (2013)	Visible haematuria and lower urinary tract infections	Patients ≥ 60 years	0.6 (0.4-1)
Shephard (2013)	Visible haematuria and fatigue	Patients ≥ 60 years	0.9 (NR)
Shephard (2013)	Visible haematuria and nausea	Patients ≥ 60 years	1.1 (NR)
Shephard (2013)	Visible haematuria and raised inflammatory markers	Patients ≥ 60 years	1.3 (0.7-2.2)
Shephard (2013)	Visible haematuria and thrombocytosis	Patients ≥ 60 years	2.1 (NR)
Shephard (2013)	Visible haematuria and microcytosis	Patients ≥ 60 years	1.5 (NR)
Shephard (2013)	Constipation and back pain	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2013)	Constipation and lower urinary tract infections	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2013)	Constipation and fatigue	Patients ≥ 60 years	0.2 (0.1-0.3)

Shephard (2013)	Constipation and nausea	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2013)	Constipation and raised inflammatory markers	Patients ≥ 60 years	0.3 (0.2-0.4)
Shephard (2013)	Constipation and thrombocytosis	Patients ≥ 60 years	0.3 (0.2-0.5)
Shephard (2013)	Constipation and microcytosis	Patients ≥ 60 years	0.6 (NR)
Shephard (2013)	Back pain and lower urinary tract infections	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2013)	Back pain and fatigue	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2013)	Back pain and nausea	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2013)	Back pain and raised inflammatory markers	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2013)	Back pain and thrombocytosis	Patients ≥ 60 years	0.3 (0.2-0.4)
Shephard (2013)	Back pain and microcytosis	Patients ≥ 60 years	0.3 (0.1-0.6)
Shephard (2013)	Lower urinary tract infections and fatigue	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2013)	Lower urinary tract infections and nausea	Patients ≥ 60 years	0.2 (0.1-0.4)
Shephard (2013)	Lower urinary tract infections and raised inflammatory markers	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2013)	Lower urinary tract infections and thrombocytosis	Patients ≥ 60 years	0.3 (0.2-0.4)
Shephard (2013)	Lower urinary tract infections and microcytosis	Patients ≥ 60 years	0.4 (0.2-0.8)
Shephard (2013)	Fatigue and nausea	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2013)	Fatigue and raised inflammatory markers	Patients ≥ 60 years	0.2 (0.2-0.3)
Shephard (2013)	Fatigue and thrombocytosis	Patients ≥ 60 years	0.5 (0.3-0.9)
Shephard (2013)	Fatigue and microcytosis	Patients ≥ 60 years	0.4 (0.2-0.8)
Shephard (2013)	Nausea and raised inflammatory markers	Patients ≥ 60 years	0.2 (0.2-0.3)
Shephard (2013)	Nausea and thrombocytosis	Patients ≥ 60 years	0.4 (0.2-0.6)
Shephard (2013)	Nausea and microcytosis	Patients ≥ 60 years	0.5 (NR)
Shephard (2013)	Raised inflammatory markers and thrombocytosis	Patients ≥ 60 years	0.4 (0.3-0.5)
Shephard (2013)	Raised inflammatory markers and microcytosis	Patients ≥ 60 years	0.7 (0.5-1)
Shephard (2013)	Thrombocytosis and microcytosis	Patients ≥ 60 years	0.6 (0.4-1)

NR = Not reported. TP = True positives, FP = False positives. Shephard (2013) calculated the positive predictive values using Bayesian statistics.

Table 5: Renal cancer: Positive predictive values for any childhood cancer: All patients

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	All included patients	0.055 (0.047-0.065) Cases: 342/1267 Control: 211/15318
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	All included patients	0.07 (0.064-0.078) Cases: 427/1267 Control: 829/15318
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	All included patients	0.083 (0.067-0.105) Cases: 108/1267 Control: 207/15318
Dommett (2012)	Headache 0-12 months before diagnosis	All included patients	0.064 (0.051-0.082) Cases: 90/1267 Control: 224/15318
Dommett (2013)	Headache 0-3 months before diagnosis	All included patients	0.06 (0.04-0.08) Cases: 73/1267 Control: 55/15318
Dommett (2013)	Headache 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.13 (0.08-0.22)
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	All included patients	0.096 (0.074-0.126) Cases: 82/1267 Control: 136/15318
Dommett (2013)	Lymphadenopathy 0-3 months before diagnosis	All included patients	0.09 (0.06-0.13) Cases: 69/1267 Control: 33/15318
Dommett (2013)	Lymphadenopathy 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.2 (0.1-0.39)
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	All included patients	0.172 (0.119-0.25) Cases: 56/1267 Control: 52/15318
Dommett (2013)	Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis	All included patients	0.11 (0.06-0.2) Cases: 42/1267 Control: 16/15318
Dommett (2013)	Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.3 (0.09-0.99)
Dommett (2012)	Fatigue 0-12 months before diagnosis	All included patients	0.085 (0.06-0.121) Cases: 47/1267 Control: 88/15318
Dommett (2013)	Fatigue 0-12 months before diagnosis	All included patients	0.07 (0.04-0.12) Cases: 42/1267 Control: 24/15318
Dommett (2013)	Fatigue 0-12 months	All included patients	0.12 (0.06-0.23)

	before diagnosis and ≥ 3 consultations		
Dommett (2012)	Back pain 0-12 months before diagnosis	All included patients	0.088 (0.06-0.128) Cases: 40/1267 Control: 73/15318
Dommett (2012)	Bruising 0-12 months before diagnosis	All included patients	0.08 (0.054-0.118) Cases: 38/1267 Control: 76/15318
Dommett (2013)	Bruising 0-3 months before diagnosis	All included patients	0.08 (0.05-0.13) Cases: 33/1267 Control: 18/15318
Dommett (2013)	Bruising 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.38 (0.09-1.64)
Dommett (2013)	Pallor 0-3 months before diagnosis	All included patients	0.41 (0.12-1.34) Cases: 33/1267 Control: 18/15318
Dommett (2013)	Pallor 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.76 (0.1-5.7)
Dommett (2013)	Lump mass swelling head and neck 0-3 months before diagnosis	All included patients	0.3 (0.1-0.84) Cases: 28/1267 Control: 4/15318
Dommett (2013)	Lump mass swelling head and neck 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.76 (0.1-5.7)
Dommett (2013)	Abnormal movement 0-3 months before diagnosis	All included patients	0.08 (0.04-0.14) Cases: 49/1267 Control: 26/15318
Dommett (2013)	Abnormal movement 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.15 (0.07-0.32)
Dommett (2013)	Bleeding 0-3 months before diagnosis	All included patients	0.06 (0.03-0.1) Cases: 28/1267 Control: 21/15318
Dommett (2013)	Bleeding 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.11 (0.04-0.31)
Dommett (2013)	Visual symptoms 0-3 months before diagnosis	All included patients	0.06 (0.03-0.10) Cases: 28/1267 Control: 21/15318
Dommett (2013)	Visual symptoms 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.23 (0.07-0.77)
Dommett (2013)	Pain 0-3 months before diagnosis	All included patients	0.04 (0.03-0.06) Cases: 42/1267 Control: 41/15318
Dommett (2013)	Pain 0-3 months before diagnosis and ≥ 3	All included patients	0.14 (0.07-0.31)

	consultations		
Dommett (2013)	Musculoskeletal symptoms 0-3 months before diagnosis	All included patients	0.04 (0.03-0.07) Cases: 107/1267 Control: 102/15318
Dommett (2013)	Musculoskeletal symptoms 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.13 (0.08-0.19)
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	All included patients	0.266 (0.117-0.609) Cases: 15/1267 Control: 9/15318
Dommett (2013)	≥ 3 consultations	All included patients	0.02
Dommett (2013)	Childhood infection 0-3 months before diagnosis	All included patients	Cases: 54/1267 Control: 236/15318
Dommett (2013)	Upper respiratory tract infection 0-3 months before diagnosis	All included patients	Cases: 143/1267 Control: 942/15318
Dommett (2013)	Vomiting 0-3 months before diagnosis	All included patients	Cases: 86/1267 Control: 105/15318
Dommett (2013)	Cough 0-3 months before diagnosis	All included patients	Cases: 77/1267 Control: 654/15318
Dommett (2013)	Rash 0-3 months before diagnosis	All included patients	Cases: 63/1267 Control: 555/15318
Dommett (2013)	Abdominal pain 0-3 months before diagnosis	All included patients	Cases: 60/1267 Control: 137/15318
Dommett (2013)	Abdominal mass 0-3 months before diagnosis	All included patients	Cases: 48/1267 Control: 0/15318
Dommett (2013)	Fever 0-3 months before diagnosis	All included patients	Cases: 49/1267 Control: 166/15318
Dommett (2013)	Eye swelling 0-3 months before diagnosis	All included patients	Cases: 39/1267 Control: 238/15318
Dommett (2013)	Shortness of breath 0-3 months before diagnosis	All included patients	Cases: 35/1267 Control: 221/15318
Dommett (2013)	Constipation 0-3 months before diagnosis	All included patients	Cases: 26/1267 Control: 61/15318
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	All included patients	2.19 (0.295-17.034) Cases: 14/1267 Control: 1/15318

The positive predictive values are calculated using Bayesian statistics.

Table 6: Renal cancer: Positive predictive values for any childhood cancer: Patients aged 0-4 years

Study	**Symptom(s)**	**Patient group**	**Positive predictive value (95% CI) Frequency**
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	Patients aged 0-4 years	0.081 (0.059-0.112) Cases: 96/436 Control: 55/4802
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	Patients aged 0-4 years	0.093 (0.077-0.113) Cases: 124/436 Control: 248/4802
Dommett (2012)	Neurological symptoms	Patients aged 0-4 years	0.076 (0.054-0.107)

	0-12 months before diagnosis		Cases: 43/436 Control: 105/4802
Dommett (2012)	Headache 0-12 months before diagnosis	Patients aged 0-4 years	0.135 (0.055-0.335) Cases: 8/436 Control: 11/4802
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	Patients aged 0-4 years	0.061 (0.037-0.1) Cases: 20/436 Control: 61/4802
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	Patients aged 0-4 years	0.198 (0.099-0.399) Cases: 16/436 Control: 15/4802
Dommett (2012)	Fatigue 0-12 months before diagnosis	Patients aged 0-4 years	0.087 (0.048-0.16) Cases: 15/436 Control: 32/4802
Dommett (2012)	Back pain 0-12 months before diagnosis	Patients aged 0-4 years	0.186 (0.047-0.742) Cases: 4/436 Control: 4/4802
Dommett (2012)	Bruising 0-12 months before diagnosis	Patients aged 0-4 years	0.155 (0.086-0.279) Cases: 20/436 Control: 24/4802
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	Patients aged 0-4 years	0.739 (0.159-3.496) Cases: 8/436 Control: 2/4802
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	Patients aged 0-4 years	1.286 (0.161-10.569) Cases: 7/436 Control: 1/4802

The positive predictive values are calculated using Bayesian statistics.

Table 7: Renal cancer: Positive predictive values for any childhood cancer: Patients aged 5-14 years

Study	**Symptom(s)**	**Patient group**	**Positive predictive value (95% CI) Frequency**
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	Patients aged 5-14 years	0.056 (0.047-0.068) Cases: 246/831 Control: 156/10516
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	Patients aged 5-14 years	0.075 (0.066-0.084) Cases: 303/831 Control: 581/10561
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	Patients aged 5-14 years	0.091 (0.067-0.123) Cases: 65/831 Control: 102/10516
Dommett (2012)	Headache 0-12 months before diagnosis	Patients aged 5-14 years	0.055 (0.043-0.07) Cases: 82/831 Control: 213/10516
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	Patients aged 5-14 years	0.118 (0.085-0.164) Cases: 62/831 Control: 75/10516
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	Patients aged 5-14 years	0.154 (0.099-0.24) Cases: 40/831 Control: 37/10516
Dommett (2012)	Fatigue 0-12 months	Patients aged 5-14	0.082 (0.053-0.125)

	before diagnosis	years	Cases: 32/831 Control: 56/10516
Dommett (2012)	Back pain 0-12 months before diagnosis	Patients aged 5-14 years	0.075 (0.05-0.111) Cases: 36/831 Control: 69/10516
Dommett (2012)	Bruising 0-12 months before diagnosis	Patients aged 5-14 years	0.049 (0.029-0.084) Cases: 18/831 Control: 52/10516
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	Patients aged 5-14 years	0.143 (0.05-0.407) Cases: 7/831 Control: 7/10516
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	Patients aged 5-14 years	Cases: 7/831 Control: 0/10516

The positive predictive values are calculated using Bayesian statistics.

Evidence statement(s):

Patients aged > 14 years

Haematuria (5 studies, N = 87161) presenting in a primary care setting is associated with overall positive predictive values of 0.65-6.48% for renal cancer, which tended to be higher in men (5.47-5.5%) than in women (2.48-2.6%; 2 studies, N = 48918) and to increase with age in men (up to 11.21%; 1 study, N = 11108) and less so in women (up to 8.53%; 1 study, N = 11108). The evidence was, however, compromised by a large number of the included cancers being non-renal cancers. Each of the studies was associated with 0-2 bias concern (see also Tables 1-3).

For renal cancer the positive predictive values of single symptoms (excluding haematuria; 6 studies, N = 344897) presenting in primary care ranged from 0.05% (for back pain) to 1.4% (for anaemia in men). The evidence was, however, compromised by a large number of the included cancers being non-renal cancers and ≤ 3 bias or applicability concerns associated with 4 of the 6 included studies (see also Table 3).

For renal cancer the positive predictive values of symptom combinations (1 study, N = 17240) presenting in primary care ranged from 0.1% (for constipation in combination with either abdominal pain, nausea or lower urinary tract infection) to > 5% (for abdominal pain combined with microcytosis). The included study was associated with 1 bias concern (see also Table 4).

Patients aged < 15 years

The positive predictive values of having any childhood cancer ranged from 0.04% (for pain and musculoskeletal symptoms) to 2.19% (for hepatosplenomegaly) in all included patients, and from 0.061% (for lymphadenopathy) to 1.286% (for hepatosplenomegaly) for patients aged 0-4 years old, and from 0.049% (for bruising) to 0.154% (for 'lump/mass/swelling' [the PPV for hepatosplenomegaly could not be calculated as none of the controls experienced this symptom]) for patients aged 5-14 years old (all from 1 study, N = 16585). The evidence quality is somewhat compromised by the case-control design of the study (see also Tables 5-7).

Evidence tables

Collins (2013)

PATIENT SELECTION
A. risk of bias

Patient sampling	Retrospective patient series using the THIN database.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 2145133 patients (1063355 men, 1081778 women) were identified from 364 practices. Symptoms: Haemoglobin < 11 g/dl recorded in the last year (N = 16961; 3969 men, 12992 women), abdominal pain (N = 253344; 105247 men, 148097 women), appetite loss (N = 6097; 2616 men, 3481 women), weight loss (N = 29369; 13332 men, 16037 women), haematuria (N = 37810; 22810 men, 15000 women), previous diagnosis of cancer apart from renal tract cancer at study entry (N = 49303; 18130 men, 31173 women). Incident cases of renal tract cancer during the 2-year follow up period: N = 2283 (1685 men, 598 women). Inclusion criteria: Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (e.g., haematuria, abdominal pain, weight loss, appetite loss, and anaemia), the date of the first recorded onset within the study period. Exclusion criteria: Patients with a prior diagnosis of renal tract cancer, registered less than 12 months with the general practice, had invalid dates, < 30 years old or ≥ 85 years old. Clinical setting: Primary care, UK
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms were defined as symptoms that might alarm the patient and also indicate the presence of renal tract cancer; that is, symptoms of haematuria, loss of appetite, weight loss, or abdominal pain.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Renal tract cancer, which was defined as incident diagnosis of cancer of the bladder, kidney, ureter, or urethra during the 2 years after study entry, recorded either on the patient's GP record using the relevant UK diagnostic Read Codes. Patients without the outcome were censored at the earliest of the date of death, date of leaving the practice study of 2 years of follow up.

Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients seem to be accounted for
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	It is unclear why no data has been presented for men for the symptoms of appetite loss and weight loss.

Deyo (1988)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective consecutive? patient series
Was a consecutive or random sample of patients enrolled?	**Unclear**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes (probably)**
Could the selection of patients have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 1975, mean (SD; range) age = 39.5 (15.4; 15-86) years, 62% females. 54% of the patients were seeking medical care for back pain for the first time and 76% of the patients had had back pain for < 3 months. 3% had a history of back pain surgery. Maximal back pain in the low back (84%) or in the upper back (16%). Inclusion criteria: Patients who sought treatment between March 1982 and September 1984 in the walk-in clinic of a public hospital where virtually all patients are self-referred. In each case back pain was part of the chief complaint. Exclusion criteria: Neck pain. Clinical setting: Walk-in clinic of a public hospital; this clinic is a source of primary care for indigent persons in a county in the USA with a population of approximately 1 million.
Are there concerns that the included patients and setting do not match the review question?	**High concern**
INDEX TEST	
A. Risk of bias	

Index test	Back pain; not further specified.	
Were the index test results interpreted without knowledge of the results of the reference standard?		**Yes**
Could the conduct or interpretation of the index test have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		**Low concern**
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	The reference standard consisted of a search on each patient name in the institutional tumour registry ≥ 6 months after the index visit. The registry included every patient with a histological diagnosis of cancer made in the authors' hospital system regardless of site of care. The authors point out that "while this method might fail to identify cancer patients who sought care elsewhere, it is likely that most patients sought follow-up for a particular illness at the same facility.	
Is the reference standard likely to correctly classify the target condition?		**Unclear**
Were the reference standard results interpreted without knowledge of the results of the index tests?		**No (but all patients had a positive index test)**
Could the reference standard, its conduct, or its interpretation have introduced bias?		**Unclear risk**
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		**Low concern**
FLOW AND TIMING		
A. risk of bias		
Flow and timing	All the patients are accounted for in the results.	
Was there an appropriate interval between index test and reference standard?		**Yes (probably)**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**Yes**
Could the patient flow have introduced bias?		**Low risk**
NOTES	It is a concern that some patients with cancer might have been missed due to the choice of reference standard because this would result in an underestimation of the positive predictive value. 38/1975 patients were found in the tumour registry. Of those 38, 13 patients had tumours that were probable causes of back pain, and 4 of these 13 patients already had a diagnosis of cancer at presentation. The 9/1975 patients who had undiagnosed cancer that the back pain could be attributed to had: Lymphoma (NOS; 2), cancer of unknown primary (1), prostate cancer (1), retroperitoneal liposarcoma (1), lung cancer (1), renal cell (1), multiple myeloma (1), mucinous adenocarcinoma (of gallbladder?; 1)	

1

2 **Dommett (2012, 2013)**

PATIENT SELECTION		

A. risk of bias	
Patient sampling	Population-based nested case-control study using data from the General Practice Research Database (GPRD)
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: 1267 children; aged 0-4 years: N = 436; aged 5-14years: N = 831; 703 males/564 females. Cancer type: Leukemia: N = 368; brain: N = 270; lymphoma: N = 142; bone: N = 107; soft tissue sarcoma: N = 91; renal: N = 82; neuroblastoma: N = 75; other ICD codes: N = 132. Controls: 15318 children; aged 0-4 years: N = 4802; aged 5-14years: N = 10516; 8461 males/6857 females. Inclusion criteria: The sample comprised all children aged 0–14 years, inclusive, drawn from all general practices contributing research-standard data to the GPRD between 1 January 1988 and 31 December 2010. To be included, the practices had to have been contributing research-standard data for a minimum of 1 year before each child's date of cancer diagnosis or the index date (see below) for matched controls. Cases: Patients diagnosed with the following cancers: leukaemia, lymphoma, neuroblastoma, soft tissue sarcoma, hepatic, renal, bone and central nervous system tumours, using pre-defined medical codes used in the GPRD. The date of diagnosis for cases was defined as the date of pathological diagnosis, but if this was unavailable, the date of the first cancer code entered in the GPRD was used. Controls: Up to 13 controls (children with no diagnosis of cancer at any time) were selected per case, using a computer-generated random sequence, matched on age (within 1 year), sex and practice, and had to be currently registered on the date of diagnosis of their matched case (the index date). Exclusion criteria: None listed Clinical setting: Primary care, UK.
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	The GPRD uses just over 100 000 medical codes to encompass all primary care events, including both symptoms and diagnoses. From this list, libraries of codes were assembled representing individual alert symptoms derived

	from the NICE referral guidelines for suspected cancer in children. *No more information reported.*
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Cancer diagnosis in the UK's General Practice Research Database.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	This study is published in two papers.

Friedlander (2014)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Retrospective cohort study, using claims data and laboratory values from the Vanderbilt University Medical Centre's (VUMC) Research Derivative, which is a "data repository that contains administrative and clinical information, including a complete record of visits and admissions, laboratory data, and diagnosis and procedure codes, on every patient treated in the Vanderbilt health system" (p 634) located in Tennessee in the USA.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**

Did the study avoid inappropriate exclusions?	**Yes (probably)**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 2455 patients, 724 males / 1731 females, median (inter-quartile range) age = 58 (49-68) years; smoking history: current smoker (N = 406), former smoker (N = 473), non-smoker (N = 1514). Inclusion criteria: "Patients aged ≥ 40 years with a first diagnosis of hematuria" "between 2004 and 2012 by urinalysis (>3 red blood counts per high power field) or International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes for hematuria (599.7, 599.70, 599.71 or 599.72) at one of the VUMC's 19 primary care clinics. To be included in the study, patients must have had records for 1 year before the date of hematuria diagnosis." Exclusion criteria: "Patients were excluded if they had a urinary tract infection (defined as a urinalysis positive for both leukocyte esterase and urine nitrites, or a positive urine culture) within 4 weeks before or 1 week after the index hematuria episode (n = 590, 9.0%) or had a prior explanatory diagnoses and procedures that would preclude the need for a hematuria evaluation (according to a convened panel of content experts; prostate/renal/bladder/other cancer, benign prostate/renal/bladder/other mass, prostate dysplasia, cystitis, urethritis, epididymitis/orchitis, prostatitis, pyelonephritis, urolithiasis, prostatic enlargement, trauma, medical renal disease, haematologic/thrombotic diease?, anatomic abnormality, prostatectomy, prostate biopsy, transurethral incision of prostate, resection of prostate, cystoscopy, cystectomy, ureteroscopy, nephrectomy, pyeloplasty, ureteral reimplantation)." We then used Physicians Current Procedural Terminology Coding System, 4th Edition and ICD-9 codes to exclude patients with an explanatory diagnosis or procedure within 180 days preceding their hematuria diagnosis (n = 3540, 53.8%)." Clinical setting: Primary care, USA.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	First diagnosis of hematuria" "by urinalysis (>3 red blood counts per high power field) or International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes for hematuria (599.7, 599.70, 599.71 or 599.72)".
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	The reference standard consisted checking the database for diagnoses of genitourinary neoplasms within 180 days after haematuria diagnosis, as determined by ICD-9 codes.

Is the reference standard likely to correctly classify the target condition?	**Unclear (is 180 days enough time to get a diagnosis of all cancers?)**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear (but all patients had a positive index test)**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	There were 66 patients with cancer: Bladder (N = 33), renal cell (N = 16), prostate (N = 15). The types of cancer for the remaining two cases were not reported.

Hippisley-Cox (2012)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective patient series using patients in the QResearch database (version 30).
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 1240722 patients were identified from 189 practices (622166 males, 618556 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6). Current symptoms and symptoms in the preceding year: Current haematuria (N = 25553), current abdominal pain (N = 128721), current appetite loss (N = 5531), current weight loss (N = 14464), constipation in the last year (N = 8472), diarrhoea in the last year (N = 12171), tiredness in the last year (N = 12669), haemoglobin recoded in the last year (N = 216201), haemoglobin < 11 g/dl in the last year (N = 16169). Incident cases of renal tract cancer during the 2-year follow up period: N = 1622; mean age at diagnosis = 70 years, 1187 males/ 435 females; **Type of cancer: Bladder: N = 1292; Kidney: N = 307; Ureter: N = 21; Urethra: N = 2.** Inclusion criteria: All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included.

	Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000) and 12 months after the patient registered with the practice, ensuring that all patients had ≥ 12 months' registration prior to study entry. For patients with incident haematuria, appetite loss, weight loss, or abdominal pain, the entry date was the date of the first consultation with the symptom within the study period. *The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.* Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of renal tract cancer at baseline, and patients with a recorded 'red-flag' (see "Definition of symptom" below) symptom in the 12 months prior to the study entry date. Clinical setting: Primary care
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms were defined as symptoms that might alarm the patient and also indicate the presence of renal tract cancer; that is, symptoms of haematuria, loss of appetite, weight loss, or abdominal pain.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Renal tract cancer, which was defined as incident diagnosis of cancer of the bladder, kidney, ureter, or urethra during the 2 years after study entry, recorded either on the patient's GP record using the relevant UK diagnostic Read Codes, or their linked Office for National Statistics cause-of-death record, using the relevant ICD-9 codes (188 or 189) or ICD-10 diagnostic codes (C64–67).
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**

FLOW AND TIMING		
A. risk of bias		
Flow and timing	A total of 1342329 patients were initially identified of whom 101607 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of renal tract cancer (N = 1506), and ≥ one 'red flag' symptom recorded in the 12 months prior to study entry (N = 29254), leaving 1240722 patients. However, data is presented for 967681 / 1240722 patients. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.	
Was there an appropriate interval between index test and reference standard?		**Yes**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**No**
Could the patient flow have introduced bias?		**High risk**
NOTES		

Jones (2007)

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Retrospective consecutive patient series using patients in the UK's General Practice Research Database.	
Was a consecutive or random sample of patients enrolled?		**Yes**
Was a case-control design avoided?		**Yes**
Did the study avoid inappropriate exclusions?		**Yes**
Could the selection of patients have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Patient characteristics and setting	A total of 923605 patients were identified, of whom 762325 were aged ≥ 15 years. Number of first occurrences in patients with no previous diagnosis of cancer: Haematuria: N = 11108, mean (SD) age at first symptom = 58.5 (18.9) years. Patients excluded due to incomplete dates for their first symptom: N = 30. Sex (of final sample): 6385 males, 4723 females. Haemoptysis: N = 4822, mean (SD) age at first symptom = 61.6 (18) years. Patients excluded due to incomplete dates for their first symptom: N = 10. Sex (of final sample): 2930 males, 1882 females. Dysphagia: N = 6003, mean (SD) age at first symptom = 54.5 (19.4) years. Patients excluded due to incomplete dates for their first symptom: N = 4. Sex (of final sample): 2628 males, 3371 females. Rectal bleeding: N = 15314, mean (SD) age at first symptom = 52.5 (18.8) years. Patients excluded due to incomplete dates for their first symptom: N = 25. Sex (of final sample): 7523 males, 7766 females. Inclusion criteria: All patients from 128 general practices that provided data of a sufficient standard from 1 January 1994 to 31 December 2000 and which provided exclusively Read coded data, who were aged between 15 and 100 years, whose first ever recorded occurrence of each alarm symptom (haematuria, haemoptysis, dysphagia, or rectal bleeding) was after 31 December 1994 and	

	who had not previously been diagnosed as having any cancer. Exclusion criteria: Patients whose date of first symptom or first relevant diagnosis of cancer was before 1 January 1995 and patients with a diagnosis of any other cancer than the ones of interest before the date of the first recorded symptom or before the index cancer diagnosis date if the related symptom was not recorded. Clinical setting: Primary care	
Are there concerns that the included patients and setting do not match the review question?		**Low concern**
INDEX TEST		
A. Risk of bias		
Index test	Identification of all patients who ever had symptoms recorded for haematuria, haemoptysis, dysphagia, or rectal bleeding.	
Were the index test results interpreted without knowledge of the results of the reference standard?		**Yes**
Could the conduct or interpretation of the index test have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		**Low concern**
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	Cancer code in the UK's General Practice Research Database (the authors report cancer diagnosis at two time points, namely in the first 6 months and 3 years after the first alarm symptom): Haematuria: Urinary tract neoplasms, including neoplasms of the urethra, bladder, ureter, and kidney but excluding neoplasms of the prostate and other reproductive organs. Haemoptysis: Respiratory tract neoplasms. Dysphagia: Oesophageal neoplasms. Rectal bleeding: Colorectal neoplasms.	
Is the reference standard likely to correctly classify the target condition?		**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?		**Unclear (but all patients had a positive index test)**
Could the reference standard, its conduct, or its interpretation have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		**Low concern**
FLOW AND TIMING		
A. risk of bias		
Flow and timing	All patients are accounted for in the results	
Was there an appropriate interval between index test and reference standard?		**Unclear**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**Yes**

Could the patient flow have introduced bias?	**Low risk**
NOTES	Diagnoses of cancer were most often made in the first three months after the onset of alarm symptoms; very few diagnoses of cancer were made later than three years after symptom onset. In the 4th and 5th years of study, the small number of observed occurrences of cancer was similar to the number expected from background incidence rates. Secondary analyses evaluating whether the incidence of neoplasms other than those prespecified was increased after the occurrence of alarm symptoms showed for: Haematuria: Inclusion of cancers of the reproductive organs yielded 21 additional cancers in women and 158 cancers in men, mostly cancers of the prostate. Inclusion of these cancers in the analysis would give a positive predictive value of 3.9% in women and 9.9% in men. Dysphagia: Inclusion of gastric cancers yielded 17 additional cancer diagnoses in women and 30 in men. Inclusion of these cancers gave positive predictive values of 5.2% in women and 6.9% in men. *Estimates based on the pre-specified cancers may be thus conservative for these symptoms.* Haemoptysis: Extension of the diagnostic criteria yielded 6 additional cancers. Rectal bleeding: Extension of the diagnostic criteria yielded 2 additional cancers.

Muris (1995)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective patient series from 80/460 general practitioners in Limburg (Holland)
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Unclear**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 933; 335 males, 598 females; age range = 18-75, aged > 30 years: N = 712, aged > 40 years: N = 517, aged > 60 years: N = 171. Inclusion criteria: Patients who in 1989 consulted one of the participating GPs for new abdominal complaints lasting ≥ 2 weeks and with whom the GPs had a diagnostic problem. Exclusion criteria: None listed. Clinical setting: GPs in Holland
Are there concerns that the included patients and setting do not match the review question?	**High concern**
INDEX TEST	
A. Risk of bias	
Index test	New abdominal complaints lasting ≥ 2 weeks. Not further specified.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test	**Low risk**

have introduced bias?	
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**High concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Follow up for ≥ 12 months (mean = 18 months).
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for
Was there an appropriate interval between index test and reference standard?	**Unclear**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	Other cancers diagnosed in these patients were: Stomach (2/933), pancreas (2/933), trachea/bronchus/lung (2/933), colorectal (4/933), cervix (1/933), other cancer of the female genital system (2/933), and other and unspecified sites (2/933).

Oudega (2006)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective study of all primary care physicians (N = 50) within a catchment area (ca 130000 inhabitants) of a non-teaching hospital in Holland.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 430; 162 males, 268 females; mean age (SD) = 60.7 (18.2) years. Inclusion criteria: Consecutive patients who consulted their GP between January 1996 and July 2002 and who, after investigation (not referral) was confirmed to have deep vein thrombosis. Exclusion criteria: Patients with a known malignancy or a malignancy

	detected within 2 weeks of deep vein thrombosis diagnosis. Clinical setting: Primary care, Holland.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Deep vein thrombosis (suspicion based on painful swollen leg ≤ 30 days). Patients were classified as having secondary deep vein thrombosis if ≥ 1 of the following risk factors for deep vein thrombosis were present: Recent surgery, prolonged immobilisation, use of oral contraceptives or hormonal replacement therapy. If no risk factors were present patients were classified as having idiopathic deep vein thrombosis.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	2 years follow up.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	In total N = 19 had cancer: 3 colorectal, 5 urogenital (not further subgrouped), 4 breast, 3 lung and 4 other. The urogenital data is added to the renal cancer evidence review.

1

2 **Shephard (2013)**

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Matched case-control study using patients in the UK's General Practice

	Research Database (GPRD).
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: N = 3149, median age at diagnosis = 69 (IQR = 61-77) years, 1930 males / 1219 females; median number of consultations = 16 (IQR = 10-25), UK. Controls: N = 14091, median age at diagnosis = 70 (IQR = 61-77) years, 8429 males / 5662 females; median number of consultations = 8 (IQR = 4-15), UK. Inclusion criteria: Cases: Patients with a record of one of 22 GPRD kidney cancer codes between January 2000 and December 2009 inclusive, aged ≥ 40 years, with min. 1 year of data before diagnosis. The first instance of a kidney cancer code was assigned the data of diagnosis/index date. Controls: Up to 5 controls were matched to cases on sex, general practice, and to 1 year of age of the case. The index date was the index date of the matched case. Exclusion criteria: Metastatic cancer to the kidney from a non-kidney primary, diagnosis before 2000, or no consultations in the year before diagnosis. Clinical setting: Primary care
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	A list of symptoms, signs and investigations (features) potentially associated with kidney cancer was compiled from the authors' literature search, augmented by viewing material from kidney cancer support organisations and online chat rooms. Internet search terms included 'kidney cancer', 'kidney cancer symptoms', and 'early signs/indications kidney cancer'. Visible and non-visible haematuria were studied separately. Only codes specifying the word 'microscopic' were assigned to the latter group, so generic codes such as the single word 'haematuria' were assumed to be visible haematuria. Over 1800 GPRD codes were compiled for the putative features of kidney cancer from the GPRD's master list of over 100,000 codes. Occurrences of these features in the year before the index date were identified. Repeated consultations for the same complaint were also identified along with all codes for fractures as a test for any recording bias between cases and controls (making the assumption that the fracture rate would be approximately equal). Variables were retained only if they

	occurred in at least 5% of either cases or controls. Investigation results were deemed to be abnormal if they fell outside their local laboratory's normal range: for analysis, patients with a normal laboratory result were grouped with those who had not been tested. The raised inflammatory markers variable was a composite of any of abnormal erythrocyte sedimentation rate, plasma viscosity, or C-reactive protein; similarly abnormal liver function tests reflected a raised value of any of the hepatic enzymes reported by each laboratory.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Kidney cancer code in the UK's General Practice Research Database.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	A total of 18890 patients were identified, 15707 controls and 3183 cases. Of the controls the following exclusions were applied: bladder cancer (N = 29), metastatic cancer (N = 104), and no data in year pre-index date (N = 1483). Of the cases the following exclusions were applied: No controls (N = 2), metastatic cancer (N = 24), and bladder cancer (N = 8).
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	24 symptoms and 22 abnormal test results were considered initially. 10 symptoms and 11 abnormal test variables were present in ≥ 5% of cases.

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Review question:
Which investigations of symptoms of suspected renal cancer should be done with clinical responsibility retained by primary care?

Results

Literature search

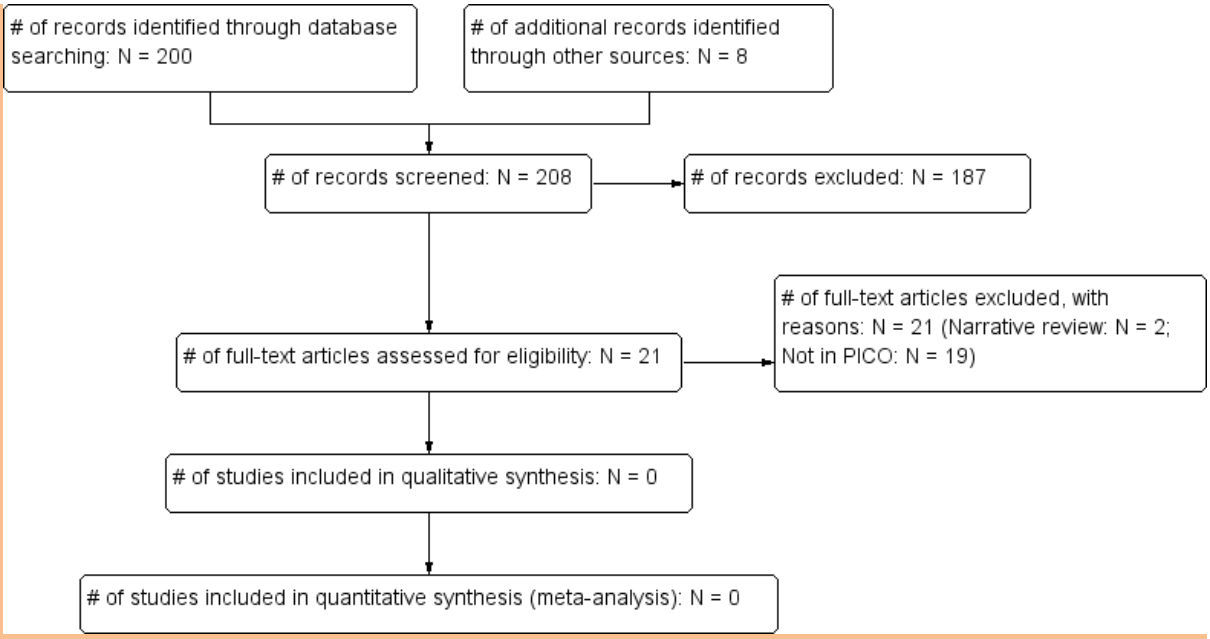
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-2013	377	127	20/02/2013
Premedline	1980-2013	11	3	20/02/2013
Embase	1980-2013	457	94	21/03/2013
Cochrane Library	1980-2013	128	1	20/02/2013
Psychinfo	1980-2013	1	0	21/03/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2013	45	8	21/03/2013
Biomed Central	1980-2013	814	0	21/03/2013

Total References retrieved (after de-duplication): 189

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2/2013-18/08/2014	10	1	18/08/2014
Premedline	2/2013-18/08/2014	15	3	18/08/2014
Embase	2/2013-18/08/2014	74	7	18/08/2014
Cochrane Library	2/2013-18/08/2014	70	0	18/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	2/2013-18/08/2014	11	2	18/08/2014

Total References retrieved (after de-duplication): 11



Study results

No evidence was identified pertaining to the diagnostic accuracy of abdominal ultrasound, urine cytology, x-ray, intravenous pyelogram, or CT scan of the abdomen and pelvis in patients with suspected renal cancer where the clinical responsibility was retained by primary care.

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None

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TESTICULAR CANCER

Review question:
What is the risk of testicular cancer in patients presenting in primary care with symptom(s)?

Results

Literature search

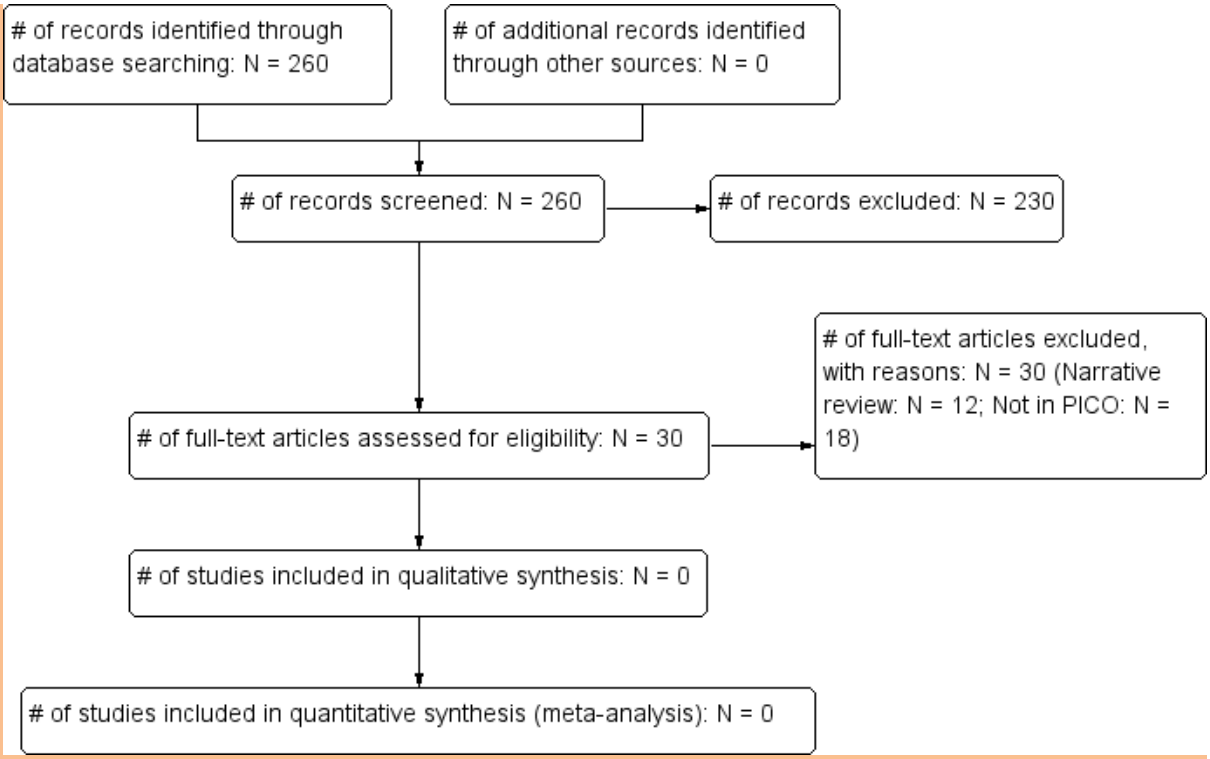
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2012	901	159	13/09/2012
Premedline	All-2012	24	6	13/09/2012
Embase	All-2012	871	167	20/09/2012
Cochrane Library	All-2012	23	1	20/09/2012
Psychinfo	All-2012	9	6	13/09/2012
Web of Science (SCI & SSCI) and ISI Proceedings	All-2012	106	23	20/09/2012
Biomed Central	All-2012	2	0	20/09/2012

Total References retrieved (after de-duplication): 258

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	9/2012-27/08/2014	30	1	27/08/2014
Premedline	9/2012-27/08/2014	52	0	27/08/2014
Embase	9/2012-27/08/2014	77	2	27/08/2014
Cochrane Library	9/2012-27/08/2014	13	0	27/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	9/2012-27/08/2014	18	0	27/08/2014

Total References retrieved (after de-duplication): 2



Study results

No evidence was identified.

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None

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Review question:
Which investigations of symptoms of suspected testicular cancer should be done with clinical responsibility retained by primary care?

Results

Literature search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-2013	266	54	22/03/2013
Premedline	1980-2013	14	6	22/03/2013
Embase	1980-2013	296	51	22/03/2013
Cochrane Library	1980-2013	0	0	22/03/2013

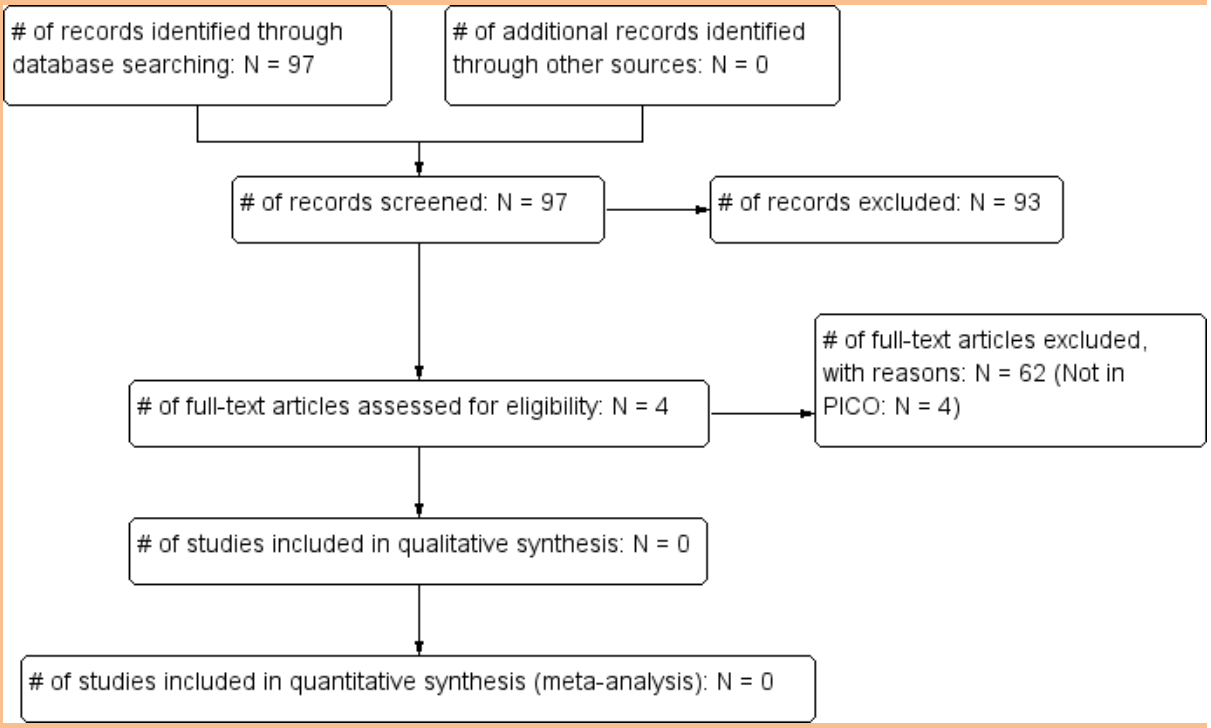
Psychinfo	1980-2013	0	0	22/03/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2013	51	2	22/03/2013

Total References retrieved (after de-duplication): 95

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	3/2013-27/08/2014	6	0	27/08/2014
Premedline	3/2013-27/08/2014	17	0	27/08/2014
Embase	3/2013-27/08/2014	36	2	27/08/2014
Cochrane Library	3/2013-27/08/2014	6	0	27/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	3/2013-27/08/2014	6	0	27/08/2014

Total References retrieved (after de-duplication): 2



Study results

No evidence was identified pertaining to the diagnostic accuracy of ultrasound in patients with suspected testicular cancer where the clinical responsibility was retained by primary care.

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Included studies

None

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PENILE CANCER

Review question:
What is the risk of penile cancer in patients presenting in primary care with symptom(s)?

Results

Literature search

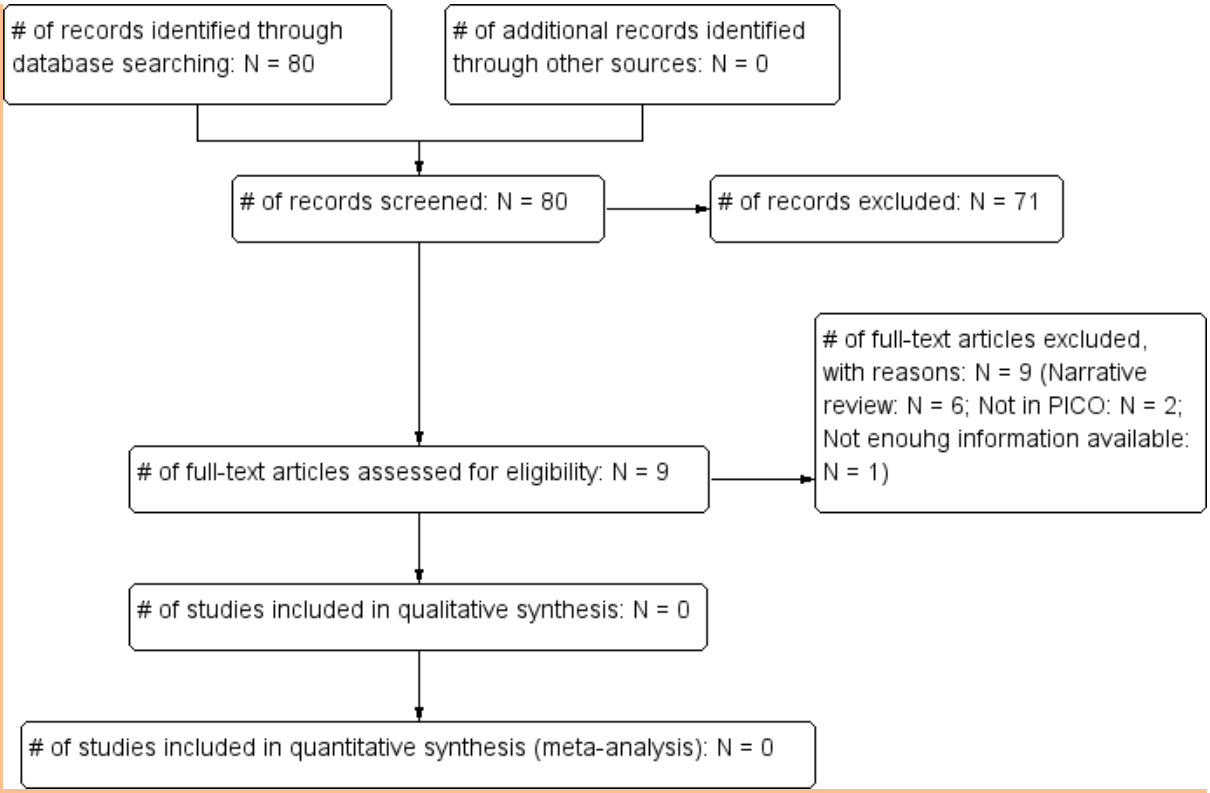
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2012	298	45	20/09/2012
Premedline	All-2012	3	1	20/09/2012
Embase	All-2012	400	44	20/09/2012
Cochrane Library	All-2012	32	0	21/09/2012
Psychinfo	All-2012	2	0	20/09/2012
Web of Science (SCI & SSCI) and ISI Proceedings	All-2012	2	0	24/09/2012
Biomed Central	All-2012	52	2	24/09/2012

Total References retrieved (after de-duplication): 76

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	9/2012-26/08/2014	25	2	26/08/2014
Premedline	9/2012-26/08/2014	18	1	26/08/2014
Embase	9/2012-26/08/2014	57	2	26/08/2014
Cochrane Library	9/2012-26/08/2014	6	0	26/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	9/2012-26/08/2014	11	0	26/08/2014

Total References retrieved (after de-duplication): 4



Study results

No evidence was identified.

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None

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Excl reason: Not in PICO

Review question:
Which investigations of symptoms of suspected penile cancer should be done with clinical responsibility retained by primary care?

Results

Literature search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-2013	85	31	14/05/2013
Premedline	1980-2013	14	2	14/05/2013
Embase	1980-2013	122	25	14/05/2013
Cochrane Library	1980-2013	32	0	14/05/2013
Psychinfo	1980-2013	0	0	14/05/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2013	23	0	14/05/2013

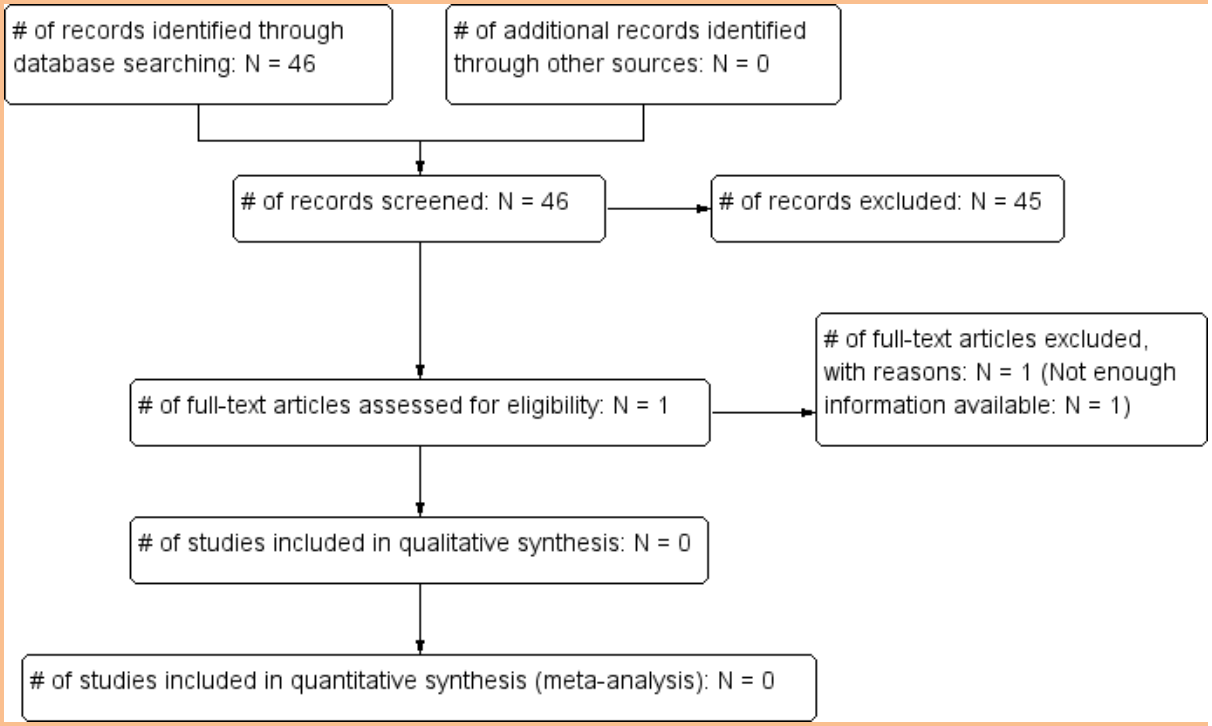
Total References retrieved (after de-duplication): 43

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	5/2013-26/08/2014	4	2	26/08/2014
Premedline	5/2013-26/08/2014	5	0	26/08/2014
Embase	5/2013-26/08/2014	25	2	26/08/2014
Cochrane Library	5/2013-26/08/2014	2	0	26/08/2014
Web of Science (SCI &	5/2013-	1	0	26/08/2014

SSCI) and ISI Proceedings	26/08/2014			

Total References retrieved (after de-duplication): 3



Study results

No evidence was identified pertaining to the diagnostic accuracy of tests used in patients with suspected penile cancer where the clinical responsibility was retained by primary care.

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Included studies

None

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Published as poster abstract only. Not enough information can be extracted to ascertain relevance, but I think it is not in PICO

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Narrative review

SKIN CANCERS

MALIGNANT MELANOMA

Review question:
What is the risk of malignant melanoma in patients presenting in primary care with symptom(s)?

Results

Literature search

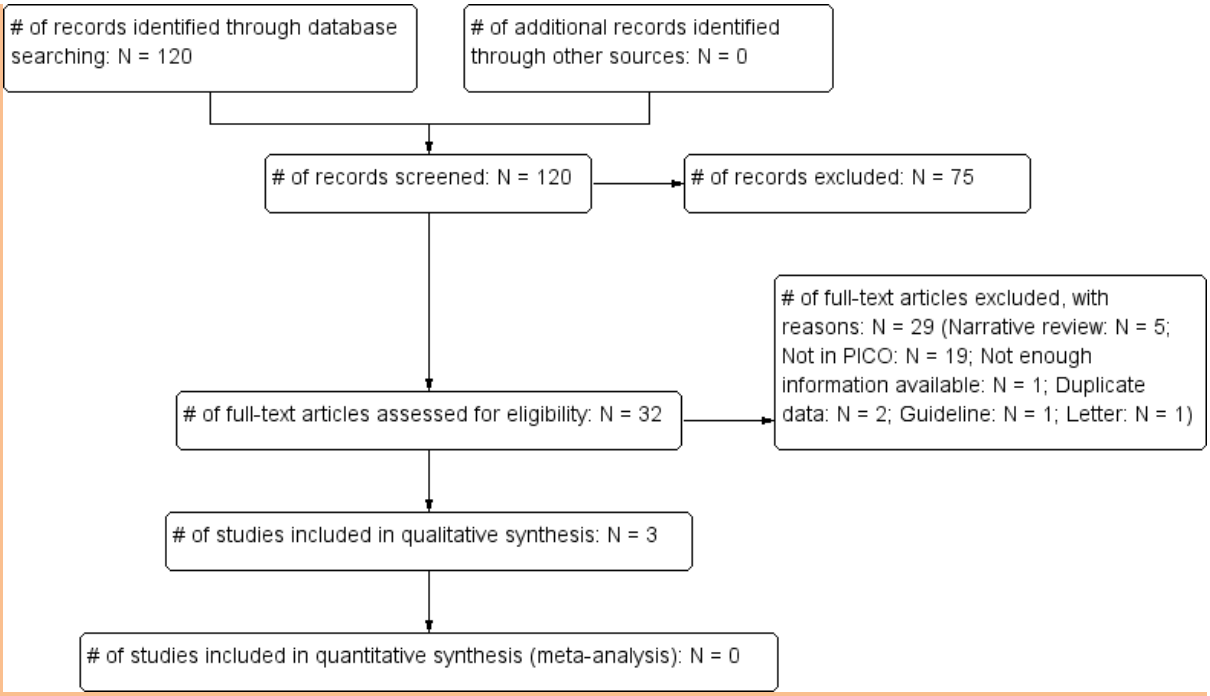
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-2013	1403	49	08/04/2013
Premedline	1980-2013	50	1	08/04/2013
Embase	1980-2013	2470	47	09/04/2013
Cochrane Library	1980-2013	199	7	09/04/2013
Psychinfo	1980-2013	10	0	08/04/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2013	275	23	09/04/2013

Total References retrieved (after de-duplication): 101

Update Search

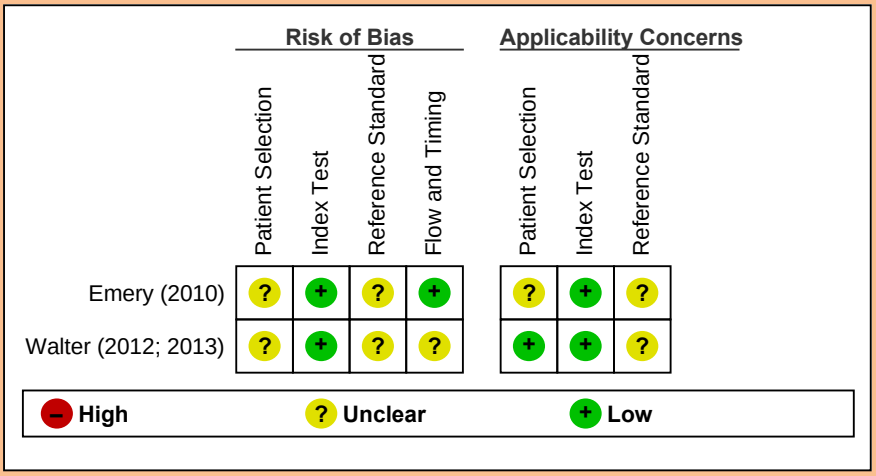
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	4/2013-19/08/2014	39	7	19/08/2014
Premedline	4/2013-19/08/2014	70	6	19/08/2014
Embase	4/2013-19/08/2014	184	11	19/08/2014
Cochrane Library	4/2013-19/08/2014	224	0	19/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	4/2013	162	3	19/08/2014

Total References retrieved (after de-duplication): 19



Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main bias risks and applicability concerns that the studies are subject to relate to (1) the patient sampling method not clearly being consecutive or random, (2) the extent to which the study setting matches UK primary care, (3) the quality of the reference standard, which may not always reliably diagnose the symptoms, (4) the fact that the reference standard did not in all cases match that of the current question, namely histology, and 5) data missing .



Study results

Table 1: Melanoma: Study results.

Study	Symptom(s)	Patient group	Positive predictive value % (95% CI) Prevalence
Emery (2010)	Pigmented lesion	All included	1.4 (0.8-2.3)

Lesion-based analysis		patients	17/1211
		England sample	0.8 (0.3-2) 5/630
		Australia sample	1.9 (1-3.5) 11/581
Walter (2012) Lesion-based analysis	Suspicious pigmented lesions	All included patients	2.3 (1.6-3.2) 36/1573
Walter (2013) Lesion-based analysis	7PCL: Suspicious pigmented lesions: Change in size of lesion	All included patients	3.8 (2.5-5.5) 26/693
Walter (2013) Lesion-based analysis	7PCL: Suspicious pigmented lesions: Irregular pigmentation	All included patients	4.4 (3.1-6.3) 31/702
Walter (2013) Lesion-based analysis	7PCL: Suspicious pigmented lesions: Irregular border	All included patients	5.1 (3.4-7.5) 25/492
Walter (2013) Lesion-based analysis	7PCL: Suspicious pigmented lesions: Inflammation	All included patients	4.5 (1.9-10.1) 6/132
Walter (2013) Lesion-based analysis	7PCL: Suspicious pigmented lesions: Itch or altered sensation	All included patients	2.3 (1.1-4.4) 9/397
Walter (2013) Lesion-based analysis	7PCL: Suspicious pigmented lesions: Lesion larger than other (diameter > 7 mm)	All included patients	3.9 (2.6-5.7) 27/695
Walter (2013) Lesion-based analysis	7PCL: Suspicious pigmented lesions: Oozing/crusting of lesion	All included patients	4.9 (2.1-10.1) 7/144
Walter (2013) Lesion-based analysis	Original 7PCL: Score ≥ 1*	All included patients	2.7 (1.9-3.8) 36/1334
Walter (2013) Lesion-based analysis	Original 7PCL: Score ≥ 2*	All included patients	3.3 (2.4-4.7) 34/1016
Walter (2013) Lesion-based analysis	Original 7PCL: Score ≥ 3*	All included patients	5.1 (3.5-7.4) 29/565
Walter (2013)	Original 7PCL: Score ≥ 4*	All included patients	8.2 (5.2-12.5) 20/245

Lesion-based analysis			
Walter (2013) Lesion-based analysis	Original 7PCL: Score ≥ 5*	All included patients	12.3 (6.1-22.6) 9/73
Walter (2013) Lesion-based analysis	Original 7PCL: Score ≥ 6*	All included patients	10.5 (1.8-34.5) 2/19
Walter (2013) Lesion-based analysis	Weighted 7PCL: Score ≥ 1**	All included patients	2.7 (1.9-3.8) 36/1334
Walter (2013) Lesion-based analysis	Weighted 7PCL: Score ≥ 2**	All included patients	2.9 (2.1-4.1) 36/1221
Walter (2013) Lesion-based analysis	Weighted 7PCL: Score ≥ 3**	All included patients	3.4 (2.4-4.8) 33/969
Walter (2013) Lesion-based analysis	Weighted 7PCL: Score ≥ 4**	All included patients	4.8 (3.4-6.8) 33/685
Walter (2013) Lesion-based analysis	Weighted 7PCL: Score ≥ 5**	All included patients	5.9 (4-8.5) 27/459
Walter (2013) Lesion-based analysis	Weighted 7PCL: Score ≥ 6**	All included patients	8.3 (5.4-12.6) 21/252
Walter (2013) Lesion-based analysis	Weighted 7PCL: Score ≥ 7**	All included patients	10.9 (6.7-17.1) 17/156
Walter (2013) Lesion-based analysis	Weighted 7PCL: Score ≥ 8**	All included patients	15.7 (7.5-29.1) 8/51
Walter (2013) Lesion-based analysis	Weighted 7PCL: Score ≥ 9**	All included patients	8.3 (0.4-40.2) 1/12

*** Original 7PCL consists of 7 items (change in shape, size and/or colour, inflammation, crusting/bleeding, sensory change, diameter ≥ 7 mm) and each present feature score 1 point. ** The Weighted 7PCL consists of the same 7 items, but these are divided into major (change in**

shape, size and/or colour) scoring 2 points each and minor (inflammation, crusting/bleeding, sensory change, diameter ≥ 7 mm) scoring 1 point.

Evidence statement(s):

Pigmented skin lesions presenting in a primary care setting are associated with positive predictive values of 0.8-5.1% for malignant melanoma (2 studies, N = 2784 *lesions*), and the positive predictive values increased proportionally to the number of different risk features the lesions displayed up to 15.7% (1 study, 1436 *lesions*). The studies were associated with 4 bias/applicability concerns (see also Table 1).

Evidence tables

Emery (2010)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective series of pigmented lesions recruited from England (6 general practices covering urban, suburban and rural areas with a registered population of 52913) and Australia (3 primary care skin cancer clinics operated by GPs from a metropolitan area)
Was a consecutive or random sample of patients enrolled?	**Unclear**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Patient characteristics and setting	England: N = 389 patients, mean age = 44.9 years, 68.6% females with, interpretable images from N = 630 lesions. 0/630 lesions were squamous cell carcinoma, 0/630 lesions were basal cell carcinoma, 5/630 lesions were melanoma, and 0/630 lesions were lentigo maligna (melanoma). Australia: N = 469 patients, mean age = 50 years, 48% females, with interpretable images from N = 581 lesions. 0/581 lesions were squamous cell carcinoma, 22/581 lesions were basal cell carcinoma, 7/581 lesions were melanoma, and 4/581 lesions were lentigo maligna (melanoma). Inclusion criteria: England: Patients aged > 18 years were recruited into the study by their GP if they presented with concerns about a pigmented skin lesion between January 2005 and January 2006. Australia: Patients aged > 18 years were recruited into the study by their GP if they presented with concerns about a pigmented skin lesion between April 2008 and January 2009. Additional lesions were also included when a pigmented skin lesion was identified as potentially suspicious during their clinical examination Exclusion criteria: None reported. Clinical setting: Primary care, UK, and primary care skin cancer practice, Queensland Australia.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**

INDEX TEST	
A. Risk of bias	
Index test	Pigmented skin lesions that concerned patients, which were evaluated using macroscopic clinical photographs, dermoscopic images and SIAscan.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Histopathology or in-person clinical review of the lesion by one expert, including the 7-point melanoma checklist and digital dermoscopy or clinical diagnosis made on the basis of the 7-point melanoma checklist, photographic and dermoscopy images
Is the reference standard likely to correctly classify the target condition?	**Unclear**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Unclear concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients are accounted for in the results
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	Analysis was on a per-lesion basis rather than a per-patient basis

1 **Walter (2012; 2013)**

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective series of suspicious pigmented lesions
Was a consecutive or random sample of patients enrolled?	**Unclear**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Unclear**
Could the selection of patients have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 1293 patients, mean age (SD) = 44.6 (16.8) years; 465 males / 828 females with N = 1573 lesions, of which 1 was squamous cell carcinoma, 10 basal cell carcinomas, and 36 melanomas. Inclusion criteria: Patients aged ≥ 18 years presenting to one of the 15

	participating general practices with a suspicious (any lesion presented buy a patient, or opportunistically seen by a family doctor or practice nurse, that could not immediately be diagnosed as benign and about which the patient could not be reassured) pigmented lesion from March 2008 to May 2010. Exclusion criteria: Patients who were unable to give informed consent or were considere3d inappropriate to include by their family doctor. Clinical setting: UK primary care.
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	Suspicious (any lesion presented buy a patient, or opportunistically seen by a family doctor or practice nurse, that could not immediately be diagnosed as benign and about which the patient could not be reassured) pigmented lesion
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Expert opinion by a histologist or dermatologist or review by two other dermatology experts of the recorded clinical history and examination, a digital photograph, and MoleMate images where available with or without follow up 3-6 months later.
Is the reference standard likely to correctly classify the target condition?	**Unclear**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Unclear concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients are accounted for in the results
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes Tests: No signs & symptoms (S&S)**
Could the patient flow have introduced bias?	**Tests: Low risk; S&S: Unclear risk**
NOTES	Data from this study published in 2 papers: Details above refer to the data from Walter (2012). Further publication-specific details for Walter (2013): Of the 1573 included lesions, 42 did not have a reference standard assessment and the 7PCL was not fully completed for a further 95 lesions. The analyses were therefore based on 1436 lesions from 1182 patients (mean age (SD) = 44.7 (16.6) years; 424 males / 758 females with 36 melanomas). Analysis was

	on a per-lesion basis rather than a per-patient basis for both papers.

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Same data as Walter 2012

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Narrative review

Wilson, E. C., Emery, J. D., Kinmonth, A. L., Prevost, A. T., Morris, H. C., Humphrys, E., Hall, P. N., Burrows, N., Bradshaw, L., Walls, J., Norris, P., Johnson, M. & Walter, F. M. (2013) The cost-effectiveness of a novel SIAscopic diagnostic aid for the management of pigmented skin lesions in primary care: a decision-analytic model. *Value in Health,* 16: 356-366.
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Not in PICO (for signs and symptoms or for tests)

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Youl, P. H., Baade, P. D., Janda, M., del Mar, C. B., Whiteman, D. C. & Aitken, J. F. (2007) Diagnosing skin cancer in primary care: how do mainstream general practitioners compare with primary care skin cancer clinic doctors? *Medical Journal of Australia,* 187: 215-220.
Not in PICO: Data only reported for 3231[excised]/8790[examined] patients.

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Review question:

Which investigations of symptoms of suspected malignant melanoma should be done with clinical responsibility retained by primary care?

Results

Literature search

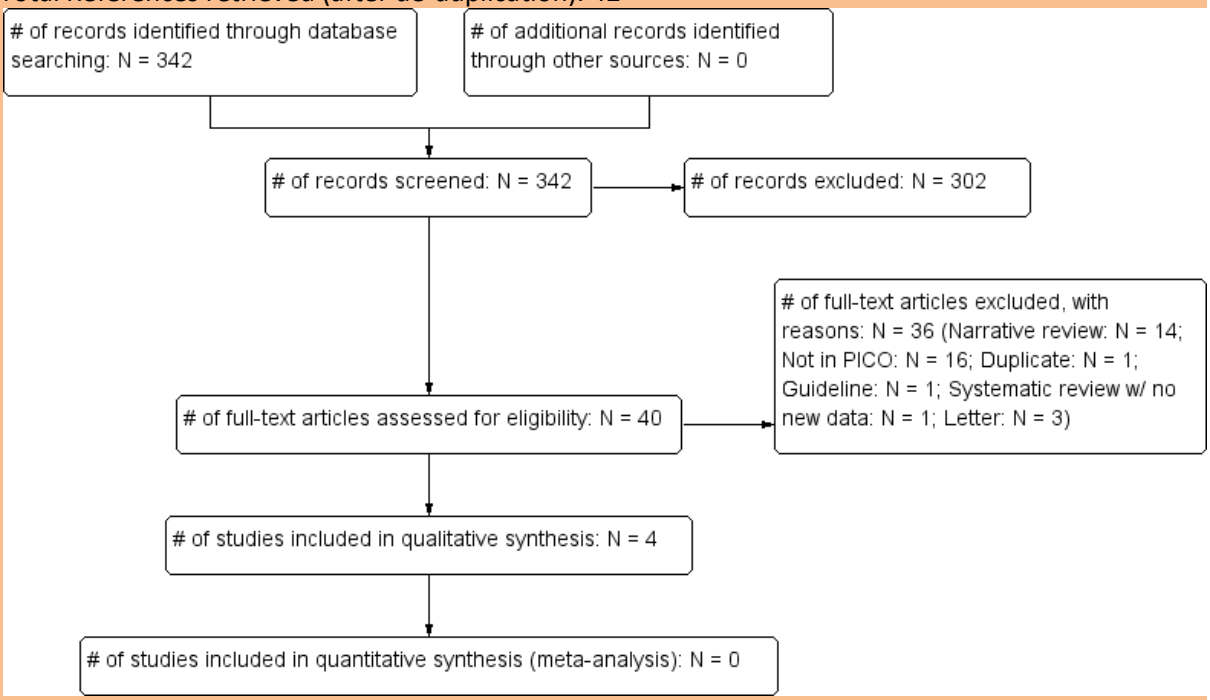
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-2013	875	206	03/05/2013
Premedline	1980-2013	69	29	03/05/2013
Embase	1980-2013	1413	130	03/05/2013
Cochrane Library	1980-2013	129	9	08/05/2013
Psychinfo	1980-2013	9	1	08/05/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2013	431	98	08/05/2013

Total number of studies identified after de-duplication: 300

Update Search

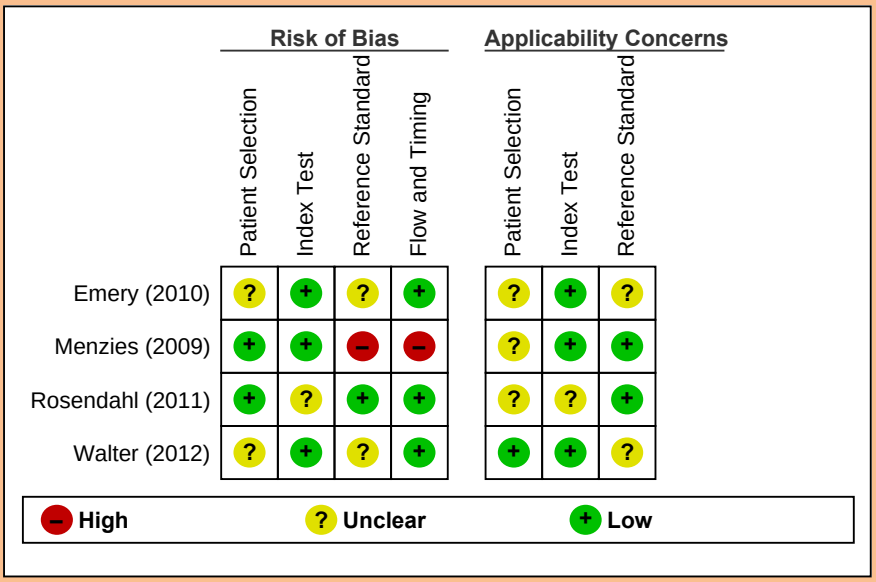
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2013-19/08/2014	34	2	19/08/2014
Premedline	2013-19/08/2014	105	17	19/08/2014
Embase	2013-19/08/2014	73	28	19/08/2014
Cochrane Library	2013-19/08/2014	52	0	19/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	2013-19/08/2014	70	20	19/08/2014

Total References retrieved (after de-duplication): 42



Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issues to note are that the study populations may not be directly representative of an unselected symptomatic population of patients presenting to the UK-based GP, that the criteria for malignancy of the index test are not specified in one case which may limit its external validity, and that the results presented are based on a best case scenario, and are therefore likely to be inflated, and only available for skin malignancy as a whole in some cases and not for malignant melanoma separately. The reference standards employed were also subject to high or unclear risk of bias in the majority of the studies.



Study results

Table 1: Melanoma: SIAscan/MoleMate

Study	Intervention	Prevalence	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive predictive value % (95% CI)	False negativity rate %
Emery (2010)	SIAscan/MoleMate: Moncrieff scoring system	England development set: 24 "suspicious" and 3 melanomas /422 lesions	54 (35-72)	77 (73-81)	12 (7.5-20)	46
Emery (2010)	SIAscan/MoleMate: Primary scare scoring algorithm	England validation set: 6 "suspicious" and 2 melanomas /208 lesions	50 (18-81)	84 (78-88)	9 (3-22)	50
Emery (2010)	SIAscan/MoleMate: Primary scare scoring algorithm	Australia dataset: 45 "suspicious" and 11 melanomas /581 lesions	44 (32-58)	95 (93-97)	52 (38-66)	56

Walter (2012)	SIAscan/MoleMate	18 melanomas/ 766 lesions	100 (78.1-100)	71.79 (68.4-75)	7.86 (4.9-12.3)	0

Table 2: Melanoma: Dermoscopy/dermatoscopy

Study	Intervention	Prevalence	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive predictive value % (95% CI)	False negativity rate %
Menzies (2009)	Dermoscopy	Unclear/331 lesions	53.1 (34.7-70.9)	89 (84.9-92.3)	34 (21.2-48.8)	46.9
Menzies (2009)	Dermoscopy ± sequential digital dermoscopy imaging	Unclear/331 lesions	71.9 (53.3-86.3)	86.6 (82.2-90.3)	36.4 (24.7-49.6)	28.1
Menzies (2009)	Sequential digital dermoscopy imaging	Unclear/149 lesions	72.7 (39-94)	92.8 (87.1-96.5)	44.4 (21.5-69.2)	27.3
Rosendahl (2011)	Clinical images and dermatoscopy	138 malignacies/463 lesions	82.6	80	Not reported	17.4

There was no evidence relating to the diagnostic accuracy of biopsy or ophthalmoscopy for diagnosing malignant melanoma in a primary care setting.

Evidence statement(s):

SIAscan/MoleMate (2 studies, N = 1977 lesions) performed in symptomatic patients presenting in a primary care setting is associated with sensitivities ranging between 44-100%, specificities ranging between 71.79-95%, positive predictive values ranging between 7.86-52%, and false negativity rates ranging between 0-56% for skin cancer/malignant melanoma. The studies were each associated with 3-4 bias/applicability concerns (see also Table 1).

Dermatoscopy/dermoscopy with and without clinical images or sequential digital dermoscopy imaging (2 studies, N = 794 lesions) performed in symptomatic patients presenting in a primary care setting is associated with sensitivities ranging between 53.1- 82.6%, specificities ranging between 80-92.8%, positive predictive values ranging between 34-44.4%, and false negativity rates ranging between 17.4-46.9% for skin cancer/malignant melanoma. The studies were each associated with 3 bias/applicability concerns (see also Table 2).

Evidence tables

Emery (2010)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective series of pigmented lesions recruited from England (6 general practices covering urban, suburban and rural areas with a registered population of 52913) and Australia (3 primary care skin

	cancer clinics operated by GPs from a metropolitan area)
Was a consecutive or random sample of patients enrolled?	**Unclear**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Patient characteristics and setting	England: N = 389 patients, mean age = 44.9 years, 68.6% females with, interpretable images from N = 630 lesions. 0/630 lesions were squamous cell carcinoma, 0/630 lesions were basal cell carcinoma, 5/630 lesions were melanoma, and 0/630 lesions were lentigo maligna (melanoma). For the evaluation of SIAscopy this sample was further split into 2 samples: Development: N = 422 lesions of which 0 were squamous cell carcinoma, 0 were basal cell carcinoma, 3 were melanoma and 0 were lentigo maligna. Validation: N = 208 lesions of which 0 were squamous cell carcinoma, 0 were basal cell carcinoma, 2 were melanoma and 0 were lentigo maligna. Australia: N = 469 patients, mean age = 50 years, 48% females, with interpretable images from N = 581 lesions. 0/581 lesions were squamous cell carcinoma, 22/581 lesions were basal cell carcinoma, 7/581 lesions were melanoma, and 4/581 lesions were lentigo maligna (melanoma). Inclusion criteria: England: Patients aged > 18 years were recruited into the study by their GP if they presented with concerns about a pigmented skin lesion between January 2005 and January 2006. Australia: Patients aged > 18 years were recruited into the study by their GP if they presented with concerns about a pigmented skin lesion between April 2008 and January 2009. Additional lesions were also included when a pigmented skin lesion was identified as potentially suspicious during their clinical examination Exclusion criteria: None reported. Clinical setting: Primary care, UK, and primary care skin cancer practice, Queensland Australia.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Pigmented skin lesions that concerned patients, which were evaluated using macroscopic clinical photographs, dermoscopic images and SIAscan. SIAscan images and data (iuncluding the location of the lkesion and the age group and sex of the patients) were assessed by a SIAscopy expert, who was blinded to the 7-itpoint melanoma checklist results snad clinical photographs. The SIAscopy expert scored the presence or absence of each specific SIAscopic feature including those previously associated with melanoma (Moncrieff et al. (2002) Br J Dermatol, 146: 448-57): Size of lesion, age of patient, dermal melanin, collagen holes anbd blkood displacement with erythematous blush. Additional features that were also scored were blood vessels, white dots on the collagen view, blood lacunes and a cerebriform melanin pattern. From this information a primary care scoring algorithm was developed:

	All lesions -> Any collagen white dots OR cerebriform pattern? Yes -> Seborrhoeic keratosis STOP No -> Any blood lacunes? Yes -> Haemangioma STOP No ->
Dermal melanin within the lesion: 3 points Presence of any blood vessels: 2 points Blood displacement with erythematous blush: 1 point Maximum diameter > 6 mm: 1 point For every COMPLETED 15 years of age: 1 point Score of 6 or more? Yes -> Suspicious No-> Not suspicious
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Histopathology or in-person clinical review of the lesion by one expert, including the 7-point melanoma checklist and digital dermoscopy or clinical diagnosis made on the basis of the 7-point melanoma checklist, photographic and dermoscopy images
Is the reference standard likely to correctly classify the target condition?	**Unclear**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Yes**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Unclear concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients are accounted for in the results
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	Analysis was on a per-lesion basis rather than a per-patient basis. Please note the diagnostic accuracy results given above relates to the diagnosis of a "suspicious" lesion, and not just melanomas. The 2-by-2 tables could not be extracted.

Menzies (2009)

PATIENT SELECTION	
A. risk of bias	

Patient sampling	Prospective consecutive patient series
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	102 GPs were initially recruited, 74 of whom completed the educational intervention and online assessment of learning. 63 GPs from 19 practices assessed 374 lesions as requiring referral or excision (median number of lesions per GP = 6, mean = 5.9, SD = 3). No other information reported. Inclusion criteria: Consecutive patients with pigmented lesions (some brown, grey, blue or black colour within some part of the lesion) which, after routine naked eye examination by the GP would have been biopsied or referred (that is, a suspicious pigmented lesion) presenting to GPs who worked in practices in metropolitan Perth with a minimum of 3 doctors. The GPS and practices had to meet the following criteria: A history of excision or referral of at least 10 pigmented skin lesions over the previous 12-month period for each doctor, and available space for a sequential digital dermoscopy imaging device. During the pretrial period all GPs underwent a training program in the use of dermoscopy and sequential digital dermoscopy imaging. This included reading a textbook in dermoscopic diagnosis and the use of sequential digital dermoscopy imaging, and a tutorial on a CD-rom showing examples of changed and unchanged monitored lesions. In addition, GPs attended a 2 hour workshop on the use of diagnostic devices and recruitment procedures. The training was assessed through an online pre- and post-education intervention test of 245 lesions not seen in the textbook or on the CD-rom. Answers were provided during the post-test as a component of the educational intervention. Bedfore formal patient recruitment began, GPs assessed at least one pretrial lesion to determine the quality of imaging with the sequential digital dermoscopy imaging device and undertake completion of the trial paperwork. GPs were allowed to practise using the dermoscopy device during this pretrial phase. The pretrial phase of education and run-in period occurred from May 2005 to January 2006. Exclusion criteria: GPs who already used dermoscopy or sequential digital dermoscopy imaging in their routine practice. Clinical setting: Primary care, Australia.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Dermoscopy examination performed using a hand-held oil immersion glass plate device (Delta 10 Dermatoscope: Heine Ltd, Herrsching, Germany). All lesions were then photographed with the dermoscopy imaging device (Sentry pilot; Polartechnics Ltd, Sydney, Australia). This incorporated a higher resolution megapixel camera which could be used for telemedicine diagnosis and for colour-calibrated sequential digital dermoscopy imaging. For melanocytic lesions that did not have dermoscopic evidence of melanoma, but were still considered to be suspicious, short term sequential digital dermoscopy imaging was performed over a period of 3 months.

Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Hierarchical diagnosis order of (1) histopathology, (2) unchanged lesions after sequential digital dermoscopy imaging indicating a benign diagnosis, (3) specialist opinion following referral, and (4) dermoscopy telemedicine. All sequential digital dermoscopy imaging and dermoscopy telemedicine images of nonexcised lesions were reviewed by an expert in dermoscopy and sequential digital dermoscopy imaging and a diagnosis recorded.
Is the reference standard likely to correctly classify the target condition?	**Unclear**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**High risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	The results only appear to be reported for 348/374 lesions for dermoscopy and dermoscopy ± sequential digital dermoscopy imaging (for melanoma: of which 9 had an unknown diagnosis and 8 had a diagnosis of basal cell carcinoma or Bowen disease – these were all excluded from the analyses) and for 160/192 lesions that received sequential digital dermoscopy imaging (for melanoma: of which 9 had an unknown diagnosis and 2 had a diagnosis of basal cell carcinoma or Bowen disease – these were all excluded from the analyses).
Was there an appropriate interval between index test and reference standard?	**Unclear, but probably**
Did all patients receive the same reference standard?	**No**
Were all patients included in the analysis?	**No**
Could the patient flow have introduced bias?	**High risk**
NOTES	Analysis appears to be on a per-lesion basis rather than a per-patient basis. The 2-by-2 tables could not be extracted.

Rosendahl (2011)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Consecutive series of lesions submitted for histology from the primary care skin cancer clinic of one of the authors.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Probably**

Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 463 pigmented lesions from 389 patients, mean (SD) age = 57 (17) years, 32.6% females. Lesion location: Trunk: N = 241; extremities: N = 128; head and face: N = 82; palms and soles: N = 10. Histopathologically, 246 pigmented lesions turned out to be melanocytic and 217 were of non-melanocytic origin. Final diagnoses: Malignant lesions: Basal cell carcinoma: N = 72; squamous cell carcinoma: N = 37; melanoma: N = 29. Benign lesions: Melanocytic nevi: N = 217; seborrheic keratosis: N = 43; solar lentigo: N = 37; lichen planus-like keratosis: N = 21, others: N = 7. Inclusion criteria: All pigmented lesions biopsied or excised during a 30-month period. *Patients included are only those who received resection. This changes the spectrum of disease as it excludes patients with lesions that were not considered concerning enough to warrant resection.* Exclusion criteria: Poor image quality (N = 3). Clinical setting: Primary care skin cancer practice in Queensland, Australia
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	For each lesion: A triplet of high-resolution digital images consisting of two clinical images (overview and close-up) followed by one dermatoscopic image. The clinical images were taken with Canon EOS digital single lens reflex cameras. The close-up was taken using a macro lens (60-mm f2.8 macro, Canon) with diffuse illumination at a constant reproduction ratio determined by a custom-fabricated spacer. The degree of magnification of the close-up images was similar to that of the dermatoscopy images. Dermatioscopic images were nonpolarising, preferentially using the Dermlite Fluid device (3 Gen, San Juan, Capistrano, Ca); alternatively Dermlite Foto (custom nonpolarised; 3 Gen) and Heine Delta 20 devices (Heines, Optotechnic GmbH< Herrsching, Germany) were used for large and inaccessible lesions, respectively. Dermatoscopic photographs were taken with Canon EOS single lens reflex cameras. Images were presented to the assessors as powerpoint slides. After inspection of the images, the assessor was required to give a diagnosis (criteria not reported, so presumably based on qualitative criteria). Dermatoscopic images were also screened for asymmetry of structure and colour ("chaos") and for clues to malignancy. Asymmetry of colour and structure were defined according to the basic principles of pattern analysis as revised by Kittler (2007, Dermatopathology: Practical & Conceptual, 13:1). Clues to malignancy included: Eccentric structureless zone (any colour except skin colour), gray or blue structures, peripheral black dots or clods, segmental radial lines or pseudopods, polymorphous vessels, white lines, thick reticular or branched lines, and parallel lines on ridges (acral lesions). *Not further information regarding the specific cut-off criteria for malignancy reported. The reporting of the results suggests that the test performance is based on best possible scenario.*
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**

Could the conduct or interpretation of the index test have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Unclear concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Histopathology
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Yes**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low concern**
NOTES	The results are presented for all malignancies combined. The 2-by-2 table could not be extracted and the results could not be separated into the different malignacies

1 **Walter (2012)**

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective series of suspicious pigmented lesions
Was a consecutive or random sample of patients enrolled?	**Unclear**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Unclear**
Could the selection of patients have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 643 patients, mean age (SD) = 44.5 (16.7) years; 230 males / 413 females with N = 788 lesions: Inclusion criteria: Patients aged ≥ 18 years presenting to one of the 15 participating general practices with a suspicious (any lesion presented buy a patient, or opportunistically seen by a family doctor or practice nurse, that could not immediately be diagnosed as benign and about which the patient could not be reassured) pigmented lesion from March 2008 to May 2010. Exclusion criteria: Patients who were unable to give informed consent or were considered inappropriate to include by their family doctor. Clinical setting: UK primary care.

Are there concerns that the included patients and setting do not match the review question?		**Low concern**
INDEX TEST		
A. Risk of bias		
Index test	Clinical assessment (clinical history and naked eye examination) followed by SIAscopy/MoleMate system (assessing clinician had completed a 2-hour training CD-ROM to identify relevant SIAscopic features of various pigmented skin lesions) .	
Were the index test results interpreted without knowledge of the results of the reference standard?		**Yes**
Could the conduct or interpretation of the index test have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		**Low concern**
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	Expert opinion by a histologist or dermatologist or review by two other dermatology experts of the recorded clinical history and examination, a digital photograph, and MoleMate images where available with or without follow up 3-6 months later.	
Is the reference standard likely to correctly classify the target condition?		**Unclear**
Were the reference standard results interpreted without knowledge of the results of the index tests?		**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?		**Unclear risk**
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		**Unclear concern**
FLOW AND TIMING		
A. risk of bias		
Flow and timing	Data are missing for 22/788 lesions	
Was there an appropriate interval between index test and reference standard?		**Yes**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**Yes Tests: No**
Could the patient flow have introduced bias?		**Low risk**
NOTES	Analysis was on a per-lesion basis rather than a per-patient basis. TP = 18, FN = 0, FP = 211, TN = 537.	

Cost-effectiveness evidence

Information sources and eligibility criteria

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED and HEED. Studies conducted in OECD countries other than the UK were considered.

Studies were selected for inclusion in the evidence review if the following criteria were met:

- Both cost and health consequences of interventions reported (i.e. true cost-effectiveness analyses)
- Conducted in an OECD country
- Incremental results are reported or enough information is presented to allow incremental results to be derived
- Studies that matched the population, interventions, comparators and outcomes specified in PICO
- Studies that meet the applicability and quality criteria set out by NICE, including relevance to the NICE reference case and UK NHS

Note that studies that measured effectiveness using quality of life based outcomes (e.g. QALYs) were desirable but, where this evidence was unavailable, studies using alternative effectiveness measures (e.g. life years) were considered.

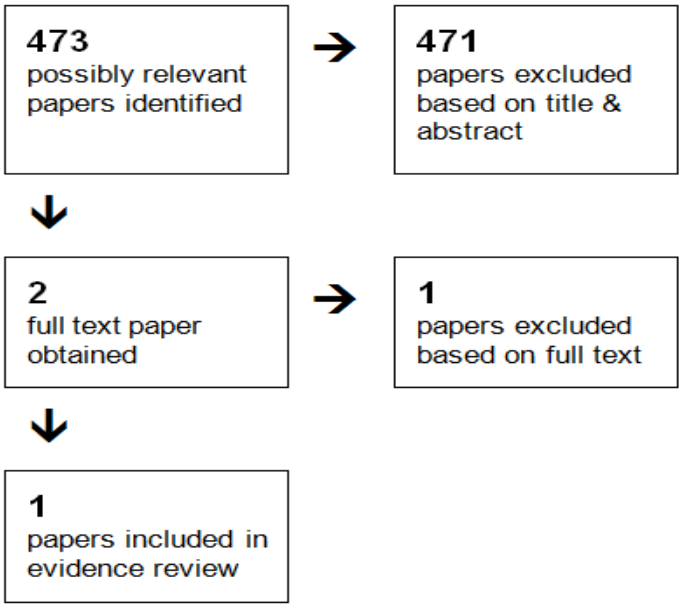
Selection of studies

The literature search results were screened by checking the article's title and abstract for relevance to the review question. The full articles of non-excluded studies were then attained for appraisal and compared against the inclusion criteria specified above.

Results

The diagram below summarises the search and sifting process for this topic.

Figure: Summary of evidence search and sifting process for this topic



It can be seen that, in total, 473 possibly relevant papers were identified. Of these, 471 papers were excluded at the initial sifting stage based on the title and abstract while two full papers were obtained for appraisal. One of these papers was excluded based on the full text as they were not applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore, only one paper was included in the systematic review of the economic evidence for this topic; Wilson et al. 2012. Mowatt et al. 2010 was a comprehensive report conducted as part of the NIHR HTA programme. The study included was a cost-effectiveness analysis comparing standard care (clinical history, naked eye examination and completion of a seven point checklist) with standard care plus the addition of the Molemate system (SIAscopy scanner integrated with a diagnostic algorithm) for the diagnosis of potentially suspicious lesions.

Quality and applicability of included study

Wilson et al. 2012 was deemed to be directly applicable to the decision problem that we are evaluating since it considers relevant comparators in the UK primary care setting and takes a NHS and PSS perspective. Results were presented in terms of cost per QALY gained. No serious limitations were identified with the analysis, which was generally of a very high standard.

Table: Methodological quality and applicability of the included study

Methodological quality	***Applicability***	
	Directly applicable	**Partially applicable**
Minor limitations	Wilson et al. 2012	

Methodological quality	*Applicability*	
Potentially serious limitations		
Very serious limitations		

Modified GRADE table

The primary results of the analysis by Wilson et al. 2012 are summarised in the modified GRADE table below.

Modified GRADE table showing the included evidence (Wilson et al. 2012) on the cost-effectiveness of adding the molemate system to standard care in patients presenting in primary care with suspected melanoma.

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Wilson et al. 2012 UK study considering NHS and PSS perspective. Cost-utility analysis (CUA).	Patients presenting in primary care with at least one suspicious pigmented lesion.	Standard Care: Lesions assessed by lead clinician following NICE guidelines including clinical history, naked eye examination and completion of 7 point checklist.	£1115	15.098 QALYs	Reference			**Threshold Sensitivity Analysis** The maximum cost per Molemate scan which would result in an ICER less than £30,000 was found to be £290 per consultation. **Deterministic Sensitivity Analysis** Use of East of England cancer registry data rather than trial data resulted in an ICER of £3,172 per QALY **Probabilistic Sensitivity Analysis** 66.1% of iterations led to an ICER below £30,000 per QALY. The molemate system was dominant in 19.6% and dominated in 7.9% of iterations.	**Directly Applicable** Analysis conducted from a UK Health Service perspective. Results reported as incremental cost per QALY. **Minor Limitations** Further one-way sensitivity analysis could have been conducted.
		Standard Care (as above) plus the addition of the Molemate system (SIAscopy scanner integrated with a diagnostic algorithm)	£1133	15.108 QALYs	£18	0.01 QALYs	£1896 per QALY		
	Comments:								

Evidence statement

Wilson et al (2012) compared the cost-effectiveness of the Molemate system (SIAscopy scanner integrated with a diagnostic algorithm) in addition to usual care (clinical history, naked eye examination and completion of a seven point checklist) in comparison to usual care alone for the diagnosis of potentially suspicious lesions. The authors found that the addition of the Molemate system would increase lifetime costs by £18 and yield an additional 0.01 QALYs per patient. The resulting ICER of £1,896 per QALY falls well below the NICE threshold of £20,000 per QALY and so the base case results suggest that Molemate is a cost-effecitve addition to usual care.

The addition of the Molemate scan also appears to be cost-effective in an alternative analysis in which East of England cancer registry data were used rather than the trial data with an ICER of £3,172 per QALY. Furthermore, a threshold analysis showed that the cost of adding the Molemate scan would have to exceed £290 for it to no longer be considered cost-effective at a threshold of £30,000 per QALY. The true cost of adding the Molemate scan is unlikely to be as high as this and so this too appears to be a strong result.

The probabilistic sensitivity analysis showed that, at a threshold of £20,000 per QALY, the addition of the Molemate scan was cost-effective in 60.3% of iterations. This suggests that there is considerable uncertainty, which the authors attribute to uncertainty in the sensitivity and specificity of Molemate versus usual care and the risk of disease progression in undiagnosed melanoma.

While these results appear favourable, further consideration needs to be given to the key effects that are driving the result. The results were primarily driven by the differences in diagnostic accuracy between the two strategies, which were informed by RCT evidence showing that Molemate had higher sensitivity and lower specificity than usual care. However, only the lower specificity result was found to be statistically significant. Indeed, the conclusion drawn from the trial was that Molemate did not add to best application of NICE guidelines in terms of appropriateness of referral.

Furthermore, the implications of the diagnostic accuracy data used in the model is that both appropriate and inappropriate referrals would be increased by using the Molemate system (driven by better sensitivity and poorer specificity, respectively). Therefore, the results of the model essentially suggest that benefits of picking up more cancer through appropriate referral outweigh the costs of making more inappropriate referrals. In other words, a policy of 'over-referring' may be cost-effective.

This interpretation has implications for the cost-effectiveness of the Molemate system itself as it could be argued that the Molemate system is not actually required to achieve such a policy. Being less strict as primary care gatekeepers would very likely lead to similarly cost-effective outcomes without the need for the additional spending on the Molemate system. Indeed, it could be further argued that it would be counter-intuitive to spend money on a system that has only been proven to decrease specificity in comparison to current best practice.

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Narrative review

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SQUAMOUS CELL CARCINOMA

Review question:
What is the risk of squamous cell carcinoma in patients presenting in primary care with symptom(s)?

Results

Literature search

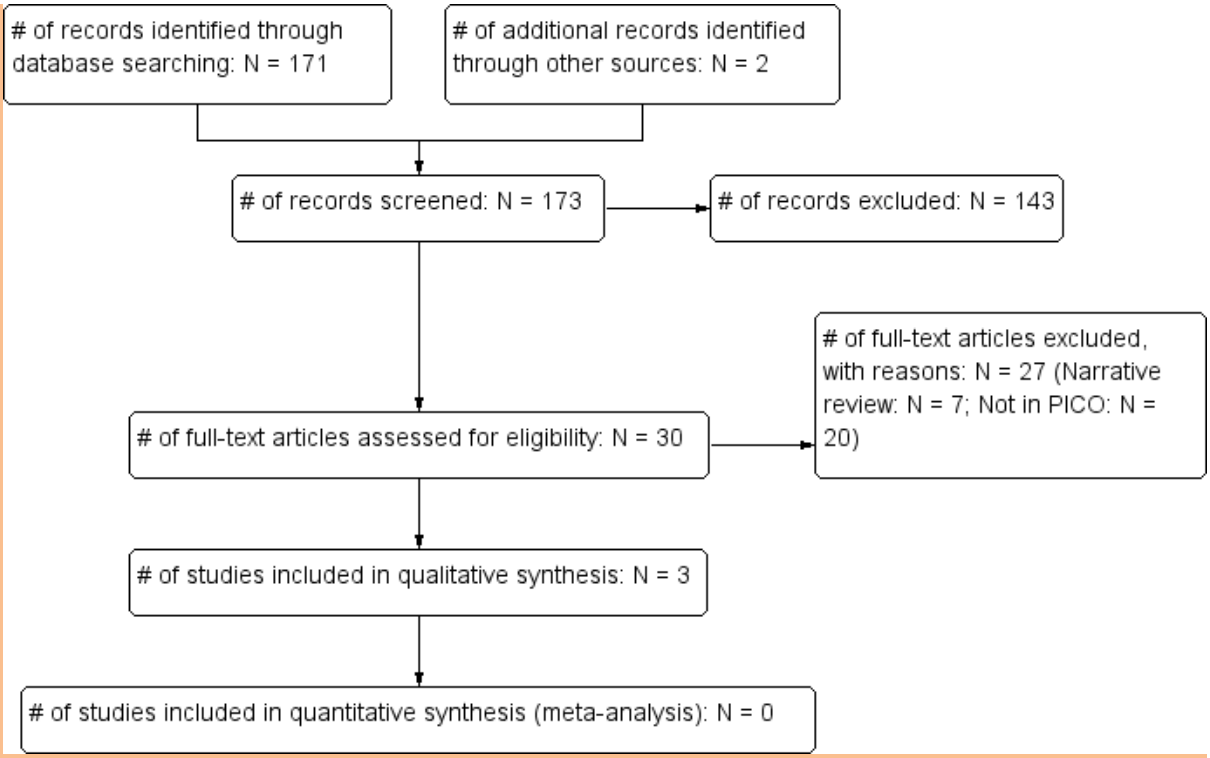
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2012	501	66	09/01/2013
Premedline	All-2012	66	5	09/01/2013
Embase	All-2012	2129	76	15/01/2013
Cochrane Library	All-2012	201	3	16/01/2013
Psychinfo	All-2012	4	1	09/01/2013
Web of Science (SCI & SSCI) and ISI Proceedings	All-2012	569	36	16/01/2013
Biomed Central	All-2012	287	3	21/01/2013

Total References retrieved (after de-duplication): 151

Update Search

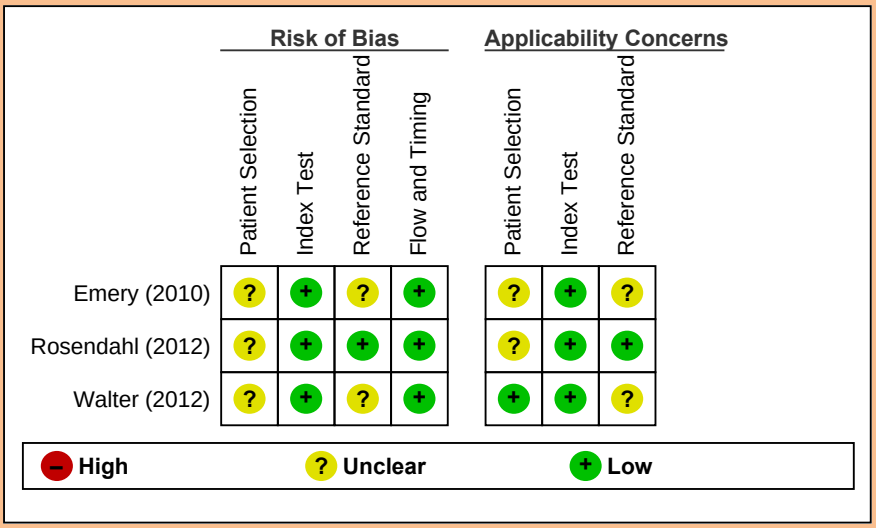
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2013-11/08/2014	78	4	11/08/2014
Premedline	2013-11/08/2014	13	3	11/08/2014
Embase	2013-11/08/2014	123	6	11/08/2014
Cochrane Library	2013-11/08/2014	48	0	11/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	2013-11/08/2014	89	7	11/08/2014

Total References retrieved (after de-duplication): 20



Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main bias risks and applicability concerns that the studies are subject to relate to (1) the patient sampling method not clearly being consecutive or random, (2) the extent to which the study setting matches UK primary care, (3) the quality of the reference standard, which may not always reliably diagnose the symptoms, and (4) the fact that the reference standard did not in all cases match that of the current question, namely histology.



Study results

Table 1: Squamous cell carcinoma of the skin: Study results.

Study	Symptom(s)	Patient group	Positive predictive value % (95% CI) Prevalence
Emery (2010) Patient-based analysis	Pigmented lesion	All included patients	0 (0-0.6) 0/858
		England sample	0 (0-1.2) 0/389
		Australia sample	0 (0-1) 0/469
Walter (2012) Lesion, not patient,-based analysis	Suspicious pigmented lesions	All included patients	0.06 (0.003-0.4) 1/1573
Rosendahl (2012) Lesion, not patient,-based analysis	Non-pigmented raised skin lesions	All included patients	SCC total: 41.26 (34.5-48.3) 85/206
			SCC: 15.53 (11-21.4) 32/206
			Keratoacanthoma: 14.08 (9.8-19.8) 29/206
			Bowen disease: 11.65 (7.8-17) 24/206
		Females	SCC and KA: 31.81 (21.2-44.6) 21/66
		Males	SCC and KA: 28.57 (21.4-36.9) 40/140
	Non-pigmented raised skin lesions on head and neck	Patients with specific symptom	SCC and KA: 23.33 (15.3-33.7) 21/90
	Non-pigmented raised skin lesions on trunk	Patients with specific symptom	SCC and KA: 14.29 (6.4-27.9) 7/49
	Non-pigmented raised skin lesions on upper extremities	Patients with specific symptom	SCC and KA: 45.16 (27.8-63.7) 14/31
	Non-pigmented raised skin lesions on lower extremities	Patients with specific symptom	SCC and KA: 52.78 (35.7-69.2) 19/36
	Non-pigmented raised skin lesions with monomorphic vascular pattern	Patients with specific symptom	SCC and KA: 26.47 (19.5-34.8) 36/136
	Non-pigmented raised skin lesions with polymorphic vascular	Patients with specific symptom	SCC and KA: 31.71 (18.6-48.2) 13/41

	pattern		
	Non-pigmented raised skin lesions with vessels absent	Patients with specific symptom	SCC and KA: 39.29 (22.1-59.3) 11/28
	Non-pigmented raised skin lesions with vessel morphologic findings: Dots	Patients with specific symptom	SCC and KA: 0 (0-95) 0/1
	Non-pigmented raised skin lesions with vessel morphologic findings: Coils	Patients with specific symptom	SCC and KA: 40 (30.1-49.8) 44/110
	Non-pigmented raised skin lesions with vessel morphologic findings: Serpentine	Patients with specific symptom	SCC and KA: 9.76 (4.6-18.8) 8/82
	Non-pigmented raised skin lesions with vessel morphologic findings: Looped	Patients with specific symptom	SCC and KA: 41.67 (22.8-63.1) 10/24
	Non-pigmented raised skin lesions with vessel arrangement: No arrangement	Patients with specific symptom	SCC and KA: 36.7 (27.8-46.5) 40/109
	Non-pigmented raised skin lesions with vessel arrangement: Radial	Patients with specific symptom	SCC and KA: 41.18 (19.4-66.5) 7/17
	Non-pigmented raised skin lesions with vessel arrangement: Centered	Patients with specific symptom	SCC and KA: 0 (0-30.1) 0/12
	Non-pigmented raised skin lesions with vessel arrangement: Branched	Patients with specific symptom	SCC and KA: 0 (0-12.3) 0/35
	Non-pigmented raised skin lesions with vessel arrangement: Branched and radial	Patients with specific symptom	SCC and KA: 2/2 (TP = 2, FP = 0)
	Non-pigmented raised skin lesions with vessel arrangement: Others	Patients with specific symptom	SCC and KA: 100 (19.8-100) 0/2
	Non-pigmented raised skin lesions and keratin	Patients with specific symptom	SCC and KA: 52.17 (41.6-62.6) 48/92
	Non-pigmented raised skin lesions and ulceration	Patients with specific symptom	SCC and KA: 27.27 (13.9-45.8) 9/33
	Non-pigmented raised skin lesions with white structures: White clods	Patients with specific symptom	SCC and KA: 20 (5.3-48.6) 3/15
	Non-pigmented raised skin lesions with white	Patients with	SCC and KA: 47.06 (3.2-61.4)

	structures: White structureless zones	specific symptom	24/51
	Non-pigmented raised skin lesions with white structures: White circles	Patients with specific symptom	SCC and KA: 58.7 (43.3-72.7) 27/46
	Non-pigmented raised skin lesions with white structures: White lines	Patients with specific symptom	SCC and KA: 6.67 (0.3-34) 1/15
	Non-pigmented raised skin lesions with white structures: White dots (milia)	Patients with specific symptom	SCC and KA: 16.67 (0.9-63.5) 1/6
	Non-pigmented raised skin lesions with white structures: Blood spots	Patients with specific symptom	SCC and KA: 45.61 (32.6-59.2) 26/57
	Non-pigmented raised skin lesions with white structures: Scale	Patients with specific symptom	SCC and KA: 40 (28.7-52.4) 28/70

KA = keratoacanthoma; TP = true positives; FP = false positives

Evidence statement(s):

Pigmented skin lesions (2 studies, N = 2784 *lesions*) presenting in a primary care setting do not seem to confer a risk of squamous cell carcinoma (1 case observed in total). The studies were associated with 3-4 bias and applicability concerns (See also Table 1).

Non-pigmented raised skin lesions (1 study, N = 206 *lesions*) presenting in a primary care setting are associated with a positive predictive value of 41.26% for squamous cell carcinoma. The study was associated with 2 bias and applicability concerns (See also Table 1).

Evidence tables

Emery (2010)

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Prospective series of pigmented lesions recruited from England (6 general practices covering urban, suburban and rural areas with a registered population of 52913) and Australia (3 primary care skin cancer clinics operated by GPs from a metropolitan area)	
Was a consecutive or random sample of patients enrolled?		**Unclear**
Was a case-control design avoided?		**Yes**
Did the study avoid inappropriate exclusions?		**Yes**
Could the selection of patients have introduced bias?		**Unclear risk**
B. Concerns regarding applicability		
Patient characteristics and setting	England: N = 389 patients, mean age = 44.9 years, 68.6% females with, interpretable images from N = 630 lesions. 0/630 lesions were squamous cell carcinoma, 0/630 lesions were basal cell carcinoma, 5/630 lesions were melanoma, and 0/630 lesions were lentigo maligna (melanoma). Australia: N = 469 patients, mean age = 50 years, 48% females, with	

	interpretable images from N = 581 lesions. 0/581 lesions were squamous cell carcinoma, 22/581 lesions were basal cell carcinoma, 7/581 lesions were melanoma, and 4/581 lesions were lentigo maligna (melanoma). Inclusion criteria: England: Patients aged > 18 years were recruited into the study by their GP if they presented with concerns about a pigmented skin lesion between January 2005 and January 2006. Australia: Patients aged > 18 years were recruited into the study by their GP if they presented with concerns about a pigmented skin lesion between April 2008 and January 2009. Additional lesions were also included when a pigmented skin lesion was identified as potentially suspicious during their clinical examination Exclusion criteria: None reported. Clinical setting: Primary care, UK, and primary care skin cancer practice, Queensland Australia.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Pigmented skin lesions that concerned patients, which were evaluated using macroscopic clinical photographs, dermoscopic images and SIAscan.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Histopathology or in-person clinical review of the lesion by one expert, including the 7-point melanoma checklist and digital dermoscopy or clinical diagnosis made on the basis of the 7-point melanoma checklist, photographic and dermoscopy images
Is the reference standard likely to correctly classify the target condition?	**Unclear**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Unclear concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients are accounted for in the results
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**

Could the patient flow have introduced bias?	**Low risk**
NOTES	

1 **Rosendahl (2012)**

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective unselected consecutive series of raised non-pigmented lesions
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Unclear**
Could the selection of patients have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 186 patients, mean (SD) age = 65 (13) years, 32.8% females with N = 206 lesions. 32/206 lesions were squamous cell carcinoma (SCC), 29/206 lesions were keratoacanthoma (SCC), 24/206 lesions were Bowen disease (SCC), and 56/ 206 lesions were basal cell carcinoma. Inclusion criteria: Patients presenting with non-pigmented raised lesions treated from March 1 through December 31 2011. All the lesions were excised or biopsied. It is unclear if there were any patients presenting with non-pigmented raised lesions not biopsied/excised who were not included. Exclusion criteria: None reported. Clinical setting: Private primary care skin cancer practice, Queensland Australia.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Non-pigmented raised skin lesions (not further defined, but see subgroup analyses) evaluated using dermoscopic images
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Histopathology
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined	**Low concern**

by the reference standard does not match the question?		
FLOW AND TIMING		
A. risk of bias		
Flow and timing	All patients are accounted for in the results	
Was there an appropriate interval between index test and reference standard?		**Yes**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**Yes**
Could the patient flow have introduced bias?		**Low risk**
NOTES	Analysis was on a per-lesion basis rather than a per-patient basis; some patients may have had more than one lesion diagnosed as skin cancer though it is not possible to ascertain the actual numbers from the data provided.	

1 **Walter (2012)**

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Prospective series of suspicious pigmented lesions	
Was a consecutive or random sample of patients enrolled?		**Unclear**
Was a case-control design avoided?		**Yes**
Did the study avoid inappropriate exclusions?		**Unclear**
Could the selection of patients have introduced bias?		**Unclear risk**
B. Concerns regarding applicability		
Patient characteristics and setting	N = 1293 patients, mean age (SD) = 44.6 (16.8) years; 465 males / 828 females with N = 1573 lesions, of which 1 was squamous cell carcinoma, 10 basal cell carcinomas, and 36 melanomas. Inclusion criteria: Patients aged ≥ 18 years presenting to one of the 15 participating general practices with a suspicious (any lesion presented buy a patient, or opportunistically seen by a family doctor or practice nurse, that could not immediately be diagnosed as benign and about which the patient could not be reassured) pigmented lesion from March 2008 to May 2010. Exclusion criteria: Patients who were unable to give informed consent or were considere3d inappropriate to include by their family doctor. Clinical setting: UK primary care.	
Are there concerns that the included patients and setting do not match the review question?		**Low concern**
INDEX TEST		
A. Risk of bias		
Index test	Suspicious (any lesion presented buy a patient, or opportunistically seen by a family doctor or practice nurse, that could not immediately be diagnosed as benign and about which the patient could not be reassured) pigmented lesion	
Were the index test results interpreted without knowledge of the results of the reference standard?		**Yes**
Could the conduct or interpretation of the index test have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		**Low concern**
REFERENCE STANDARD		

A. risk of bias		
Reference standard(s)	Expert opinion by a histologist or dermatologist or review by two other dermatology experts of the recorded clinical history and examination, a digital photograph, and MoleMate images where available with or without follow up 3-6 months later.	
Is the reference standard likely to correctly classify the target condition?		**Unclear**
Were the reference standard results interpreted without knowledge of the results of the index tests?		**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?		**Unclear risk**
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		**Unclear concern**
FLOW AND TIMING		
A. risk of bias		
Flow and timing	All patients are accounted for in the results	
Was there an appropriate interval between index test and reference standard?		**Yes**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**Yes Tests: No**
Could the patient flow have introduced bias?		**Low risk**
NOTES	Analysis was on a per-lesion basis rather than a per-patient basis.	

References

Included Studies

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Narrative review
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Narrative review

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Not in PICO as results only reported for excised lesions (N = 11116, GPs and skin cancer clinic doctors), not examined lesions (N = 28755, GPs and skin cancer clinic doctors).

Zalaudek, I., Kreusch, J., Giacomel, J., Ferrara, G., Catricala, C. & Argenziano, G. (2010) How to diagnose nonpigmented skin tumors: A review of vascular structures seen with dermoscopy Part II. Nonmelanocytic skin tumors. *Journal of the American Academy of Dermatology,* 63: 377-386.
Narrative review

Review question:

Which investigations of symptoms of suspected squamous cell carcinoma should be done with clinical responsibility retained by primary care?

Results

Literature search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-2013	2206	141	07/02/2013
Premedline	1980-2013	85	9	07/02/2013

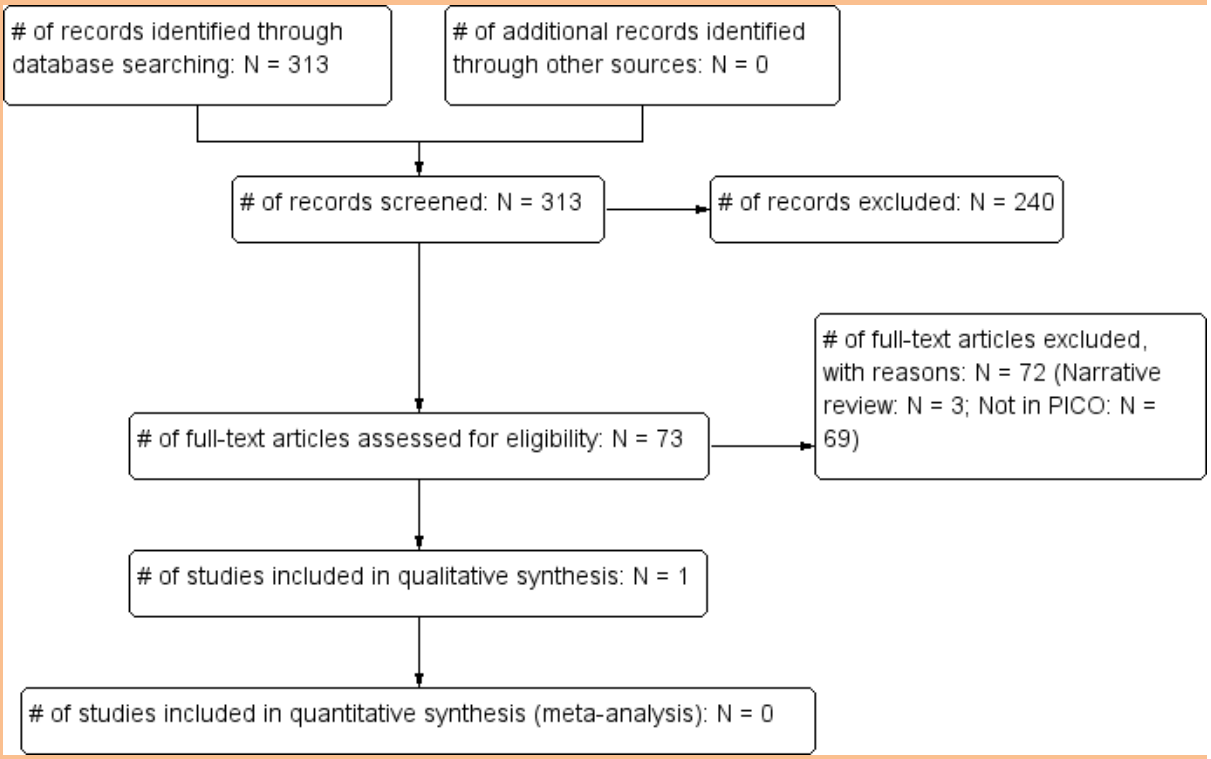
Embase	1980-2013	2263	146	08/02/2013
Cochrane Library	1980-2013	37	1	07/02/2013
Psychinfo	1980-2013	3	0	07/02/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2013	309	63	07/02/2013
Biomed Central	1980-2013	1026	4	07/02/2013

Total number of studies identified after de-duplication: 290

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2013-11/08/2014	87	7	11/08/2014
Premedline	2013-11/08/2014	123	6	11/08/2014
Embase	2013-11/08/2014	181	16	11/08/2014
Cochrane Library	2013-11/08/2014	55	0	11/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	2013-11/08/2014	53	2	11/08/2014

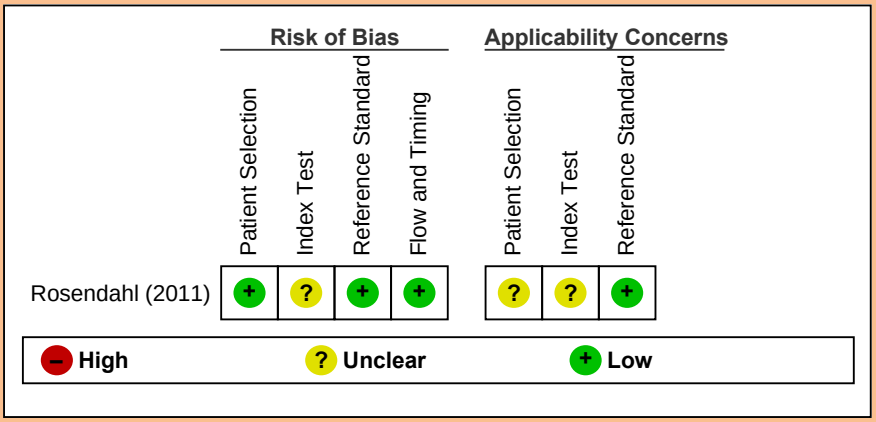
Total References retrieved (after de-duplication): 23



Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issues to note are that the study population may not be directly representative of an unselected symptomatic population of patients presenting to the UK-based GP, that the index test does not specify the criteria for malignancy which may limit its external validity, and that the results

presented are based on a best case scenario, and are therefore likely to be inflated, and only available for skin malignancy as a whole and not for squamous cell carcinoma separately.



Study results

Table 1: Squamous cell carcinoma of the skin: Study results.

Study	Intervention	Prevalence	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	False negativity rate
Rosendahl (2011)	Clinical images and dermatoscopy	138 malignacies/463 lesions	82.6% (NR)	80% (NR)	NR (NR)	17.4% (NR)

NR = Not reported

No evidence was identified pertaining to the diagnostic accuracy of excision biopsy of the lesion in patients with suspected squamous cell cancer where the clinical responsibility was retained by primary care.

Evidence statement(s):

Dermatoscopy and clinical images (1 study, N = 463 lesions/389 patients) performed in symptomatic patients presenting in a primary care setting is associated with a best-case sensitivity of 82.6%, specificity of 80%, and false negativity rate of 17.4% for skin malignancy. The study was associated with 1 bias and 2 applicability concerns (See also Table 1)..

Evidence tables

Rosendahl (2011)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Consecutive series of lesions submitted for histology from the primary care skin cancer clinic of one of the authors.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Probably**
Could the selection of patients have introduced bias?	**Low risk**

B. Concerns regarding applicability	
Patient characteristics and setting	N = 463 pigmented lesions from 389 patients, mean (SD) age = 57 (17) years, 32.6% females. Lesion location: Trunk: N = 241; extremities: N = 128; head and face: N = 82; palms and soles: N = 10. Histopathologically, 246 pigmented lesions turned out to be melanocytic and 217 were of non-melanocytic origin. Final diagnoses: Malignant lesions: Basal cell carcinoma: N = 72; squamous cell carcinoma: N = 37; melanoma: N = 29. Benign lesions: Melanocytic nevi: N = 217; seborrheic keratosis: N = 43; solar lentigo: N = 37; lichen planus-like keratosis: N = 21, others: N = 7. Inclusion criteria: All pigmented lesions biopsied or excised during a 30-month period. *Patients included are only those who received resection. This changes the spectrum of disease as it excludes patients with lesions that were not considered concerning enough to warrant resection.* Exclusion criteria: Poor image quality (N = 3). Clinical setting: Primary care skin cancer practice in Queensland, Australia
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	For each lesion: A triplet of high-resolution digital images consisting of two clinical images (overview and close-up) followed by one dermatoscopic image. The clinical images were taken with Canon EOS digital single lens reflex cameras. The close-up was taken using a macro lens (60-mm f2.8 macro, Canon) with diffuse illumination at a constant reproduction ratio determined by a custom-fabricated spacer. The degree of magnification of the close-up images was similar to that of the dermatoscopy images. Dermatioscopic images were nonpolarising, preferentially using the Dermlite Fluid device (3 Gen, San Juan, Capistrano, Ca); alternatively Dermlite Foto (custom nonpolarised; 3 Gen) and Heine Delta 20 devices (Heines, Optotechnic GmbH< Herrsching, Germany)were used for large and inaccessible lesions, respectively. Dermatoscopic photographs were taken with Canon EOS single lens reflex cameras. Images were presented to the assessors as powerpoint slides. After inspection of the images, the assessor was required to give a diagnosis (criteria not reported, so presumably based on qualitative criteria). Dermatoscopic images were also screened for asymmetry of structure and colour ("chaos") and for clues to malignancy. Asymmetry of colour and structure were defined according to the basic principles of pattern analysis as revised by Kittler (2007, Dermatopathology: Practical & Conceptual, 13:1). Clues to malignancy included: Eccentric structureless zone (any colour except skin colour), gray or blue structures, peripheral black dots or clods, segmental radial lines or pseudopods, polymorphous vessels, white lines, thick reticular or branched lines, and parallel lines on ridges (acral lesions). *Not further information regarding the specific cut-off criteria for malignancy reported. The reporting of the results suggests that the test performance is based on best possible scenario.*
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test	**Unclear risk**

have introduced bias?	
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Unclear concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Histopathology
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Yes**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	The results are presented for all malignancies combined. The 2-by-2 table could not be extracted and the results could not be separated into the different malignacies

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Prout MN, Sidari JN, Witzburg RA, Grillone GA, Vaughan CW. Head and neck cancer screening among 4611 tobacco users older than forty years. Otolaryngology - Head & Neck Surgery 1997;116(2):201-8.
Exclusion Reason: Not in PICO

Quereux G, Lequeux Y, Cary M, Jumbou O, Nguyen JM, Dreno B. Feasibility and effectiveness of a melanoma targeted screening strategy. Melanoma Research 2011;21:e1-2.
Exclusion Reason: Not in PICO

Raasch B, Maclennan R, Wronski I, Robertson I. Body site specific incidence of basal and squamous cell carcinoma in an exposed population, Townsville, Australia. Mutation Research 1998;422(1):101-6.
Exclusion Reason: Not in PICO

Raasch BA. Suspicious skin lesions and their management. Australian Family Physician 1999;28(5):466-71.
Exclusion Reason: Not in PICO: Clinical versus histological diagnosis (not biopsy or dermatoscopy versus histology or follow up)

Rademaker M, Thorburn M. Pathology referrals for skin lesions - Are we giving the pathologist sufficient clinical information? New Zealand Medical Journal 2010;123(1325):53-8.
Exclusion Reason: Not in PICO

Radziszewski J, Kowalewska M, Jedrzejczak T, Kozlowicz-Gudzinska I, Nasierowska-Guttmejer A, Bidzinski M, et al. The accuracy of the sentinel lymph node concept in early stage squamous cell vulvar carcinoma. Gynecologic Oncology 2010;116(3):473-7.
Exclusion Reason: Not in PICO

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Exclusion Reason: Not in PICO

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Exclusion Reason: Not in PICO

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Exclusion Reason: Not in PICO

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Exclusion Reason: Not in PICO

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Exclusion Reason: Narrative Review

Rezze GG, De Sa BCS, Neves RI. Dermoscopy: The pattern analysis. Anais Brasileiros de Dermatologia 2006;81(3):261-8.
Exclusion Reason: Narrative Review

Rice SA, Swale VJ, Cerio R. Are we relying too heavily on dermoscopy? British Journal of Dermatology 2012;167:105.
Exclusion Reason: Narrative review

Richert, B., Lecerf, P., Caucanas, M. & Andre, J. (2013) Nail tumors. *Clinics in Dermatology,* 31: 602-617.
Exclusion Reason: Narrative review

Robison Sean, Kljakovic Marjan, Barry Peter. Choosing to biopsy or refer suspicious melanocytic lesions in general practice. BMC Family Practice 2012;13(1):78.
Exclusion Reason: Not in PICO

Roozeboom, M. H., Mosterd, K., Winnepenninckx, V. J., Nelemans, P. J. & Kelleners-Smeets, N. W. (2013) Agreement between histological subtype on punch biopsy and surgical excision in primary basal cell carcinoma. *Journal of the European Academy of Dermatology & Venereology,* 27: 894-898.
Exclusion Reason: Not in PICO

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Exclusion Reason: Narrative Review

Rosen R. Managing nonmelanoma skin cancer. Modern Medicine of Australia 1999;42(2):74-85.
Exclusion Reason: Narrative Review

Rosendahl C, Cameron A, Argenziano G, Zalaudek I, Tschandl P, Kittler H. Dermoscopy of Squamous Cell Carcinoma and Keratoacanthoma. Archives of Dermatology 2012;148(12):1386-92.
Exclusion Reason: Not in PICO

Rosendahl C, Hansen C, Cameron A, Bourne P, Wilson T, Cook B, et al. Measuring performance in skin cancer practice: the SCARD initiative. International Journal of Dermatology 2011;50(1):44-51.
Exclusion Reason: Not in PICO

Rosendahl C, Tschandl P, Cameron A, Kittler H. Diagnostic accuracy of dermatoscopy for melanocytic and nonmelanocytic pigmented lesions. Journal of the American Academy of Dermatology 2011;64(6):1068-73.
Exclusion Reason: Duplicate

Rousset, J., Abgral, R., Chinellato, S., Garetier, M., Barberot, C., Valette, G., Potard, G., Le, B. T. & Salaun, P. Y. (2013) Early recurrence or submucosal residual of laryngeal squamous cell carcinoma: diagnosis by CT-guided endolaryngeal core biopsy on a transcutaneous approach. *Head & Neck,* 35: E202-E204.
Exclusion Reason: Not in PICO

Rudkin AK, Dodd T, Muecke JS. The differential diagnosis of localised amelanotic limbal lesions: a review of 162 consecutive excisions. British Journal of Ophthalmology 2011;95(3):350-4.
Exclusion Reason: Not in PICO
Russell EB, Carrington PR, Smoller BR. Basal cell carcinoma: a comparison of shave biopsy versus punch biopsy techniques in subtype diagnosis. Journal of the American Academy of Dermatology 1999;41(1):69-71.
Exclusion Reason: Not in PICO
Ryu IS, Choi SH, Kim do H, Han MW, Roh JL, Kim SY, et al. Detection of the primary lesion in patients with cervical metastases from unknown primary tumors with narrow band imaging endoscopy: preliminary report. Head & Neck 2013;35(1):10-4.
Exclusion Reason: Not in PICO
Sabir F, Aziz M, Afroz N, Amin SS. Clinical and cyto-histopathological evaluation of skin lesions with special reference to bullous lesions. Indian Journal of Pathology and Microbiology 2010;53(1):41-6.
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Saldanha G, Fletcher A, Slater DN. Basal cell carcinoma: a dermatopathological and molecular biological update. British Journal of Dermatology 2003;148(2):195-202.
Exclusion Reason: Narrative Review
Sandison A. Common head and neck cases in our consultation referrals: diagnostic dilemmas in inverted papilloma. [Review] [13 refs]. Head and neck pathology 2009;3(3):260-2
Exclusion Reason: Narrative Review
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Exclusion Reason: Not in PICO
Sanyal, S., Holme, A. & Kemmett, D. (2013) How are patients with actinic keratoses managed in primary care? *British Journal of Dermatology,* 169: 45.
Exclusion Reason: Not in PICO
Schlemper RJ, Dawsey SM, Itabashi M, Iwashita A, Kato Y, Koike M, et al. Differences in diagnostic criteria for esophageal squamous cell carcinoma between Japanese and Western pathologists. Cancer 2000;88(5):996-1006.
Exclusion Reason: Not in PICO
Schofield J, Hepburn N, Scharrer K, Hussain K. The costs of diagnosing and treating skin cancer using the 2-week-wait referral process. British Journal of Dermatology 2011;165:22-3.
Exclusion Reason: Not in PICO
Schroeder BM, American Cancer Society. ACS updates guideline for the early detection of cervical neoplasia and cancer. American Cancer Society. American Family Physician 2003;67(9):2011-6.
Exclusion Reason: Not in PICO
Schwartzberg JB, Elgart GW, Romanelli P, Fangchao M, Federman DG, Kirsner RS. Accuracy and predictors of basal cell carcinoma diagnosis. Dermatologic Surgery 2005;31(5):534-7.
Exclusion Reason: Not in PICO
Scully C, Newman L, Bagan JV. The role of the dental team in preventing and diagnosing cancer: 3. oral cancer diagnosis and screening. Dental Update 331;32(6):326-8.
Exclusion Reason: Not in PICO
Sendagorta E, Herranz P, Guadalajara H, Zamora FX. [Early detection of anal intraepithelial neoplasia in high-risk patients]. [Review] [Spanish]. Actas Dermo-Sifiliograficas 2011;102(10):757-65.
Exclusion Reason: Narrative Review
Senel E. Dermatoscopy of non-melanocytic skin tumors. Indian Journal of Dermatology Venereology & Leprology 2011;77(1):16-21.
Exclusion Reason: Narrative Review

Shariff Z, Roshan A, Williams AM, Platt AJ. 2-Week wait referrals in suspected skin cancer: does an instructional module for general practitioners improve diagnostic accuracy? Surgeon Journal of the Royal Colleges of Surgeons of Edinburgh & Ireland 2010;8(5):247-51.
Exclusion Reason: Not in PICO

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Exclusion Reason: Not in PICO

Shimizu Y, Omori T, Yokoyama A, Yoshida T, Hirota J, Ono Y, et al. Endoscopic diagnosis of early squamous neoplasia of the esophagus with iodine staining: high-grade intra-epithelial neoplasia turns pink within a few minutes. Journal of Gastroenterology & Hepatology 2008;23(4):546-50.
Exclusion Reason: Not in PICO

Shitara, D., Ishioka, P., Alonso-Pinedo, Y., Palacios-Bejarano, L., Carrera, C., Malvehy, J. & Puig, S. (2014) Shiny White Streaks: A Sign of Malignancy at Dermoscopy of Pigmented Skin Lesions. *Acta Dermato-Venereologica,* 94: 132-137.
Exclusion Reason: Setting not in PICO

Shum WY, Hsieh TC, Yeh JJ, Chen JH, Su CC, Liang JA, et al. Clinical usefulness of dual-time FDG PET-CT in assessment of esophageal squamous cell carcinoma. European Journal of Radiology 2012;81(5):1024-8.
Exclusion Reason: Not in PICO

Singh, T. & Schenberg, M. (2013) Delayed diagnosis of oral squamous cell carcinoma following dental treatment. *Annals of the Royal College of Surgeons of England,* 95: 369-373.
Exclusion Reason: Not in PICO

Skiljevic D, Stojkovic-Filipovic J, Nikolic M, Medenica L. Early-onset basal cell carcinoma. Melanoma Research 2010;20:e68.
Exclusion Reason: N=1

Smithers BM, Fahey PP, Corish T, Gotley DC, Falk GL, Smith GS, et al. Symptoms, investigations and management of patients with cancer of the oesophagus and gastro-oesophageal junction in Australia. Medical Journal of Australia 2010;193(10):572-7.
Exclusion Reason: Not in PICO

Sober AJ. Diagnosis and management of skin cancer. Cancer 1983;51(12:Suppl):Suppl-52.
Exclusion Reason: Not in PICO

Socha, A. & Niedzielska, I. (2013) Exophytic tumours of skin of the head - Case study and review of the literature. *Dental and Medical Problems,* 50: 229-237.
Exclusion Reason: Not in PICO

Speel E-J, Leusink FKJ, Van Hooff SR, Kummer JA, van Diest PJ, Koole R, et al. Multi-center validation of a lymph node metastasis gene-expression signature for head and neck squamous cell carcinomas. Cancer Research 2011;71(8 SUPPL. 1).
Exclusion Reason: Not in PICO

Spencer JM, Tannenbaum A, Sloan L, Amonette RA. Does inflammation contribute to the eradication of basal cell carcinoma following curettage and electrodesiccation? Dermatologic Surgery 1997;23(8):625-30.
Exclusion Reason: Not in PICO

Spencer RJ, Young RH, Goodman A. The risk of squamous cell carcinoma in persistent vulvar ulcers. Menopause 2011;18(10):1067-71.
Exclusion Reason: Not in PICO

Stegman SJ. Basal cell carcinoma and squamous cell carcinoma. Recognition and treatment. [Review] [28 refs]. Medical Clinics of North America 1986;70(1):95-107.
Exclusion Reason: Narrative Review

Stell PM, Wood GD, Scott MH. Early oral cancer: treatment by biopsy excision. British Journal of Oral Surgery 1982;20(4):234-8.

Exclusion Reason: Not in PICO
Stockfleth E. Non melanoma skin cancer - Early excision is still the standard in therapy. [German]. Klinikarzt 2002;31(5):122-5.
Exclusion Reason: Narrative Reivew
Stoeckli SJ, Broglie MA. Sentinel node biopsy for early oral carcinoma. Current Opinion in Otolaryngology & Head and Neck Surgery 2012;20(2):103-8.
Exclusion Reason: Narrative Review
Stolte M. [The new "Vienna Classification" for epithelial neoplasia of the gastrointestinal tract. Pros or cons?]. [Review] [34 refs] [German]. Pathologe 2001;22(1):4-12.
Exclusion Reason: Narrative Review
Streeton CL, Gospodarevskaya E, Harris A. Treatment of basal cell carcinomas by general practitioners in Australia. International Journal of Dermatology 2006;45(4):345-51.
Exclusion Reason: Not in PICO
Stulberg DL, Crandell B, Fawcett RS. Diagnosis and treatment of basal cell and squamous cell carcinomas. American Family Physician 2004;70(8):1481-8.
Exclusion Reason: Narrative Review
Szalai K, Hatvani Z, Harsing J, Somlai B, Karpati S. High frequency ultrasonography in the diagnosis of cutaneous pigmented lesions and melanoma reduce the possibilities of diagnostic pitfalls. Melanoma Research 2011;21:e4-5.
Exclusion Reason: Narrative Review
Talbot S, Hitchcock B. Incomplete primary excision of cutaneous basal and squamous cell carcinomas in the Bay of Plenty. New Zealand Medical Journal 2004;117(1192):U848.
Exclusion Reason: Not in PICO
Tan E, Yung A, Jameson M, Oakley A, Rademaker M. Successful triage of patients referred to a skin lesion clinic using teledermoscopy (IMAGE IT trial). British Journal of Dermatology 2010;162(4):803-11.
Exclusion Reason: Not in PICO
Tandon Y, Brodell RT. Local reactions to imiquimod in the treatment of basal cell carcinoma. Dermatology Online Journal 2012;18(9):1.
Exclusion Reason: Not in PICO
Tangjaturonrasme, N., Rerknimitr, R., Pittayanon, R., Wisedopas, N. & Kullavanijaya, P. (2013) The difference in detection rates during surveillance endoscopy for early squamous cell neoplasia of the esophagus between patients with previous nasopharyngeal cancer and patients with other ent related squamous cell cancers pornphan thienchanachaiya1. *Gastrointestinal Endoscopy,* 77: AB339-AB340.
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Tannapfel A, Weber A. Tumor markers in squamous cell carcinoma of the head and neck: clinical effectiveness and prognostic value. European Archives of Oto-Rhino-Laryngology 2001;258(2):83-8.
Exclusion Reason: Narrative Review
Teoh YL, Halpern SM, Shall L. Factors associated with incomplete excision of basal cell carcinomas. British Journal of Dermatology 2010;163:55-6.
Exclusion Reason: Not in PICO
TerKonda SP, Perdikis G. Non-melanotic skin tumors of the upper extremity. [Review] [50 refs]. Hand Clinics 104;20(3):293-301.
Exclusion Reason: Narrative Review
Terrill PJ, Fairbanks S, Bailey M. Is there just one lesion? The need for whole body skin examination in patients presenting with non-melanocytic skin cancer. ANZ Journal of Surgery 2009;79(10):707-12.
Exclusion Reason: Not in PICO

Terstappen K, Larko O, Wennberg AM. Pigmented basal cell carcinoma - Comparing the diagnostic methods of SIAscopy and dermoscopy. Acta Dermato-Venereologica 2007;87(3):238-42.
Exclusion Reason: Narrative Review
Terushkin V, Braga JC, Dusza SW, Scope A, Busam K, Marghoob AA, et al. Agreement on the Clinical Diagnosis and Management of Cutaneous Squamous Neoplasms. Dermatologic Surgery 2010;36(10):1514-20.
Exclusion Reason: Not in PICO
Thienchanachaiya P, Rerknimitr R, Pittayanon R, Wisedopas N, Tangjaturonrasme N, Kullavanijaya P. Preliminary study of FICE for detection of early esophageal neoplasm in patients with history of ENT related squamous cell cancers. Journal of Gastroenterology and Hepatology 2012;27:319-20.
Exclusion Reason: Not in PICO
Thissen MR, Neumann HA, Berretty PJ, Ideler AH. [The treatment of basal cell carcinoma patients by dermatologists in Netherland]. [Dutch]. Nederlands Tijdschrift Voor Geneeskunde 1998;142(27):1563-7.
Exclusion Reason: Not in PICO
Tochigi, T., Shuto, K., Staito, H., Kono, T. & Matsubara, H. (2013) Early esophageal squamous cell cancer by high-barium esophagography using flat panel X-ray detector in comparison with histological findings. *European Journal of Cancer,* 49: S252-S253.
Exclusion Reason: Not in PICO
Tomas S. Difficult to diagnose skin cancer The 'aggressive' BCC. Australian Family Physician 2009;38(7):492-7.
Exclusion Reason: Narrative Review
Trotter MJ, Bruecks AK. Interpretation of Skin Biopsies by General Pathologists: Diagnostic Discrepancy Rate Measured by Blinded Review. Archives of Pathology and Laboratory Medicine 2003;127(11):1489-92.
Exclusion Reason: Not in PICO
Turan, E., Yurt, N., Yesilova, Y. & Turkcu, G. (2013) Early-onset basal cell carcinoma. *Turkish Journal of Pediatrics,* 55: 354-356.
Exclusion Reason: Not in PICO
Ulrich M, Lange-Asschenfeldt S, Gonzalez S. In vivo reflectance confocal microscopy for early diagnosis of nonmelanoma skin cancer. Actas Dermo-Sifiliograficas 2012;103(9):784-9.
Exclusion Reason: Narrative Review
Vacher-Lavenu MC. [Histology and cytology of cervical cancers]. [Review] [24 refs] [French]. Revue du Praticien 2001;51(13):1417-23.
Exclusion Reason: Narrative Review
Vargo N. Basal cell and squamous cell carcinoma. [Review] [46 refs]. Seminars in Oncology Nursing 2003;19(1):12-21.
Exclusion Reason: Narrative Review
Vermaak, P. V. & Manushakian, J. (2013) Rapidly enlarging skin lesion on the lip. *BMJ Case Reports,* 2013, 2013.
Exclusion Reason: Not in PICO
Viglizzo G, Rongioletti F. Clinical, dermoscopic and pathologic correlation of pigmentary lesions observed in a dermoscopy service in the year 2003. [Italian, English]. Giornale Italiano di Dermatologia e Venereologia 2004;139(4):339-44.
Exclusion Reason: Not in PICO
Viola KV, Tolpinrud WL, Gross CP, Kirsner RS, Imaeda S, Federman DG. Outcomes of referral to dermatology for suspicious lesions: implications for teledermatology. Archives of Dermatology 2011;147(5):556-60.
Exclusion Reason: Not in PICO

Wade S, Gonzalez ML, Basra M. An audit of the diagnostic accuracy and complete excision rate for skin cancers in primary and secondary care in the Cardiff area. British Journal of Dermatology 2011;165:105.
Exclusion Reason: Not in PICO
Wagoner J, Keehn C, Morgan MB. CD-10 immunostaining differentiates superficial basal cell carcinoma from cutaneous squamous cell carcinoma. American Journal of Dermatopathology 2007;29(6):555-8.
Exclusion Reason: Narrative Review
Wan A, Savage NW. Biopsy and diagnostic histopathology in dental practice in Brisbane: usage patterns and perceptions of usefulness. Australian Dental Journal 2010;55(2):162-9.
Exclusion Reason: Not in PICO
Watson Tony, Walter Fiona, Wood Annabel, Morris Helen, Hall Per, Karner Simone, et al. Learning a novel technique to identify possible melanomas: are Australian general practitioners better than their U.K. colleagues? Asia Pacific Family Medicine 2009;8(1):3.
Exclusion Reason: Narrative Review
Wetzig T, Woitek M, Eichhorn K, Simon JC, Paasch U. Surgical Excision of Basal Cell Carcinoma with Complete Margin Control: Outcome at 5-Year Follow-Up. Dermatology 2010;220(4):363-9.
Exclusion Reason: Not in PICO
White, G. M., Zhou, H. C. & Burchette, R. J. (2013) Biopsy followed by immediate curettage and electrodesiccation of suspected basal cell carcinomas at the first visit. *JAMA Dermatology,* 149: 980-981.
Exclusion Reason: Not in PICO
Whitesides LM, Ferreira LR, Ord RA. Audit of clinical information and diagnoses supplied to the pathologist following biopsy of oral squamous cell carcinomas. MSDA Journal 1995;38(2):63-5.
Exclusion Reason: Narrative Review
Wilkinson D, Askew DA, Dixon A. Skin cancer clinics in Australia: workload profile and performance indicators from an analysis of billing data. Medical Journal of Australia 2006;184(4):162-4.
Exclusion Reason: Not in PICO
Williams RB, Burdge AH, Lewis Jones S. Skin biopsy in general practice. British Medical Journal 1991;303(6811):1179-80.
Exclusion Reason: Not in PICO
Wilson RL, Yentzer BA, Isom SP, Feldman SR, Fleischer AB Jr. How good are US dermatologists at discriminating skin cancers? A number-needed-to-treat analysis. Journal of Dermatological Treatment 2012;23(1):65-9.
Exclusion Reason: Not in PICO
Winzenburg SM, Niehans GA, George E, Daly K, Adams GL. Basaloid squamous carcinoma: a clinical comparison of two histologic types with poorly differentiated squamous cell carcinoma. Otolaryngology - Head & Neck Surgery 1998;119(5):471-5.
Exclusion Reason: Not in PICO
Wlodarczyk J. [Application of Lugol solution in the gastroesophageal reflux disease]. [Polish]. Przeglad Lekarski 2007;64(9):549-51Won S-S, Jung D-S, Kim H-S, Kwon K-S, Hee S-S. Clinicopathologic features of postlaser basal cell carcinoma: Does it differ from primary basal cell carcinoma? Journal of the American Academy of Dermatology 2010;62(3 SUPPL. 1):AB146.
Exclusion Reason: Not in PICO
Wolberink, E. A. W., Pasch, M. C., Zeiler, M., Van Erp, P. E. J. & Gerritsen, M. J. P. (2013) High discordance between punch biopsy and excision in establishing basal cell carcinoma subtype: Analysis of 500 cases. *Journal of the European Academy of Dermatology and Venereology,* 27: 985-989.
Exclusion Reason: Not in PICO

Wong KY, Gilleard O, Price R. Non-melanoma skin cancer incomplete excision rates of different grades of plastic surgeons and the implications for service provision. European Journal of Surgical Oncology 2012;38(11):1121.
Exclusion Reason: Not in PICO

Woolley, S. D. & Hughes, C. (2013) A young military pilot presents with a periocular Basal Cell Carcinoma: A case report. *Travel Medicine and Infectious Disease,* 11: 435-437.
Exclusion Reason: Not in PICO

Wray, E. V., Brant, B., Hussain, F. & Muller, F. M. (2013) A new model of teledermoscopy combining service and education. *British Journal of Dermatology,* 169: 139.
Exclusion Reason: Not in PICO

Wright VC. When to suspect squamous cancer at colposcopy. [Review] [22 refs]. Nurse Practitioner 1959;26(9):50-6.
Exclusion Reason: Narrative Review

Wustrow J, Rudert H, Diercks M, Beigel A. Squamous cell carcinoma and undifferentiated carcinoma of the inner nose and the paranasal sinuses. [German]. Strahlentherapie und Onkologie 1989;165(6):468-73.
Exclusion Reason: Not in PICO

Yamazaki N. [Squamous cell carcinoma]. [Review] [9 refs] [Japanese]. Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy] 2006;33(10):1392-7.
Exclusion Reason: Narrative Review

Youl PH, Baade PD, Janda M, Del Mar CB, Whiteman DC, Aitken JF. Diagnosing skin cancer in primary care: how do mainstream general practitioners compare with primary care skin cancer clinic doctors? Medical Journal of Australia 2007;187(4):215-20.
Exclusion Reason: Not in PICO: Clinical versus histological diagnosis (not biopsy or dermatoscopy versus histology or follow up)

Youl PH, Janda M, Aitken JF, Del Mar CB, Whiteman DC, Baade PD. Body-site distribution of skin cancer, pre-malignant and common benign pigmented lesions excised in general practice. British Journal of Dermatology 2011;165(1):35-43
Exclusion Reason: Not in PICO

Zalaudek I, Argenziano G, Soyer HP, Corona R, Sera F, Blum A, et al. Three-point checklist of dermoscopy: an open internet study. British Journal of Dermatology 2006;154(3):431-7.
Exclusion Reason: Not in PICO

Zedek DC, Smith ET Jr, Hitchcock MG, Feldman SR, Shelton BJ, White WL. Cutaneous lupus erythematosus simulating squamous neoplasia: the clinicopathologic conundrum and histopathologic pitfalls. Journal of the American Academy of Dermatology 2007;56(6):1013-20.
Exclusion Reason: Not in PICO

Zheng W, Soo KC, Sivanandan R, Olivo M. Detection of squamous cell carcinomas and pre-cancerous lesions in the oral cavity by quantification of 5-aminolevulinic acid induced fluorescence endoscopic images. Lasers in Surgery & Medicine 2002;31(3):151-7.
Exclusion Reason: Not in PICO

Zhou XH. Primary squamous cell carcinoma of the thyroid. European Journal of Surgical Oncology 2002;28(1):42-5.
Exclusion Reason: N=2

BASAL CELL CARCINOMA

Review question:
What is the risk of basal cell carcinoma in patients presenting in primary care with symptom(s)?

Results

Literature search

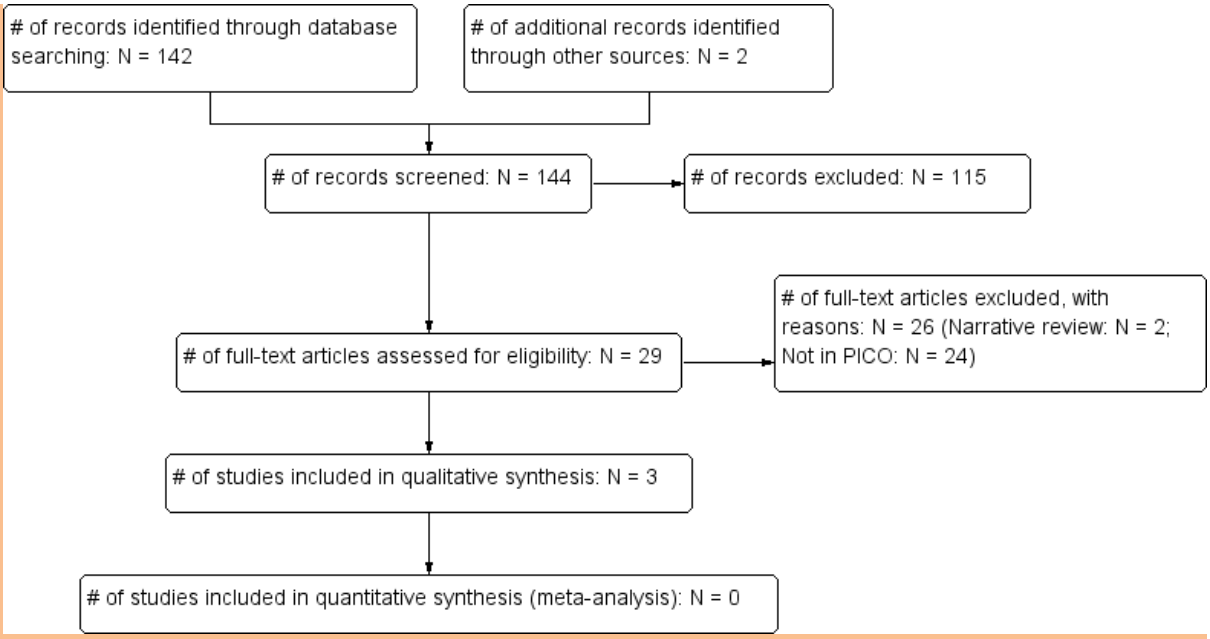
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2012	501	66	09/01/2013
Premedline	All-2012	66	5	09/01/2013
Embase	All-2012	2129	76	15/01/2013
Cochrane Library	All-2012	201	3	16/01/2013
Psychinfo	All-2012	4	1	09/01/2013
Web of Science (SCI & SSCI) and ISI Proceedings	All-2012	569	36	16/01/2013
Biomed Central	All-2012	287	3	21/01/2013

Total References retrieved (after de-duplication): 127

Update Search

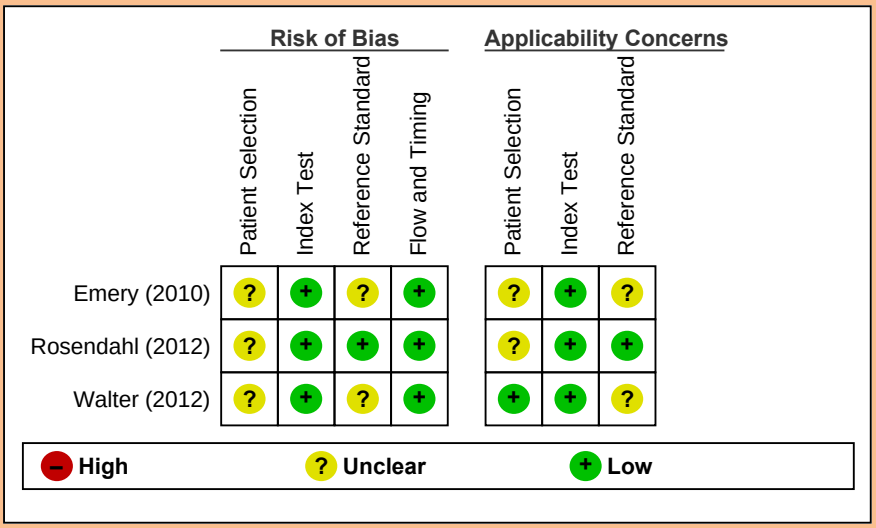
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2013-11/08/2014	17	2	11/08/2014
Premedline	2013-11/08/2014	26	2	11/08/2014
Embase	2013-11/08/2014	101	15	11/08/2014
Cochrane Library	2013-11/08/2014	63	0	11/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	2013-11/08/2014	114	0	11/08/2014

Total References retrieved (after de-duplication): 15



Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main bias risks and applicability concerns that the studies are subject to relate to (1) the patient sampling method not clearly being consecutive or random, (2) the extent to which the study setting matches UK primary care, (3) the quality of the reference standard, which may not always reliably diagnose the symptoms, and (4) the fact that the reference standard did not in all cases match that of the current question, namely histology.



Study results

Table 1: Basal cell carcinoma: Study results

Study	Symptom(s)	Patient group	Positive predictive value % (95% CI) Prevalence

Emery (2010) Lesion, not patient,-based analysis	Pigmented lesion	All included patients	1.82 (1.2-2.8) 22/1211
		England sample	0/630 (0-0.8)
		Australia sample	3.79 (2.4-5.8) 22/581
Walter (2012) Lesion, not patient,-based analysis	Suspicious pigmented lesions	All included patients	0.64 (0.3-1.2) 10/1573
Rosendahl (2010) Lesion, not patient,-based analysis	Non-pigmented raised lesion	All included patients	27.18 (21.3-33.9) 56/206

Evidence statement(s):

Pigmented skin lesions (2 studies, N = 2784 *lesions*) presenting in a primary care setting are associated with positive predictive value of 0.64-1.82% for basal cell carcinoma. The studies were associated with 3-4 bias and applicability concerns (see also Table 1).

Non-pigmented skin lesions (1 study, N = 206 *lesions*) presenting in a primary care setting are associated with a positive predictive value of 27.18% for basal cell carcinoma. The study was associated with 2 bias and applicability concerns (see also Table 1).

Evidence tables

Emery (2010)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective series of pigmented lesions recruited from England (6 general practices covering urban, suburban and rural areas with a registered population of 52913) and Australia (3 primary care skin cancer clinics operated by GPs from a metropolitan area)
Was a consecutive or random sample of patients enrolled?	**Unclear**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Patient characteristics and setting	England: N = 389 patients, mean age = 44.9 years, 68.6% females with, interpretable images from N = 630 lesions. 0/630 lesions were squamous cell carcinoma, 0/630 lesions were basal cell carcinoma, 5/630 lesions were melanoma, and 0/630 lesions were lentigo maligna (melanoma). Australia: N = 469 patients, mean age = 50 years, 48% females, with interpretable images from N = 581 lesions. 0/581 lesions were squamous cell carcinoma, 22/581 lesions were basal cell carcinoma, 7/581 lesions were melanoma, and 4/581 lesions were lentigo maligna (melanoma). Inclusion criteria:

	England: Patients aged > 18 years were recruited into the study by their GP if they presented with concerns about a pigmented skin lesion between January 2005 and January 2006. Australia: Patients aged > 18 years were recruited into the study by their GP if they presented with concerns about a pigmented skin lesion between April 2008 and January 2009. Additional lesions were also included when a pigmented skin lesion was identified as potentially suspicious during their clinical examination Exclusion criteria: None reported. Clinical setting: Primary care, UK, and primary care skin cancer practice, Queensland Australia.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Pigmented skin lesions that concerned patients, which were evaluated using macroscopic clinical photographs, dermoscopic images and SIAscan.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Histopathology or in-person clinical review of the lesion by one expert, including the 7-point melanoma checklist and digital dermoscopy or clinical diagnosis made on the basis of the 7-point melanoma checklist, photographic and dermoscopy images
Is the reference standard likely to correctly classify the target condition?	**Unclear**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Unclear concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients are accounted for in the results
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	Analysis was on a per lesion basis rather than a per patient basis

1 **Rosendahl (2012)**

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective unselected consecutive series of raised non-pigmented lesions
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Unclear**
Could the selection of patients have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 186 patients, mean (SD) age = 65 (13) years, 32.8% females with N = 206 lesions. 32/206 lesions were squamous cell carcinoma (SCC), 29/206 lesions were keratoacanthoma (SCC), 24/206 lesions were Bowen disease (SCC), and 56/ 206 lesions were basal cell carcinoma. Inclusion criteria: Patients presenting with non-pigmented raised lesions treated from March 1 through December 31 2011. All the lesions were excised or biopsied. It is unclear if there were any patients presenting with non-pigmented raised lesions not biopsied/excised who were not included. Exclusion criteria: None reported. Clinical setting: Private primary care skin cancer practice, Queensland Australia.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Non-pigmented raised skin lesions (not further defined, but see subgroup analyses) evaluated using dermoscopic images
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Histopathology
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients are accounted for in the results

Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	Analysis was on a per lesion basis rather than a per patient basis; some patients may have had more than one lesion diagnosed as skin cancer though it is not possible to ascertain the actual numbers from the data provided.

1 **Walter (2012)**

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective series of suspicious pigmented lesions
Was a consecutive or random sample of patients enrolled?	**Unclear**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Unclear**
Could the selection of patients have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 1293 patients, mean age (SD) = 44.6 (16.8) years; 465 males / 828 females with N = 1573 lesions, of which 1 was squamous cell carcinoma, 10 basal cell carcinomas, and 36 melanomas. Inclusion criteria: Patients aged ≥ 18 years presenting to one of the 15 participating general practices with a suspicious (any lesion presented buy a patient, or opportunistically seen by a family doctor or practice nurse, that could not immediately be diagnosed as benign and about which the patient could not be reassured) pigmented lesion from March 2008 to May 2010. Exclusion criteria: Patients who were unable to give informed consent or were considere3d inappropriate to include by their family doctor. Clinical setting: UK primary care.
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	Suspicious (any lesion presented buy a patient, or opportunistically seen by a family doctor or practice nurse, that could not immediately be diagnosed as benign and about which the patient could not be reassured) pigmented lesion
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Expert opinion by a histologist or dermatologist or review by two other dermatology experts of the recorded clinical history and examination, a digital photograph, and MoleMate images where available with or without

	follow up 3-6 months later.
Is the reference standard likely to correctly classify the target condition?	**Unclear**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Unclear concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients are accounted for in the results
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes Tests: No**
Could the patient flow have introduced bias?	**Low risk**
NOTES	Analysis was on a per lesion basis rather than a per patient basis.

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Reason Single Case

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Reason Not relevant to PICO

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Reason Narrative Review

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Reason Not relevant to PICO

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Reason Not in PICO

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Reason Single Case

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Reason Not in PICO

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Reason Not in PICO

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Reason Single Case

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Reason Not relevant to PICO

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Reason Narrative Review
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Reason Narrative Review
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Reason Narrative review
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Reason Narrative Review
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Reason Not in PICO
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Reason Narrative Review
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Reason Not relevant to PICO
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Reason Not relevant to PICO
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Reason Single Case

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Reason Not relevant to PICO

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Reason Not in PICO

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Reason Population not relevant to PICO

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Reason Not relevant to PICO

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Reason Not relevant to PICO

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Reason Not relevant to PICO

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Reason Not in PICO

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Reason Not in PICO

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Reason Population not relevant to PICO

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Reason Narrative Review

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Reason Not relevant to PICO

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Reason Not relevant to PICO

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Reason Narrative Review

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Reason Not relevant to PICO

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Reason Not relevant to PICO

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Reason Not in PICO

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Reason Narrative review

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Reason Not relevant to PICO

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Reason Setting not relevant to PICO

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Reason Not in PICO

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Reason Not in PICO (only excised lesions, not examined lesions)

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Reason Not relevant to PICO

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Reason Not in PICO

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Reason Narrative Review

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Reason Narrative Review

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Reason Not in PICO

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Reason Awaiting arrival of paper

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Reason Health Economics

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Reason Narrative Review

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Reason Not relevant to PICO

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Reason Not in PICO

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Reason Not in PICO

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Reason Not in PICO

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Reason Not in PICO

Steel, B. J. (2014) - Skin cancer - an overview for dentists. - *British Dental Journal,* 216: 575-581.
Reason Narrative review

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Reason Outcomes not relevant to PICO

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Reason Narrative Review

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Reason Narrative Review

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Reason Narrative Review

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Reason N=2

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Reason Not relevant to PICO

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Reason Not in PICO

Tate, B. Checking pigmented skin lesions. Medicine Today 8[3], 38-46. 2007. Australia.
Reason Narrative Review

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Reason Population not relevant to PICO

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Reason Not in PICO

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Reason Outcomes not relevant to PICO

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Reason Narrative review

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Reason Not in PICO

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Reason Narrative Review
Twist, M. Rate of incomplete excision of basal cell carcinomas by General Practitioners with Special Interest. British Journal of Dermatology 161[1], 187. 2009.
Reason Not relevant to PICO
Ubriani, R. Grossman. Facial Papules as a Marker of Internal Malignancy. Medical Clinics of North America 93[6], 1305-1331. 2009. United States.
Reason Narrative Review
Uslu, M. Karaman. A case of nevoid basal cell carcinoma syndrome. Turkderm Deri Hastaliklari ve Frengi Arsivi 40[4], 136-138. 2006. Turkey.
Reason Single Case
van Rijsingen, M. C., Van, B. B., Van Der Wilt, G. J., Lagro-Janssen, A. L. & Gerritsen, M. J. (2014) - The current and future role of general practitioners in skin cancer care: an assessment of 268 general practitioners. - *British Journal of Dermatology,* 170: 1366-1368.
Reason Not in PICO
Van Rijsingen, M. C. J., Hanssen, S. C. A., Groenewoud, J. M. M., Van Der Wilt, G. J. & Gerritsen, M.-J. (2014) Referrals by general practitioners for suspicious skin lesions: The urgency of training. *Acta Dermato-Venereologica,* 94: 138-141.
Reason Not in PICO
Vermaak, P. V. & Manushakian, J. (2013) Rapidly enlarging skin lesion on the lip. *BMJ Case Reports,* 2013, 2013.
Reason Not in PICO
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Reason Setting not relevant to PICO
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Reason Not relevant to PICO
Warshaw, E. M., Lederle, F. A., Grill, J. P., Gravely, A. A., Bangerter, A. K., Fortier, L. A., Bohjanen, K. A., Chen, K., Lee, P. K., Rabinovitz, H. S., Johr, R. H., Kaye, V. N., Bowers, S., Wenner, R., Askari, S. K., Kedrowski, D. A., Nelson, D. B., Warshaw, Erin M., Lederle, Frank A., Grill, Joseph P., Gravely, Amy A., Bangerter, Ann K., Fortier, Lawrence A., Bohjanen, Kimberly A., Chen, Karen, Lee, Peter K., Rabinovitz, Harold S., Johr, Robert H., Kaye, Valda N., Bowers, Sacharitha, Wenner, Rachel, Askari, Sharone K., Kedrowski, Deborah A., and Nelson, David B. Accuracy of teledermatology for pigmented neoplasms.[Erratum appears in J Am Acad Dermatol. 2010 Feb;62(2):319]. Journal of the American Academy of Dermatology 61[5], 753-765. 2009. United States.
Reason Not relevant to PICO
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Reason Narrative Review
Westbrook, R. H. G. Diagnostic accuracy for skin cancer: Comparison of general practitioner with dermatologist and dermatopathologist [1]. Journal of Dermatological Treatment 17[1], 57-58. 2006. United Kingdom.
Reason Narrative Review
White, G. M., Zhou, H. C. & Burchette, R. J. (2013) Biopsy followed by immediate curettage and electrodesiccation of suspected basal cell carcinomas at the first visit. *JAMA Dermatology,*

149: 980-981.
Reason Not in PICO
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Reason Not relevant to PICO
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Reason Narrative Review
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Reason Not relevant to PICO
Wolberink, E. A. W., Pasch, M. C., Zeiler, M., Van Erp, P. E. J. & Gerritsen, M. J. P. (2013) High discordance between punch biopsy and excision in establishing basal cell carcinoma subtype: Analysis of 500 cases. *Journal of the European Academy of Dermatology and Venereology,* 27: 985-989.
Reason Not in PICO
Woolley, S. D. & Hughes, C. (2013) A young military pilot presents with a periocular Basal Cell Carcinoma: A case report. *Travel Medicine and Infectious Disease,* 11: 435-437.
Reason Not in PICO
Wray, E. V., Brant, B., Hussain, F. & Muller, F. M. (2013) A new model of teledermoscopy combining service and education. *British Journal of Dermatology,* 169: 139.
Reason Not in PICO
Youl, P. H., Janda, M., Aitken, J. F., Del Mar, C. B., Whiteman, D. C., Baade, P. D., Youl, P. H., Janda, M., Aitken, J. F., Del Mar, C. B., Whiteman, D. C. & Baade, P. D. (2011) Body-site distribution of skin cancer, pre-malignant and common benign pigmented lesions excised in general practice. *British Journal of Dermatology,* 165: 35-43.
Reason Same data as Youl (20067), which is not in PICO as results only reported for excised lesions (N = 11116, GPs and skin cancer clinic doctors), not examined lesions (N = 28755, GPs and skin cancer clinic doctors).
Youl, P.H. et. Al. (2007) Diagnosing skin cancer in primary care: how do mainstream general practioners compare with primary care skin cancer clinic doctors? *Medical Journal of Australia*187;215-220
Reason Not in PICO as results only reported for excised lesions (N = 11116, GPs and skin cancer clinic doctors), not examined lesions (N = 28755, GPs and skin cancer clinic doctors).
Zalaudek, I., Kreusch, J., Giacomel, J., Ferrara, G., Catricala, C., and Argenziano, G. How to diagnose nonpigmented skin tumors: A review of vascular structures seen with dermoscopy Part II. Nonmelanocytic skin tumors. Journal of the American Academy of Dermatology 63[3], 377-386. 2010.
Reason Narrative Review
Zucker, J. L. The eyelids: Some common disorders seen in everyday practice. Geriatrics 64[4], 14-19+28. 2009. United States.
Reason Narrative Review

Review question:
Which investigations of symptoms of suspected basal cell carcinoma should be done with clinical responsibility retained by primary care?

Results

Literature search

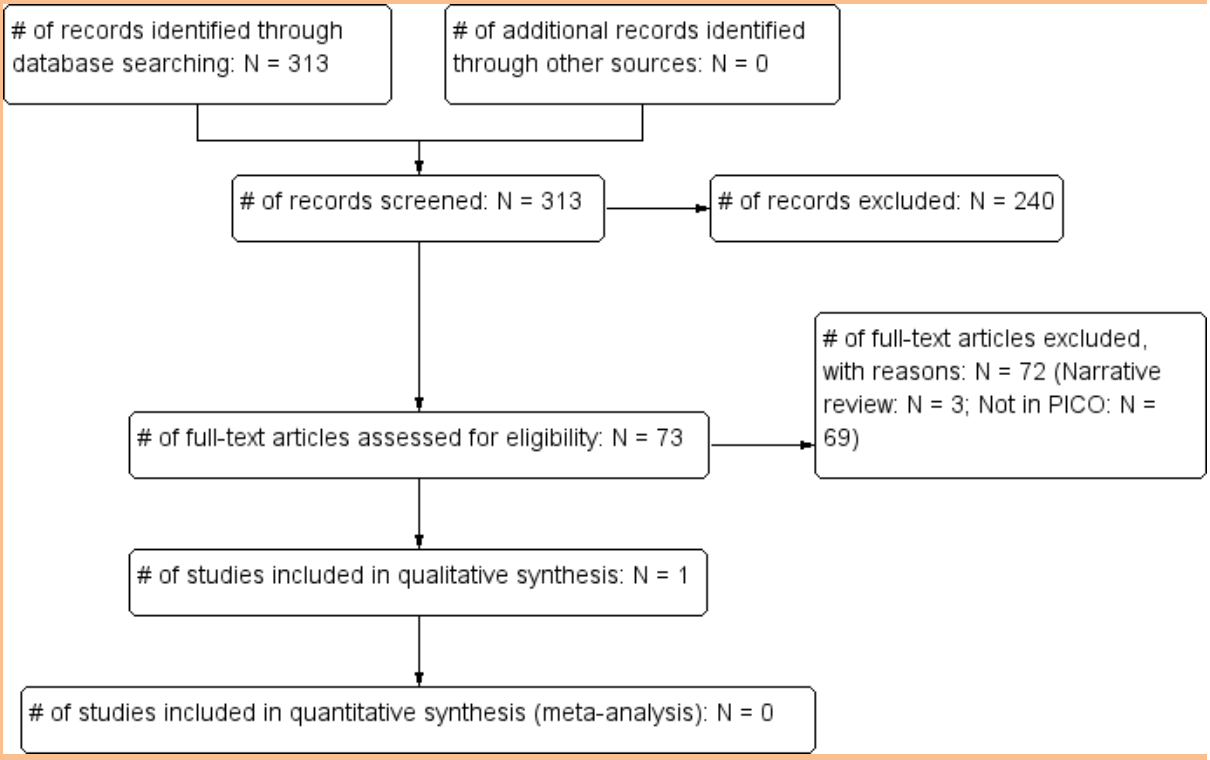
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-2013	2206	141	07/02/2013
Premedline	1980-2013	85	9	07/02/2013
Embase	1980-2013	2263	146	08/02/2013
Cochrane Library	1980-2013	37	1	07/02/2013
Psychinfo	1980-2013	3	0	07/02/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2013	309	63	07/02/2013
Biomed Central	1980-2013	1026	4	07/02/2013

Total number of studies identified after de-duplication: 290

Update Search

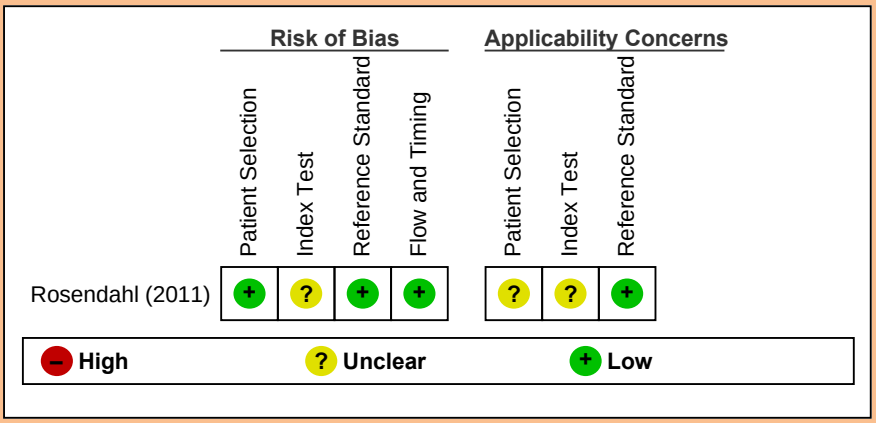
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2013-11/08/2014	87	7	11/08/2014
Premedline	2013-11/08/2014	123	6	11/08/2014
Embase	2013-11/08/2014	181	16	11/08/2014
Cochrane Library	2013-11/08/2014	55	0	11/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	2013-11/08/2014	53	2	11/08/2014

Total References retrieved (after de-duplication): 23



Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issues to note are that the study population may not be directly representative of an unselected symptomatic population of patients presenting to the UK-based GP, that the index test does not specify the criteria for malignancy which may limit its external validity, and that the results presented are based on a best case scenario, and are therefore likely to be inflated, and only available for skin malignancy as a whole and not for basal cell carcinoma separately.



Study results

Table 1: Basal cell carcinoma: Study results

Study	Intervention	Prevalence	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	False negativity rate
Rosendahl (2011)	Clinical images and dermatoscopy	138 malignacies/463 lesions	82.6% (NR)	80% (NR)	NR (NR)	17.4% (NR)

NR = not reported

No evidence was identified pertaining to the diagnostic accuracy of excision biopsy of the lesion in patients with suspected basal cell cancer where the clinical responsibility was retained by primary care.

Evidence statement(s):

Dermatoscopy and clinical images (1 study, N = 463 lesions/389 patients) performed in symptomatic patients presenting in a primary care setting is associated with a best-case sensitivity of 82.6%, specificity of 80%, and false negativity rate of 17.4% for basal cell carcinoma. The study was associated with 1 bias and 2 applicability concerns (see also Table 1).

Evidence tables

Rosendahl (2011)

PATIENT SELECTION

A. risk of bias	
Patient sampling	Consecutive series of lesions submitted for histology from the primary care skin cancer clinic of one of the authors.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Probably**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 463 pigmented lesions from 389 patients, mean (SD) age = 57 (17) years, 32.6% females. Lesion location: Trunk: N = 241; extremities: N = 128; head and face: N = 82; palms and soles: N = 10. Histopathologically, 246 pigmented lesions turned out to be melanocytic and 217 were of non-melanocytic origin. Final diagnoses: Malignant lesions: Basal cell carcinoma: N = 72; squamous cell carcinoma: N = 37; melanoma: N = 29. Benign lesions: Melanocytic nevi: N = 217; seborrheic keratosis: N = 43; solar lentigo: N = 37; lichen planus-like keratosis: N = 21, others: N = 7. Inclusion criteria: All pigmented lesions biopsied or excised during a 30-month period. *Patients included are only those who received resection. This changes the spectrum of disease as it excludes patients with lesions that were not considered concerning enough to warrant resection.* Exclusion criteria: Poor image quality (N = 3). Clinical setting: Primary care skin cancer practice in Queensland, Australia
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	For each lesion: A triplet of high-resolution digital images consisting of two clinical images (overview and close-up) followed by one dermatoscopic image. The clinical images were taken with Canon EOS digital single lens reflex cameras. The close-up was taken using a macro lens (60-mm f2.8 macro, Canon) with diffuse illumination at a constant reproduction ratio determined by a custom-fabricated spacer. The degree of magnification of the close-up images was similar to that of the dermatoscopy images. Dermatioscopic images were nonpolarising, preferentially using the Dermlite Fluid device (3 Gen, San Juan, Capistrano, Ca); alternatively Dermlite Foto (custom nonpolarised; 3 Gen) and Heine Delta 20 devices (Heines, Optotechnic GmbH< Herrsching, Germany)were used for large and inaccessible lesions, respectively. Dermatoscopic photographs were taken with Canon EOS single lens reflex cameras. Images were presented to the assessors as powerpoint slides. After inspection of the images, the assessor was required to give a diagnosis (criteria not reported, so presumably based on qualitative criteria). Dermatoscopic images were also screened for asymmetry of structure and colour ("chaos") and for clues to malignancy. Asymmetry of colour and structure were defined according to the basic principles of pattern analysis as revised by Kittler (2007, Dermatopathology: Practical & Conceptual, 13:1). Clues to malignancy included: Eccentric structureless zone (any colour except skin colour), gray or blue structures, peripheral black dots or clods, segmental radial lines or pseudopods,

	polymorphous vessels, white lines, thick reticular or branched lines, and parallel lines on ridges (acral lesions). *Not further information regarding the specific cut-off criteria for malignancy reported. The reporting of the results suggests that the test performance is based on best possible scenario.*
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Unclear concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Histopathology
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Yes**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	The results are presented for all malignancies combined. The 2-by-2 table could not be extracted and the results could not be separated into the different malignacies

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Exclusion Reason: Not in PICO

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Exclusion Reason: Not in PICO

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Exclusion Reason: Narrative Review

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Exclusion Reason: Not in PICO

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Exclusion Reason: Not in PICO

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Exclusion Reason: Not in PICO

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Exclusion Reason: Narrative Review

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Exclusion Reason: Not in PICO

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Exclusion Reason: Narrative Review

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HEAD AND NECK CANCERS

LARYNGEAL CANCER

Review question:
What is the risk of laryngeal cancer in patients presenting in primary care with symptom(s)?

Results

Literature search

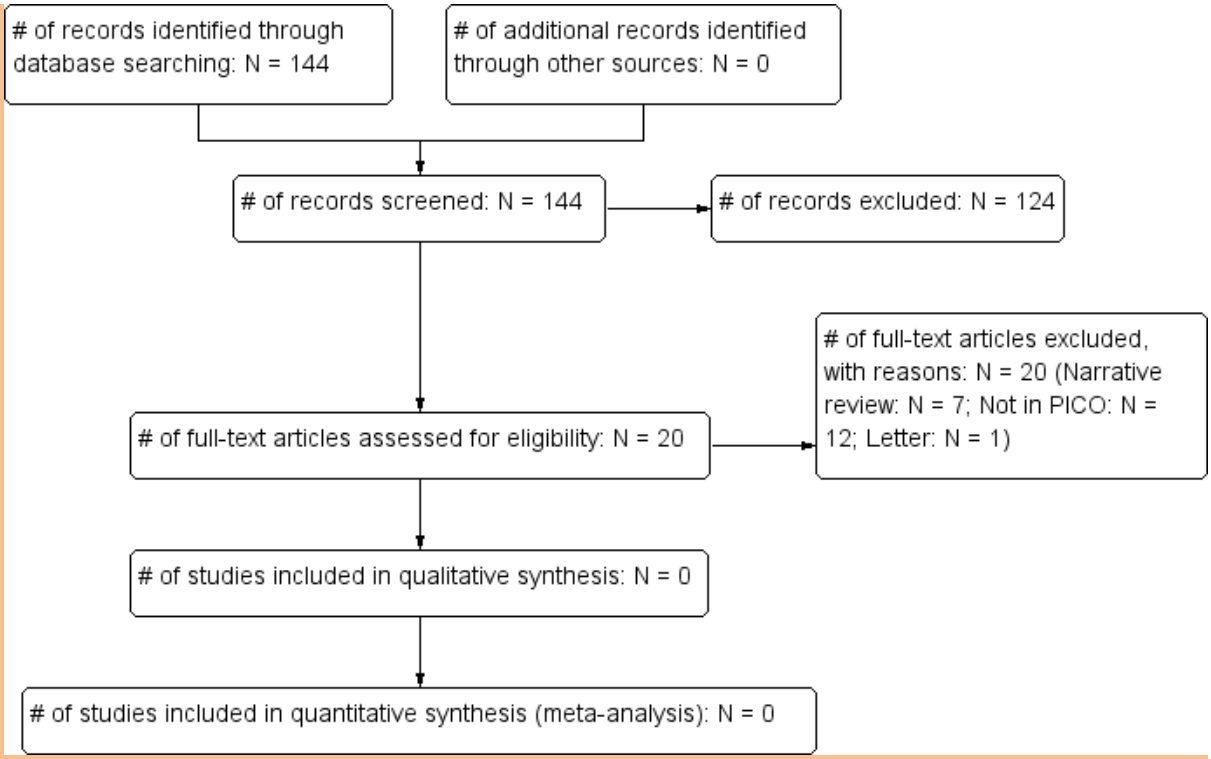
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2012	1085	97	08/10/2012
Premedline	All-2012	19	1	08/10/2012
Embase	All-2012	1352	75	08/10/2012
Cochrane Library	All-2012	89	0	10/10/2012
Psychinfo	All-2012	6	0	08/10/2012
Web of Science (SCI & SSCI) and ISI Proceedings	All-2012	149	10	10/10/2012
Biomed Central	All-2012	200	3	08/10/2012

Total References retrieved (after de-duplication): 137

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	10/2012-26/08/2014	66	3	26/08/2014
Premedline	10/2012-26/08/2014	74	3	26/08/2014
Embase	10/2012-26/08/2014	262	5	26/08/2014
Cochrane Library	10/2012-26/08/2014	45	0	26/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	10/2012-26/08/2014	26	2	26/08/2014

Total References retrieved (after de-duplication): 7



Study results

No evidence was identified.

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None

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Review question:

Which investigations of symptoms of suspected laryngeal cancer should be done with clinical responsibility retained by primary care?

Results

Literature search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-2013	210	47	10/04/2013
Premedline	1980-2013	10	2	10/04/2013
Embase	1980-2013	348	47	10/04/2013
Cochrane Library	1980-2013	2	0	10/04/2013
Psychinfo	1980-2013	0	0	10/04/2013

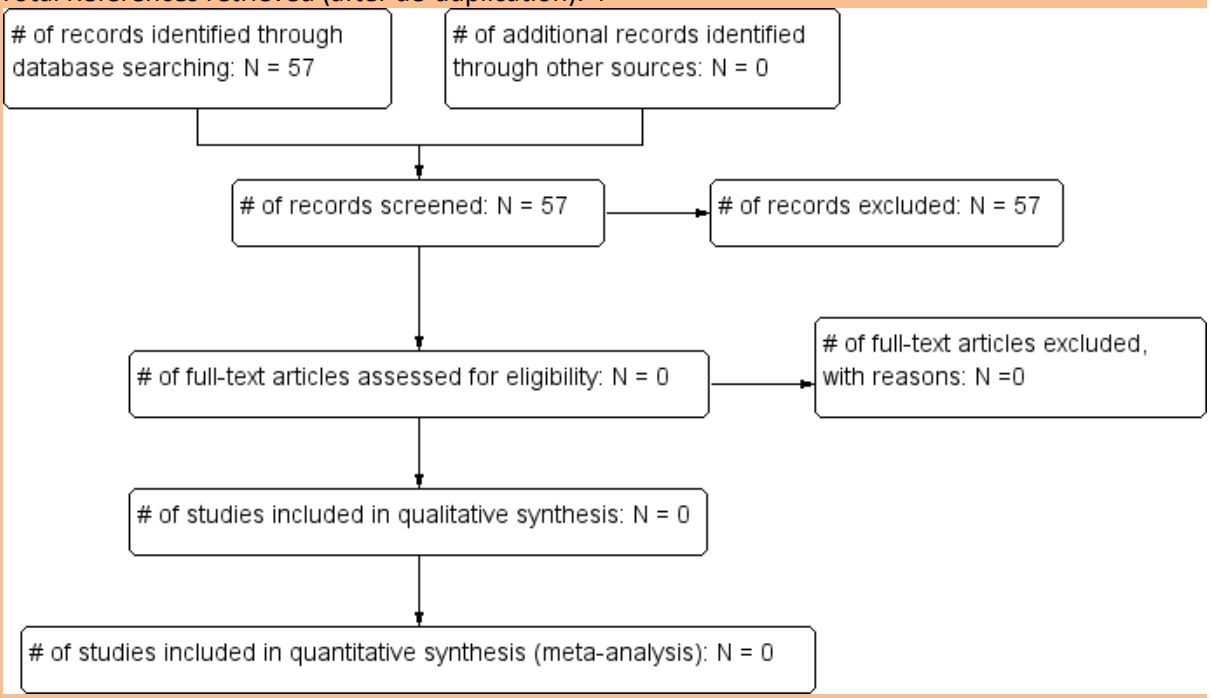
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2013	20	2	10/04/2013

Total References retrieved (after de-duplication): 53

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	4/2013-26/08/2014	3	0	26/08/2014
Premedline	4/2013-26/08/2014	15	2	26/08/2014
Embase	4/2013-26/08/2014	28	3	26/08/2014
Cochrane Library	4/2013-26/08/2014	5	0	26/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	4/2013-26/08/2014	3	0	26/08/2014

Total References retrieved (after de-duplication): 4



Study results

No evidence was identified pertaining to the diagnostic accuracy of chest x-ray in patients with suspected laryngeal cancer where the clinical responsibility was retained by primary care.

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None

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ORAL CANCER

Review question:
What is the risk of oral cancer in patients presenting in primary care with symptom(s)?

Results

Literature search

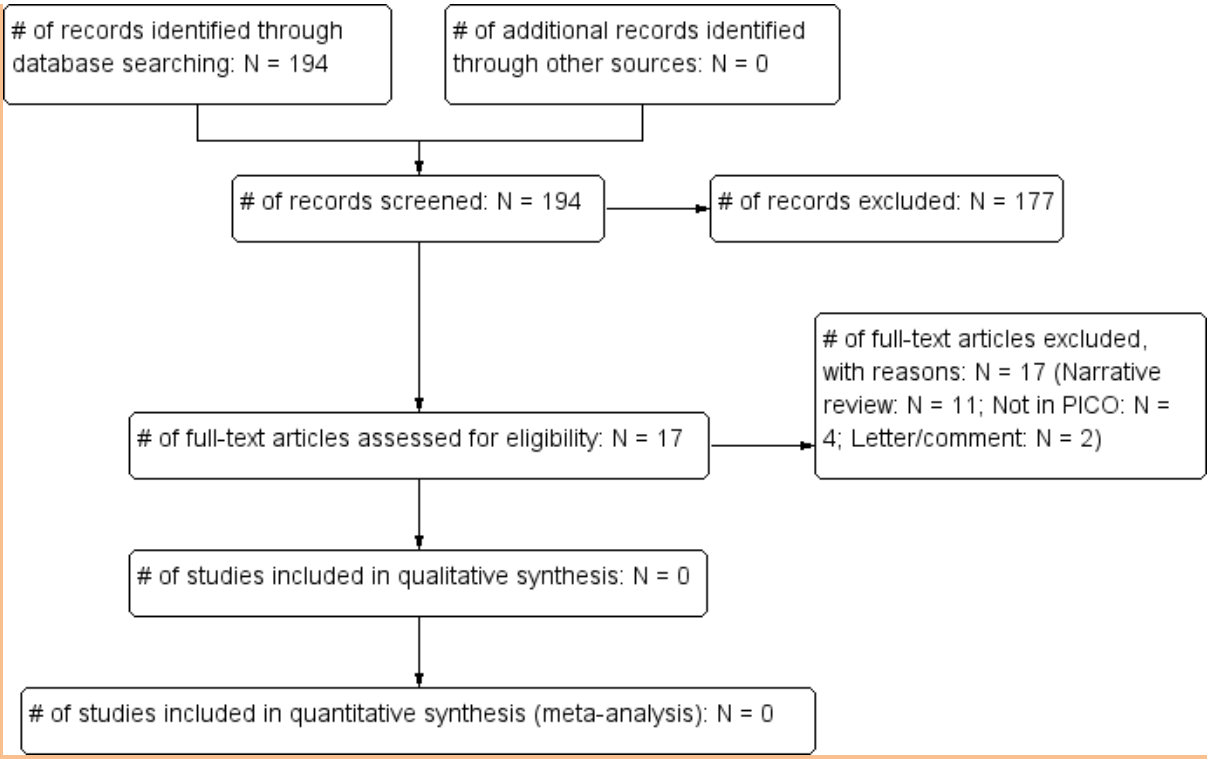
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-2013	766	43	15/04/2013
Premedline	1980-2013	31	9	15/04/2013
Embase	1980-2013	1551	118	16/04/2013
Cochrane Library	1980-2013	137	9	17/04/2013
Psychinfo	1980-2013	4	0	17/04/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2013	594	70	17/04/2013

Total References retrieved (after de-duplication): 184

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	4/2013-20/08/2014	23	4	20/08/2014
Premedline	4/2013-20/08/2014	25	4	20/08/2014
Embase	4/2013-20/08/2014	85	2	20/08/2014
Cochrane Library	4/2013-20/08/2014	279	0	20/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	4/2013-20/08/2014	57	1	20/08/2014

Total References retrieved (after de-duplication): 10



Study results

No evidence was identified.

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None

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Review question:
Which investigations of symptoms of suspected oral cancer should be done with clinical responsibility retained by primary care?

Results

Literature search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-5/2013	499	116	09/05/2013
Premedline	1980-5/2013	47	20	09/05/2013
Embase	1980-5/2013	937	93	09/05/2013
Cochrane Library	1980-5/2013	194	3	09/05/2013
Psychinfo	1980-5/2013	2	0	09/05/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-5/2013	246	5	09/05/2013

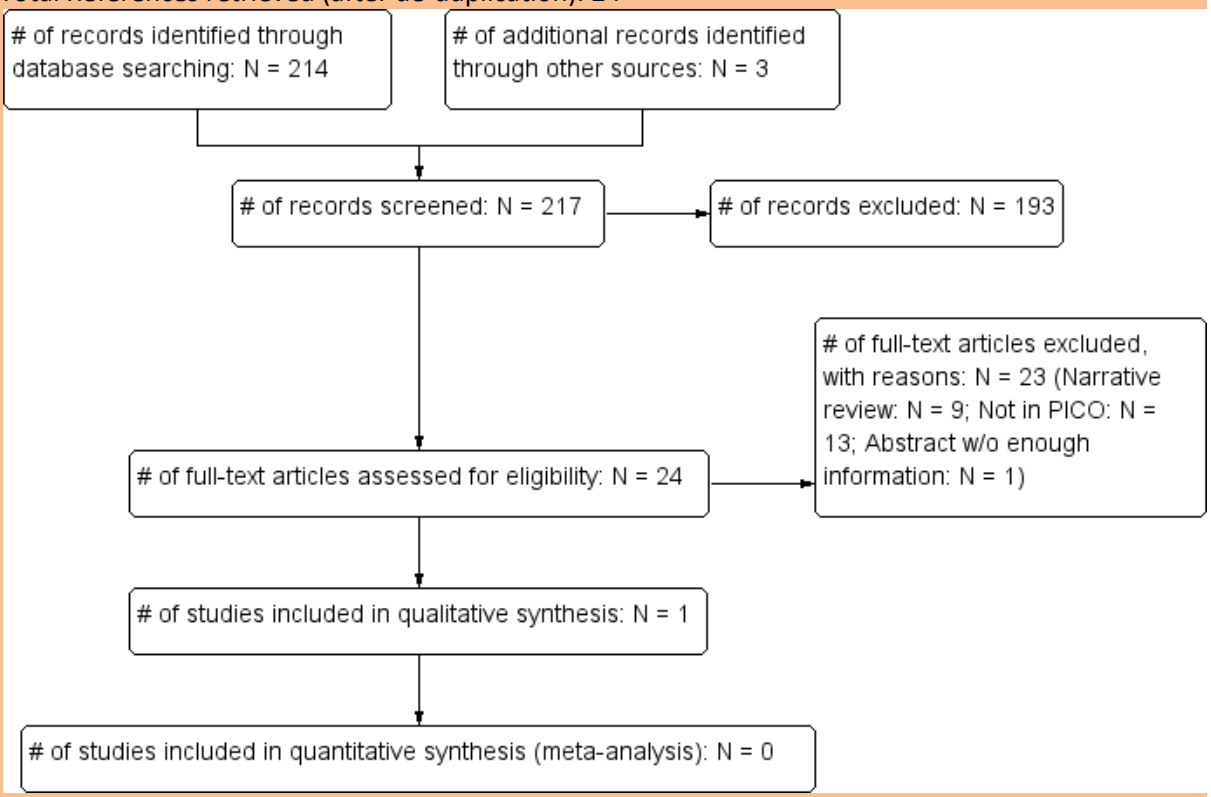
Total References retrieved (after de-duplication): 190

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	5/2013-20/08/2014	23	0	20/08/2014

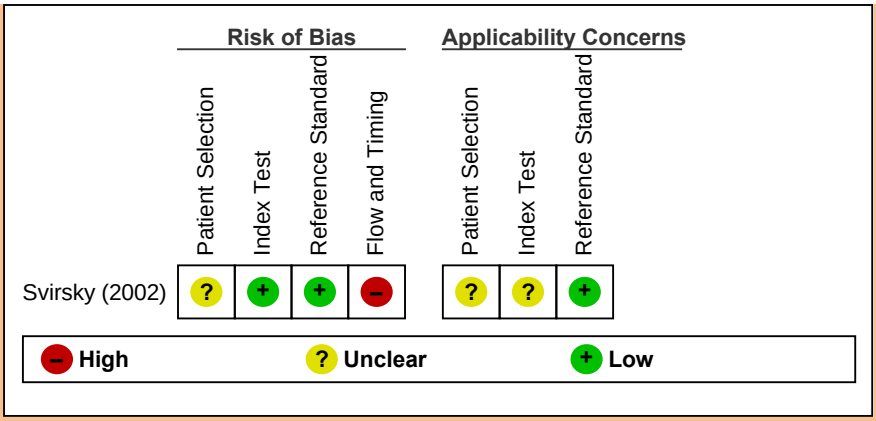
Premedline	5/2013-20/08/2014	75	20	20/08/2014
Embase	5/2013-20/08/2014	58	6	20/08/2014
Cochrane Library	5/2013-20/08/2014	98	0	20/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	5/2013-20/08/2014	11	1	20/08/2014

Total References retrieved (after de-duplication): 24



Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included study in the figure below. The study was associated with a number of bias and validity issues. The following issues compromise the validity and applicability of this study, (1) it is unclear (and probably unlikely) that the patient population consists of consecutive or randomly recruited patients (and may therefore bias the results), (2) the study is conducted in the USA in an unclear setting and it is therefore not clearly transferable to UK-based primary care, and (3) the timspan between the index test and reference standard is unclear in all but one patient and the results are therefore compromised to an unknown extent.



Study results

Table 1: Oral cancer: Study results

Study	Test	Prevalence	Sensitivity (95% CI) %	Specificity (95% CI) %	Other results (95% CI)
Svirsky (2002)	Transepithelial oral brush biopsy with a computer-assisted method of analysis	15/298	93.3 (66-99.7)	19.1 (14.8-24.3)	Malignancy: TP = 14 FN = 1 TN = 54 FP = 229 Positive predictive value = 5.76 (3.3-9.7)% Negative predictive value = 98.18 (89-99.9)% False negativity rate = 6.7%
Svirsky (2002)	Transepithelial oral brush biopsy with a computer-assisted method of analysis	97/298	95.88 (89.2-98.7)%	25.37 (19.6-32.1)%	Malignancy and dysplasia: TP = 93 FN = 4 TN = 51 FP = 150 Positive predictive value = 38.27 (32.2-44.7) % Negative predictive value = 92.73 (81.6-97.6)% False negativity rate = 4.12%

TP = true positives, FP = false positives, TN = true negatives, FN = false negatives.

Evidence statement(s):

Transepithelial oral brush biopsy with a computer-assisted method of analysis (1 study, N = 298) is associated with a sensitivity of 93.3%, a specificity of 19.1%, a positive predictive value of 5.76%, and a false negativity rate of 6.7% for oral cancer. Transepithelial oral brush biopsy with a computer-assisted method of analysis (1 study, N = 298) is associated with a sensitivity of 95.88%, a specificity of 25.37%, a positive predictive value of 38.27%, and a false negativity rate of 4.12% for oral cancer/dysplasia. The study was associated with 4 bias or applicability concerns (see also Table 1).

Evidence tables

Svirsky (2002)

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Retrospective patient series	
Was a consecutive or random sample of patients enrolled?		**Unclear**
Was a case-control design avoided?		**Yes**
Did the study avoid inappropriate exclusions?		**Unclear**
Could the selection of patients have introduced bias?		**Unclear risk**
B. Concerns regarding applicability		
Patient characteristics and setting	N = 298 (146 males/152 females), mean (range) age = 52 (18-89); location of surgical biopsy: Ventral/lateral tongue (N = 90), palate (N = 63), gingival (N = 65, buccal/alveolar mucosa (N = 43), floor of mouth (N = 8), unspecified/other (N = 29). Inclusion criteria: "This study analyzed scalpel biopsies with test requisition forms that either were accompanied by an oral brush biopsy report or contained the findings of an oral brush biopsy report. Only oral pathology laboratories were included." "A total of 298 patients with scalpel biopsies that were accompanied by prior brush biopsy results were identified in the authors' laboratories". Exclusion criteria: None reported. Clinical setting: Unclear, USA	
Are there concerns that the included patients and setting do not match the review question?		**Unclear concern**
INDEX TEST		
A. Risk of bias		
Index test	Transepithelial oral brush biopsy with a computer-assisted method of analysis (OralCDx, CDx Laboratories, NY).	
Were the index test results interpreted without knowledge of the results of the reference standard?		**Yes**
Could the conduct or interpretation of the index test have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		**Unclear concern**
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	Scalpel biopsy	
Is the reference standard likely to correctly classify the target condition?		**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?		**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		**Low concern**

FLOW AND TIMING	
A. risk of bias	
Flow and timing	Data are available for all the included patients, but for least one of the patients the brush and scalpel biopsies were obtained 8 months apart.
Was there an appropriate interval between index test and reference standard?	**Unclear**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**High risk**
NOTES	

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THYROID CANCER

Review question:
What is the risk of thyroid cancer in patients presenting in primary care with symptom(s)?

Results

Literature search

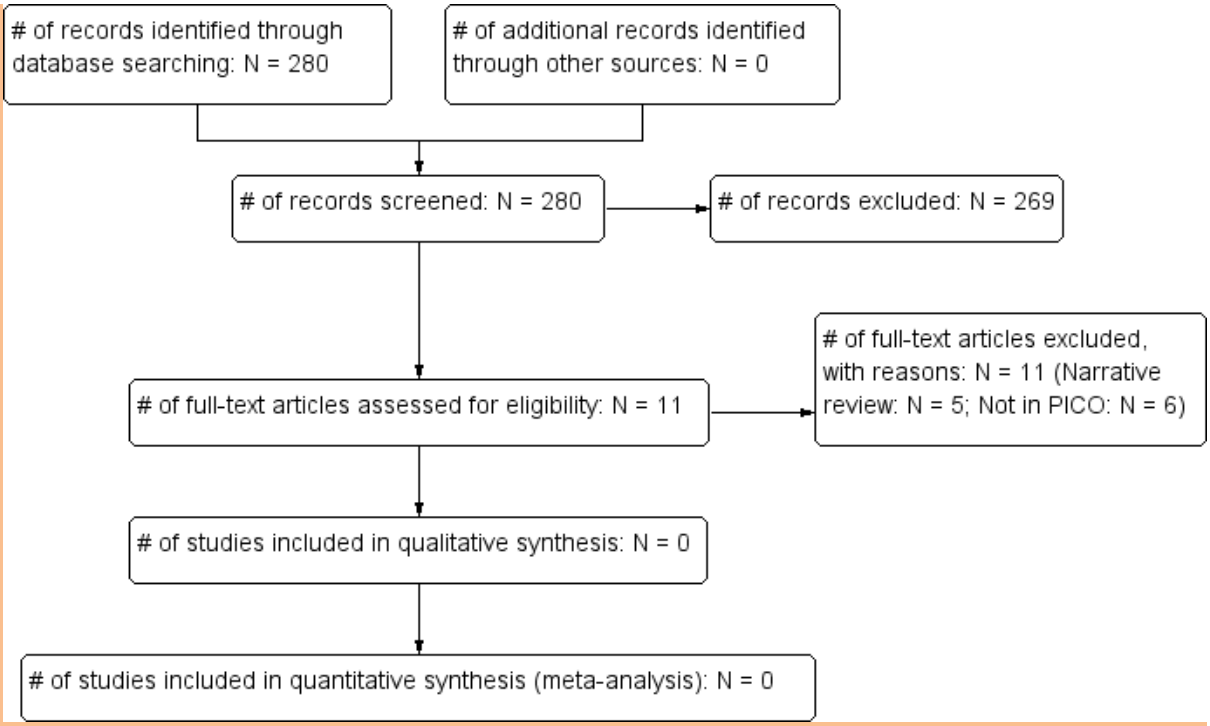
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2012	1325	162	03/10/2012
Premedline	All-2012	44	0	03/10/2012
Embase	All-2012	1696	137	04/10/2012
Cochrane Library	All-2012	147	1	01/10/2012
Psychinfo	All-2012	5	1	03/10/2012
Web of Science (SCI & SSCI) and ISI Proceedings	All-2012	196	32	01/10/2012
Biomed Central	All-2012	460	4	01/10/2012

Total References retrieved (after de-duplication): 274

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	10/2012-27/08/2014	65	4	27/08/2014
Premedline	10/2012-27/08/2014	105	3	27/08/2014
Embase	10/2012-27/08/2014	126	2	27/08/2014
Cochrane Library	10/2012-27/08/2014	89	0	27/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	10/2012-27/08/2014	45	0	27/08/2014

Total References retrieved (after de-duplication): 6



Study results

No evidence was identified.

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Included studies

None

Excluded studies (with excl reason)

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Review question:
Which investigations of symptoms of suspected thyroid cancer should be done with clinical responsibility retained by primary care?

Results

Literature search

Database name	Dates Covered	No of references	No of references	Finish date of

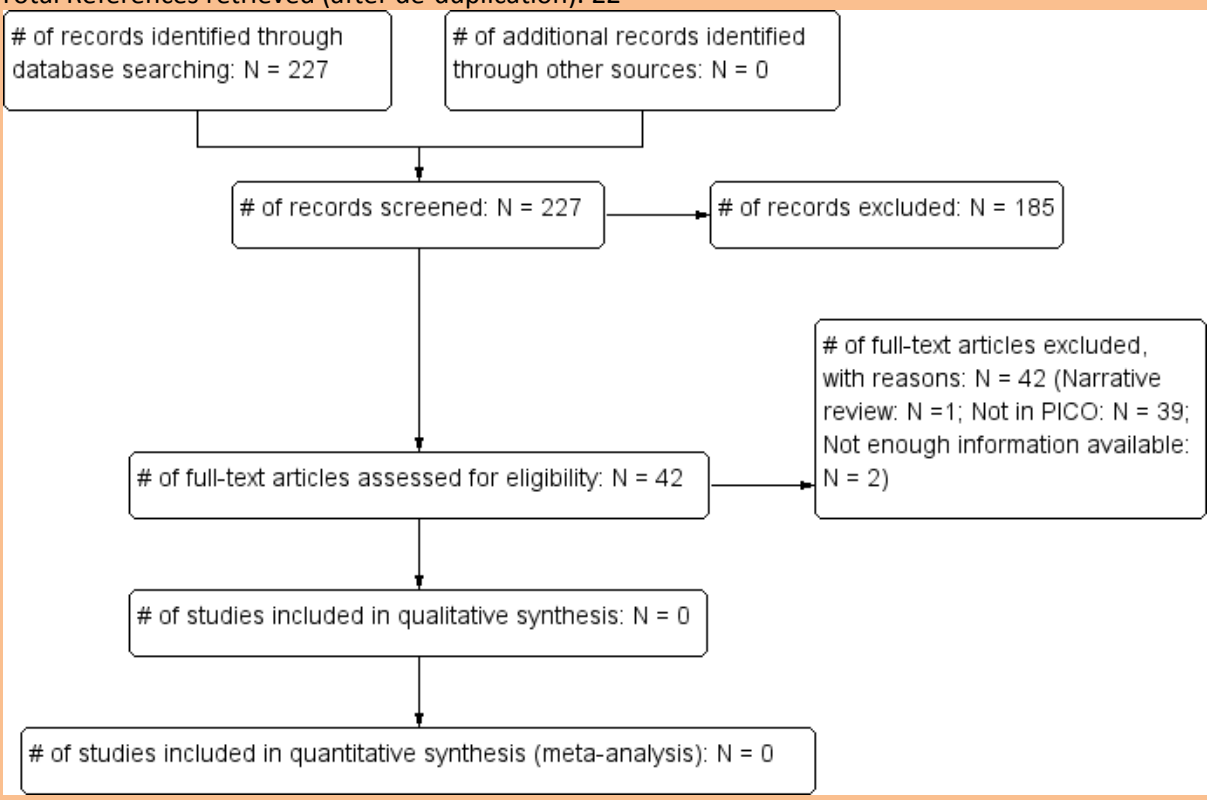
		found	retrieved	search
Medline	1980-2013	545	118	16/05/2013
Premedline	1980-2013	53	9	16/05/2013
Embase	1980-2013	770	150	17/05/2013
Cochrane Library	1980-2013	70	13	20/05/2013
Psychinfo	1980-2013	2	1	16/05/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2013	65	12	20/05/2013

Total References retrieved (after de-duplication): 205

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	5/2013-27/08/2014	16	5	27/08/2014
Premedline	5/2013-27/08/2014	48	10	27/08/2014
Embase	5/2013-27/08/2014	47	8	27/08/2014
Cochrane Library	5/2013-27/08/2014	3	1	27/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	5/2013-27/08/2014	13	1	27/08/2014

Total References retrieved (after de-duplication): 22



Study results

No evidence was identified pertaining to the diagnostic accuracy of ultrasound, thyroid function tests, or fine needle aspiration in patients with suspected thyroid cancer where the clinical responsibility was retained by primary care.

References

Included studies

None

Excluded studies (with excl reason)

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BRAIN AND CENTRAL NERVOUS SYSTEM CANCERS

Review question:
What is the risk of brain and CNS cancer in patients presenting in primary care with symptom(s)?

Results

Literature search

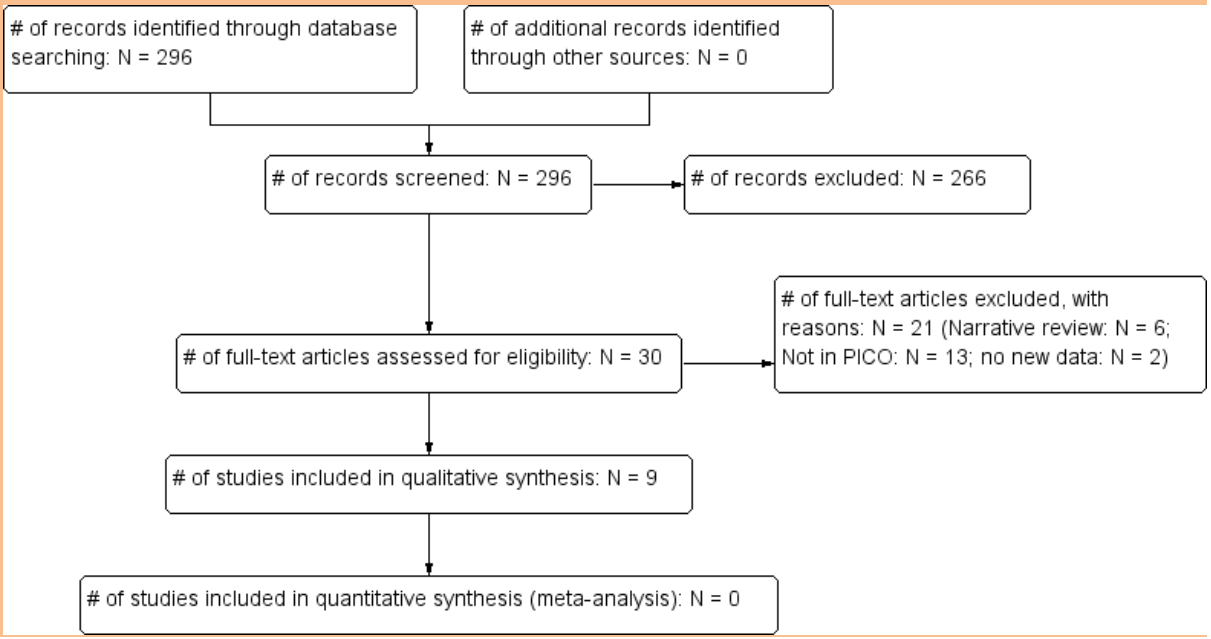
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-2012	1668	138	20/02/2013
Premedline	1980-2012	24	1	20/02/2013
Embase	1980-2012	3631	174	25/02/2013
Cochrane Library	1980-2012	489	1	26/02/2013
Psychinfo	1980-2012	43	6	20/02/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2012	974	33	26/02/2013

Total References retrieved (after de-duplication): 277

Update Search

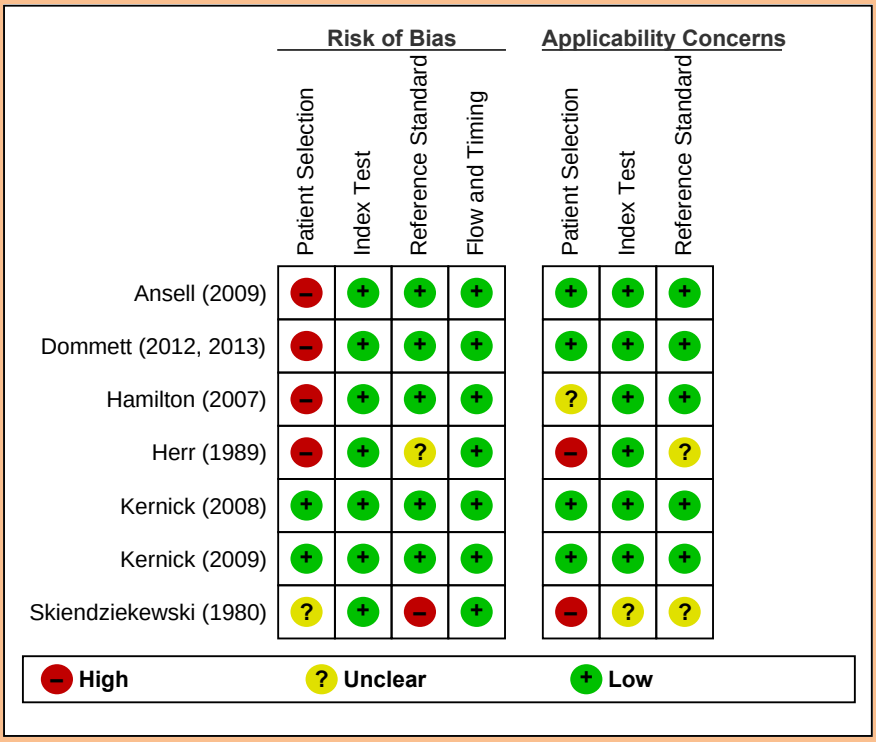
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2013-12/08/2014	53	5	12/08/2014
Premedline	2013-12/08/2014	58	6	12/08/2014
Embase	2013-12/08/2014	304	6	12/08/2014
Cochrane Library	2013-12/08/2014	224	0	12/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	2013-12/08/2014	87	2	12/08/2014

Total References retrieved (after de-duplication): 19



Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included study in the figure below. The main issue to note is that a number of the studies employed case-control (or other non-consecutive, non-randomised) designs which have been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence. Other issues of concern include that some of the studies were conducted abroad and their direct relevance to UK-based primary care may therefore be limited, that the symptoms were underspecified in one study and therefore of limited use for the present purposes, and that some of the reference standards employed were of questionable quality and applicability.



Study results

Table 1: Brain & CNS cancer: Study results for adult populations.

Study	Symptom(s)	Patient group	Positive predictive value % (95% CI) Frequency
Hamilton (2007)	Headache	All included patients	0.09 (0.08-0.1)
Hamilton (2007)	Headache*	Patients 60-69 years	0.12 (NR)
Kernick (2008)	Undifferentiated headache	All included patients	0.15 (0.12-0.19) 97/63921
Kernick (2008)	Undifferentiated headache	Patients < 50 years	0.08 (0.05-0.11) 32/40866
Kernick (2008)	Undifferentiated headache	Patients ≥ 50 years	0.28 (0.22-0.36) 65/23055
Kernick (2008)	Primary headache	All included patients	0.045 (0.023-0.088) 10/21758
Kernick (2008)	Primary headache	Patients < 50 years	0.03 (0.01-0.08)

			5/16282
Kernick (2008)	Primary headache	Patients ≥ 50 years	0.09 (0.03-0.23) 5/5476
Hamilton (2007)	Motor loss	All included patients	0.026 (0.024-0.03)
Hamilton (2007)	New-onset seizure	All included patients	1.2 (1-1.4)
Hamilton (2007)	New-onset seizure*	Patients 60-69 years	2.3 (NR)
Hamilton (2007)	Confusion	All included patients	0.2 (0.16-0.24)
Hamilton (2007)	Memory loss	All included patients	0.036 (0.026-0.052)
Hamilton (2007)	Visual disorder	All included patients	0.035 (0.025-0.051)
Hamilton (2007)	Headache + any of the other symptoms reported by Hamilton (2007)	All included patients	0.39 (0.31-0.48)
Herr (1989)	Dizziness	All included patients	0 (0-3.7) 0/125
Skiendziekewski (1980)	Weakness and/or dizziness	All included patients	0 (0-4.4) 0/106
Hamilton (2007)	Weakness	All included patients	0.14 (0.11-0.18)

* Peak PPVs for these symptoms are in this age group.

Table 2: Brain & CNS cancer: Positive predictive values for any childhood cancer: Patients aged 0-14 years

Study	**Symptom(s)**	**Patient group**	**Positive predictive value % (95% CI) Frequency**
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	All included patients	0.055 (0.047-0.065) Cases: 342/1267 Control: 211/15318
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	All included patients	0.07 (0.064-0.078) Cases: 427/1267 Control: 829/15318
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	All included patients	0.083 (0.067-0.105) Cases: 108/1267 Control: 207/15318
Dommett (2012)	Headache 0-12 months before diagnosis	All included patients	0.064 (0.051-0.082) Cases: 90/1267 Control: 224/15318
Dommett (2013a)	Headache 0-3 months before diagnosis	All included patients	0.06 (0.04-0.08) Cases: 73/1267 Control: 55/15318
Dommett (2013a)	Headache 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.13 (0.08-0.22)
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	All included patients	0.096 (0.074-0.126) Cases: 82/1267 Control: 136/15318
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis	All included patients	0.09 (0.06-0.13) Cases: 69/1267 Control: 33/15318
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis	All included patients	0.2 (0.1-0.39)

	and ≤ 3 consultations		
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	All included patients	0.172 (0.119-0.25) Cases: 56/1267 Control: 52/15318
Dommett (2013a)	Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis	All included patients	0.11 (0.06-0.2) Cases: 42/1267 Control: 16/15318
Dommett (2013a)	Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.3 (0.09-0.99)
Dommett (2012)	Fatigue 0-12 months before diagnosis	All included patients	0.085 (0.06-0.121) Cases: 47/1267 Control: 88/15318
Dommett (2013a)	Fatigue 0-12 months before diagnosis	All included patients	0.07 (0.04-0.12) Cases: 42/1267 Control: 24/15318
Dommett (2013a)	Fatigue 0-12 months before diagnosis and ≥ 3 consultations	All included patients	0.12 (0.06-0.23)
Dommett (2012)	Back pain 0-12 months before diagnosis	All included patients	0.088 (0.06-0.128) Cases: 40/1267 Control: 73/15318
Dommett (2012)	Bruising 0-12 months before diagnosis	All included patients	0.08 (0.054-0.118) Cases: 38/1267 Control: 76/15318
Dommett (2013a)	Bruising 0-3 months before diagnosis	All included patients	0.08 (0.05-0.13) Cases: 33/1267 Control: 18/15318
Dommett (2013a)	Bruising 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.38 (0.09-1.64)
Dommett (2013a)	Pallor 0-3 months before diagnosis	All included patients	0.41 (0.12-1.34) Cases: 33/1267 Control: 18/15318
Dommett (2013a)	Pallor 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.76 (0.1-5.7)
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis	All included patients	0.3 (0.1-0.84) Cases: 28/1267 Control: 4/15318
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.76 (0.1-5.7)
Dommett (2013a)	Abnormal movement 0-3 months before diagnosis	All included patients	0.08 (0.04-0.14) Cases: 49/1267 Control: 26/15318
Dommett (2013a)	Abnormal movement 0-	All included patients	0.15 (0.07-0.32)

	3 months before diagnosis and ≥ 3 consultations		
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included patients	0.06 (0.03-0.1) Cases: 28/1267 Control: 21/15318
Dommett (2013a)	Bleeding 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.11 (0.04-0.31)
Dommett (2013a)	Visual symptoms 0-3 months before diagnosis	All included patients	0.06 (0.03-0.1) Cases: 28/1267 Control: 21/15318
Dommett (2013a)	Visual symptoms 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.23 (0.07-0.77)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included patients	0.04 (0.03-0.06) Cases: 42/1267 Control: 41/15318
Dommett (2013a)	Pain 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.14 (0.07-0.31)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included patients	0.04 (0.03-0.07) Cases: 107/1267 Control: 102/15318
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.13 (0.08-0.19)
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	All included patients	0.266 (0.117-0.609) Cases: 15/1267 Control: 9/15318
Dommett (2013a)	≥ 3 consultations	All included patients	0.02
Dommett (2013a)	Childhood infection 0-3 months before diagnosis	All included patients	Cases: 54/1267 Control: 236/15318
Dommett (2013a)	Upper respiratory tract infection 0-3 months before diagnosis	All included patients	Cases: 143/1267 Control: 942/15318
Dommett (2013a)	Vomiting 0-3 months before diagnosis	All included patients	Cases: 86/1267 Control: 105/15318
Dommett (2013a)	Cough 0-3 months before diagnosis	All included patients	Cases: 77/1267 Control: 654/15318
Dommett (2013a)	Rash 0-3 months before diagnosis	All included patients	Cases: 63/1267 Control: 555/15318
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included patients	Cases: 60/1267 Control: 137/15318
Dommett (2013a)	Abdominal mass 0-3 months before diagnosis	All included patients	Cases: 48/1267 Control: 0/15318
Dommett (2013a)	Fever 0-3 months before diagnosis	All included patients	Cases: 49/1267 Control: 166/15318
Dommett (2013a)	Eye swelling 0-3 months before diagnosis	All included patients	Cases: 39/1267 Control: 238/15318

Dommett (2013a)	Shortness of breath 0-3 months before diagnosis	All included patients	Cases: 35/1267 Control: 221/15318
Dommett (2013a)	Constipation 0-3 months before diagnosis	All included patients	Cases: 26/1267 Control: 61/15318
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	All included patients	2.19 (0.295-17.034) Cases: 14/1267 Control: 1/15318

The positive predictive values are calculated using Bayesian statistics.

Table 3: Brain & CNS cancer: Positive predictive values for central nervous system (CNS) child- or young adulthood cancer tumour

Study	**Symptom(s)**	**Patient group**	**Positive predictive value % (95% CI) Frequency**
Dommett (2013a)	Abnormal movement 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.11 (0.03-0.35)
Dommett (2013a)	Visual symptoms 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.07 (0.02-0.24)
Dommett (2013a)	Vomiting 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.04 (0.02-0.07)
Ansell (2009)	Vomiting and unsteadiness	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.15 (0.01-0.1) 1/654
Ansell (2009)	Vomiting and visual difficulties	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.088 (0.005-0.6) 1/1142
Ansell (2009)	Headache and unsteadiness	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.085 (0.005-0.6) 1/1172
Ansell (2009)	"All other symptom combinations (except vomiting or headache with anorexia) had a predictive probability [of a child having a brain tumour given a visit to a GP with both symptoms] of between 1 in 1500 and 1 in 8000 children". *The predictive probabilities of vomiting or headache with anorexia appeared to be even lower.*		
Dommett (2013a)	Headache 0-3 months before diagnosis	All included CNS childhood cancer	0.03 (0.02-0.06)

		tumour patients and controls aged 0-14 years	
Kernick (2009)	Headache (any type)	All included patients aged 5-17 years	0.03 (0.01-0.05) 13/48575
Kernick (2009)	Primary headache	All included patients aged 5-17 years	0 (0-0.05) 0/9321
Kernick (2009)	Undifferentiated headache	All included patients aged 5-17 years	0.03 (0.02-0.06) 13/38705
Dommett (2013a)	Pain 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.03 (0.01-0.08)
Dommett (2013a)	Seizure 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.02 (0.01-0.06)
Dommett (2013a)	≥ 3 consultations	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013b)	Seizure	All included CNS patients and controls aged 15-24 years	0.0238 (0.0082-0.0695) Cases: 18/154 Controls: 4/1906
Dommett (2013b)	Headache	All included CNS patients and controls aged 15-24 years	0.0145 (0.0077-0.0276) Cases: 33/154 Controls: 12/1906
Dommett (2013b)	Vomiting	All included CNS patients and controls aged 15-24 years	0.0116 (0.0041-0.031) Cases: 11/154 Controls: 5/1906
Dommett (2013b)	Pain	All included CNS patients and controls aged 15-24 years	0.0029 (0.0014-0.006) Cases: 11/154 Controls: 20/1906
Dommett (2013b)	Visual symptoms	All included CNS patients and controls aged 15-24 years	Cases: 8.4% Controls: 0%
Dommett (2013b)	≥ 3 consultations	All included CNS patients and controls aged 15-24 years	0.0023 (0.0019-0.0029) Cases: 73/154 Controls: 165/1906

1 The positive predictive values are calculated using Bayesian statistics.

2

3 **Evidence statement(s):**

The positive predictive values of having a brain tumour in adulthood ranged from 0% (for dizziness and/or weakness) to 2.3% (for new-onset seizure in 60-69 year old patients) for symptomatic patients presenting to primary care (4 studies, N = 106588). The included studies were associated with 0-4 bias/applicability concerns each (see also Table 1).

The positive predictive values of having any childhood cancer ranged from 0.04% (for pain or musculoskeletal symptoms) to 2.19% (for hepatosplenomegaly) for symptomatic patients aged 0-14 years old presenting to primary care (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 2).

The positive predictive values of having central nervous system childhood or young adulthood cancer tumours ranged from < 0.013% (for vomiting or headache with anorexia) to 0.15 (for vomiting in combination with unsteadiness) for patients aged 0-14 years old, from 0% (for primary headache) to 0.03% (for undifferentiated headache) for patients aged 5-17 years, and from 0.0029% (for pain) to 0.0238% (for seizure) for patients aged 15-24 years (3 studies, N = 79910). The evidence quality is somewhat compromised by the case-control design of two of the studies (see also Table 3).

Evidence tables

Ansell (2009)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	National population-based case-control study (United Kingdom Childhood Cancer Study; UKCCS)
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: 195 children; mean (SE) age = 7.31 (0.27) years; 93 males/102 females; astrocytoma: N = 78; medulloblastoma: N = 46; other: N = 71. Controls: 285 children; mean (SE) age = 7.25 (0.22) years; 142 males/143 females; Inclusion criteria: Cases: Children aged 0–14 years newly diagnosed with cancer between 1992-1996 in Great Britain were eligible to take part. Children with brain tumours were recruited from 1992-1994. These data were systematically collected from primary care records by 4 of the 10 UKCCS regions: “GP records were abstracted for 195 of 221 (88%) children with brain tumours and for 286 controls.” Controls: (1-?)2 gender-, month and year of birth-, and region of residence-matched controls were randomly recruited from primary care population

	registers. Exclusion criteria: None listed Clinical setting: Primary care, UK.
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	Relevant signs and symptoms were defined as those that might be suggestive of a brain tumour: Anorexia, abnormal movements, back problems, cognitive impairment, congenital anomalies, drowsiness, emotional problems, focal weakness, growth problems, head tilt, headache, hearing problems, hydrocephalus, incontinence, papilloedema, problem behaviour, seizures, unsteady on feet, visual problems, vomiting, other neurological signs and symptoms not already included.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Cancer diagnosis or not in their General Practice record.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	
1	

1 **Dommett (2012; 2013a,b)**

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Population-based nested case-control study using data from the General Practice Research Database (GPRD)
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: 1267 children; aged 0-4 years: N = 436; aged 5-14 years: N = 831; 703 males/564 females. Cancer type: Leukemia: N = 368; brain: N = 270; lymphoma: N = 142; bone: N = 107; soft tissue sarcoma: N = 91; renal: N = 82; neuroblastoma: N = 75; other ICD codes: N = 132. 1064 teenagers and young adults (TYA): 15-24 years: Gender not reported. Cancer type: Leukemia: N = 143; brain: N = 154; lymphoma: N = 270; bone: N = 96; soft tissue sarcoma: N = 100; other ICD codes: N = 301 (including testis: N = 60; skin: N = 49; ovary: N = 20 and thyroid: N = 17). Controls: 15318 children; aged 0-4 years: N = 4802; aged 5-14 years: N = 10516; 8461 males/6857 females. 13206 TYA. Gender not reported Inclusion criteria: The sample comprised all children and TYU aged 0–24 years, inclusive, drawn from all general practices contributing research-standard data to the GPRD between 1 January 1988 and 31 December 2010. To be included, the practices had to have been contributing research-standard data for a minimum of 1 year before each child's date of cancer diagnosis or the index date (see below) for matched controls. Cases: Patients diagnosed with the following cancers: leukaemia, lymphoma, neuroblastoma, soft tissue sarcoma, hepatic, renal, bone and central nervous system tumours, using pre-defined medical codes used in the GPRD. The date of diagnosis for cases was defined as the date of pathological diagnosis, but if this was unavailable, the date of the first cancer code entered in the GPRD was used. Controls: Up to 13 controls (children with no diagnosis of cancer at any time) were selected per case, using a computer-generated random sequence, matched on age (within 1 year), sex and practice, and had to be currently registered on the date of diagnosis of their matched case (the index date). Exclusion criteria: None listed Clinical setting: Primary care, UK.

Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	The GPRD uses just over 100 000 medical codes to encompass all primary care events, including both symptoms and diagnoses. From this list, libraries of codes were assembled representing individual alert symptoms derived from the NICE referral guidelines for suspected cancer in children. *No more information reported.*
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Cancer diagnosis in the UK's General Practice Research Database.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	This study is published in three papers. There is almost complete overlap between the patients used in Kernick (2009) with the patients aged 5-17 years in this study.

Hamilton (2007)

PATIENT SELECTION	
A. risk of bias	

Patient sampling	Population-based nested case-control study using data from the General Practice Research Database (GPRD)
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: 3505 patients with 2397 *malignant tumours (incl 948 gliomas and 280 astrocytomas, and other rare tumours; the rest were benign)*; aged 18-29 years: N = 159 (malignant tumours N = 134); aged 30-39 years: N = 276 (malignant tumours N = 206); aged 40-49 years: N = 432 (malignant tumours N = 280); aged 50-59 years: N = 675 (malignant tumours N = 471); aged 60-69 years: N = 822 (malignant tumours N = 584); aged 70-79 years: N = 767 (malignant tumours N = 511); aged 80-89 years: N = 339 (malignant tumours N = 191); aged >90 years: N = 35 (malignant tumours N = 20); 1661 males/1844 females. Controls: N = 17173 or 24824 Inclusion criteria: Cases: Patients aged 18 years or over with a brain tumour diagnosed between May 1988 and March 2006, and with at least 2 years of data before the first tumour code (the index date), who had consulted at least once within the 6 months before the index date Controls: 7 randomly selected, practice-, sex- and age (within 1 year)-matched controls were selected per case, who had consulted at least once within the 6 months before the index date. Exclusion criteria: Controls: Prior brain tumour. Clinical setting: Primary care, UK.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	"Libraries of codes for clinical variables previously described with brain tumours were assembled... Occurrences of these variables in the 6 months before the index date in cases and controls were identified. Variables were retained only if they occurred in at least 1% of cases or controls..... Re-consultations with the same symptom were also retained if the subsequent symptom was also present in 1% or more cases or controls. No restriction was placed on reporting of the variable before the 6 month period of study, except for seizures which were only used if the patient had no previous seizure or anticonvulsant therapy code in their records."
Were the index test results interpreted without knowledge	**Yes**

of the results of the reference standard?	
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Brain tumour diagnosis in the UK's General Practice Research Database.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	This study includes a significant minority with benign tumours (see "Patient characteristics and setting" above).

Herr (1989)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective patient series from a North American hospital emergency department
Was a consecutive or random sample of patients enrolled?	**Unclear**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Unclear**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	137 patients *"representing 46% of the logbook entries for dizziness over this period"*; 12 patients were excluded due to missing data leaving 125 patients; 51 males/73 females; mean age (range) = 46.9 (18-82) years.

	Inclusion criteria: "From March 1, 1986, to August 1, 1987, we sought consecutive patients presenting to the Northwestern Memorial Hospital ED with a chief complaint of "dizzy," "lightheaded," "faint," or synonymous phrase. Each was required to have one or more attributes of dizziness as described by Drachman and Hart [ref given] (Figure 1*). Syncope, medical problems, or previous dizziness were not exclusions provided dizziness was among the presenting chief complaints." *A definite rotational sensation; a sensation of impending faint or loss of consciousness; disequilibrium or loss of balance without head sensation; ill-defined "lightheadedness" other than vertigo, syncope, or disequilibrium. Exclusion criteria: None listed Clinical setting: Hospital emergency department, USA.
Are there concerns that the included patients and setting do not match the review question?	**High concern**
INDEX TEST	
A. Risk of bias	
Index test	Chief complaint of "dizzy," "lightheaded," "faint," or synonymous phrase, with one or more of the following attributes of dizziness: A definite rotational sensation; a sensation of impending faint or loss of consciousness; disequilibrium or loss of balance without head sensation; ill-defined "lightheadedness" other than vertigo, syncope, or disequilibrium.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Emergency physicians' diagnosis and minimum 1-4 weeks follow up.
Is the reference standard likely to correctly classify the target condition?	**Unclear**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Unclear concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for.
Was there an appropriate interval between index test and reference standard?	**Yes**

Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	

Kernick (2008)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Cases [patients with a code of headache in their records] from a case-control study using data from the General Practice Research Database (GPRD)
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	85679 patients with a primary or undifferentiated headache: Primary headache: N = 21758, with migraine (N = 15891), tension-type headache (N = 4987), and cluster headache (N = 880); 5795 males/15963 females; median (IQR) age = 38 (29-50) years. Undifferentiated headache: N = 63921; 23200 males/40721 females; median (IQR) age = 41 (30-58) years. Inclusion criteria: Patients were aged 18 years or over, with a description of headache in their records and no other headache classification code in the previous year. Patients were accepted from the inception of the database in January 1987 to June 2005 who had at least 1 year of full data in their records after the index headache consultation. Exclusion criteria: Patients with a secondary headache that had a further descriptor. Clinical setting: Primary care, UK.
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	Index headache codes were categorised into primary headache (migraine, tension-type headache, or cluster headache). Secondary headaches that had a further descriptor were discarded. All other codes were classified as undifferentiated headache.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or	**Low concern**

interpretation differ from the review question?		
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	Headache-related outcome/diagnosis in the UK's General Practice Research Database in the year after the index consultation.	
Is the reference standard likely to correctly classify the target condition?		**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?		**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		**Low concern**
FLOW AND TIMING		
A. risk of bias		
Flow and timing	All patients appear to be accounted for.	
Was there an appropriate interval between index test and reference standard?		**Yes**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**Yes**
Could the patient flow have introduced bias?		**Low risk**
NOTES		

Kernick (2009)

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Cases [patients with a code of headache in their records] from a case-control study using data from the General Practice Research Database (GPRD)	
Was a consecutive or random sample of patients enrolled?		**Yes**
Was a case-control design avoided?		**Yes**
Did the study avoid inappropriate exclusions?		**Yes**
Could the selection of patients have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Patient characteristics and setting	48575 patients with a primary, secondary or undifferentiated headache (21180 males/27395 females; age bands: 5-8 years: N = 3623; 9-12 years: N = 13804; 13-17 years: N = 31148): Primary headache: N = 9321, with migraine (N = 7468), tension-type headache (N = 1565), and cluster headache (N = 288); Secondary headache: N = 549 Undifferentiated headache: N = 38705. Inclusion criteria: Patients were aged 5-17 years, with a description of headache in their records and no other headache classification code in the previous year. Patients were accepted from the inception of the database in January 1987 to June 2005 who had at least 1 year of full data in their	

	records after the index headache consultation. Exclusion criteria: None listed. Clinical setting: Primary care, UK.
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	Index headache codes were categorised into primary headache (migraine, tension-type headache, or cluster headache) or secondary headaches if they had a further descriptor. All other codes were classified as undifferentiated headache.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Headache-related outcome/diagnosis in the UK's General Practice Research Database in the year after the index consultation.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	There is almost complete overlap between the patients used in this study and the patients aged 5-17 years in Dommett (2012, 2013a,b).

Skiendzielewski (1980)

PATIENT SELECTION	

A. risk of bias	
Patient sampling	Retrospective patient series from a North American hospital emergency department
Was a consecutive or random sample of patients enrolled?	**Unclear**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Unclear**
Could the selection of patients have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Patient characteristics and setting	106 patients; ca 35% were aged < 30 years; age range = 7-88 years; 38 males/68 females; N = 10 with weakness only, N = 85 with dizziness, and N = 15 with a combination of weakness and dizziness. Inclusion criteria: "We retrospectively studied the cases of 106 patients who presented to the Geisinger Medical Center Emergency Department with the chief complaints of weakness and/or dizziness during a six-month period. The patients were examined by a number of physicians whose experience varied from that of a first-year resident to a staff emergency physician". Exclusion criteria: Cases with specific muscle weakness, e.g., paralysis of a limb. Clinical setting: Hospital emergency department, USA.
Are there concerns that the included patients and setting do not match the review question?	**High concern**
INDEX TEST	
A. Risk of bias	
Index test	Weakness and/or dizziness. Special attention was given to the presence of true vertigo, current medications, physical findings, abnormal laboratory data, and diagnosis on discharge.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Unclear concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	"Follow-up was obtained either from records of subsequent outpatient visits or, more frequently, from personal telephone conversations." 1-7 months.
Is the reference standard likely to correctly classify the target condition?	**Unclear**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**High risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined	**Unclear concern**

by the reference standard does not match the question?	
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	

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Review question:
Which investigations of symptoms of suspected brain and CNS cancer should be done with clinical responsibility retained by primary care?

Results

Literature search

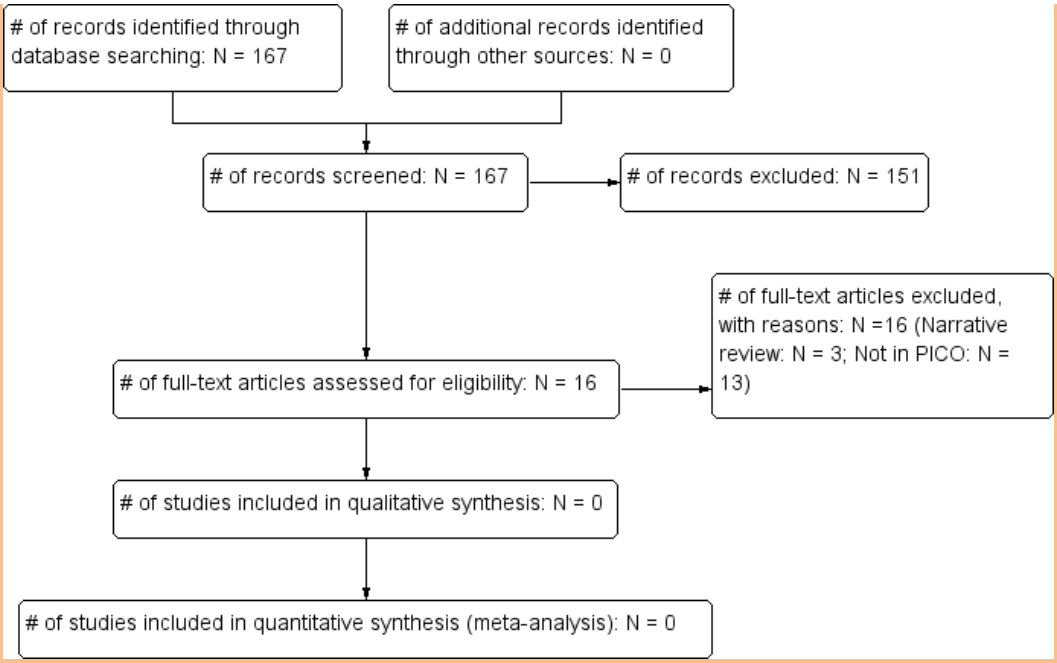
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-6/2013	1173	101	17/06/2013
Premedline	1980-6/2013	112	6	19/06/2013
Embase	1980-6/2013	2171	90	19/06/2013
Cochrane Library	1980-6/2013	209	2	19/06/2013
Psychinfo	1980-6/2013	62	2	17/02/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-6/2013	57	1	19/06/2013

Total References retrieved (after de-duplication): 162

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	6/2013-12/08/2014	40	2	12/08/2014
Premedline	6/2013-12/08/2014	22	1	12/08/2014
Embase	6/2013-12/08/2014	62	6	12/08/2014
Cochrane Library	6/2013-12/08/2014	96	0	12/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	6/2013-12/08/2014	22	0	12/08/2014

Total References retrieved (after de-duplication): 5



Study results

No evidence was identified pertaining to the diagnostic accuracy of CT or MRI scans in patients with suspected brain or CNS cancer where the clinical responsibility was retained by primary care.

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None

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HAEMATOLOGICAL CANCERS

LEUKEMIA

Review question:
What is the risk of leukaemia in adults and children presenting in primary care with symptom(s)?

Results

Literature search

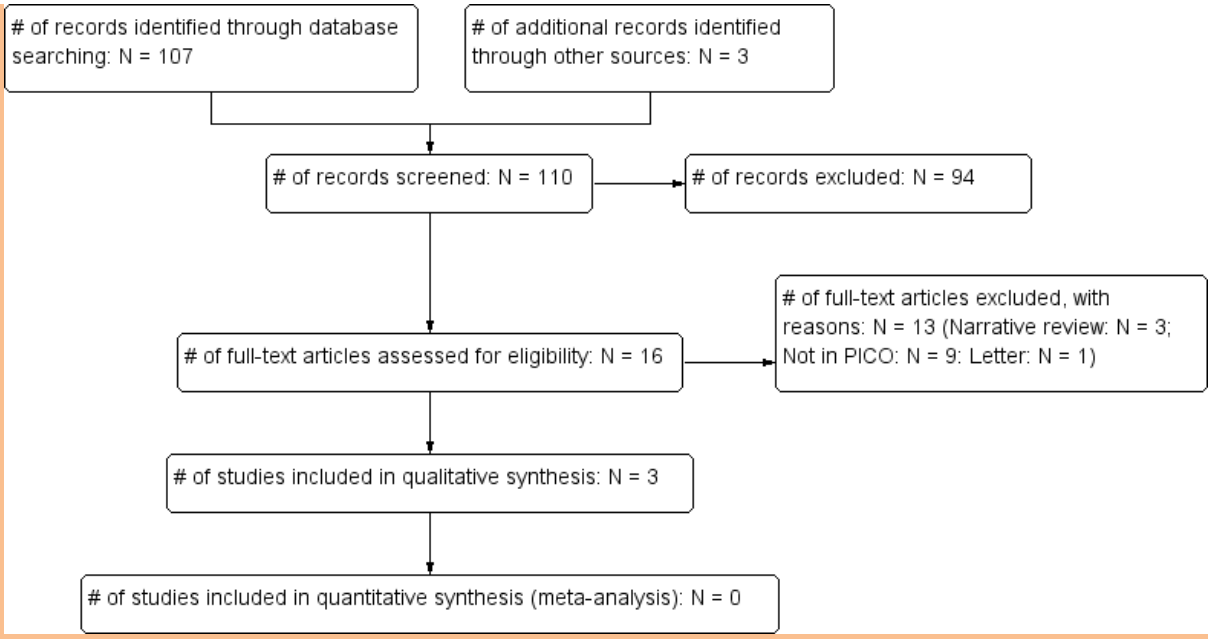
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2012	1689	42	11/03/2013
Premedline	All-2012	33	1	11/03/2013
Embase	All-2012	3598	57	13/03/2013
Cochrane Library	All-2012	427	0	13/03/2013
Psychinfo	All-2012	12	0	11/03/2013
Web of Science (SCI & SSCI) and ISI Proceedings	All-2012	648	10	18/03/2013
Database name	**Dates Covered**	**No of references found**	**No of references retrieved**	**Finish date of search**

Total References retrieved (after de-duplication): 98

Update Search

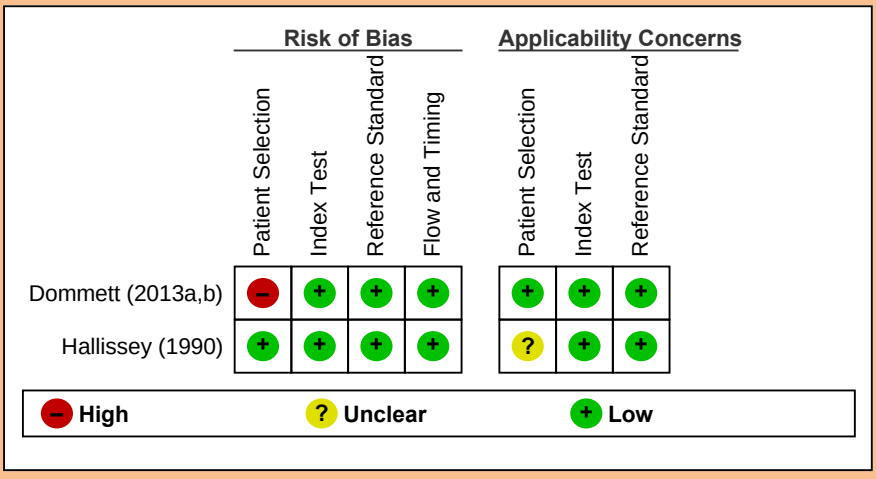
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	3/2013-18/08/2014	30	3	18/08/2014
Premedline	3/2013-18/08/2014	85	7	18/08/2014
Embase	3/2013-18/08/2014	195	4	18/08/2014
Cochrane Library	3/2013-18/08/2014	88	0	18/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	3/2013-18/08/2014	135	3	18/08/2014

Total References retrieved (after de-duplication): 9



Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included studis in the figure below. One main issue to note is that one study employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence. Another potential threat to the applicability of the findings concerns the fact that the second study employed a patient sample which may not be directly applicable to the current question.



Study results

Table 1: Leukaemia: Positive predictive values for leukaemia/lymphoma childhood cancer

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013a)	Bruising 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.53 (0.07-3.91)
Dommett (2013a)	Pallor 0-3 months before	All included	0.43 (0.06-3.15)

	diagnosis	leukemia/lymphoma patients and controls aged 0-14 years	
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.35 (0.05-2.65)
Dommett (2013a)	Fatigue 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.07 (0.03-0.15)
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.06 (0.04-0.11)
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.05 (0.02-0.13)
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.03 (0.01-0.08)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.03 (0.01-0.06)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.02 (0.01-0.03)
Dommett (2013a)	Fever 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0.01-0.01)
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013a)	≥ 3 consultations	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0.01-0.01)

The positive predictive values are calculated using Bayesian statistics.

Table 2: Leukaemia: Positive predictive values for teenage and young adult, and adult leukaemia

Study	**Symptom(s)**	**Patient group**	**Positive predictive value (95% CI)**
Dommett (2013b)	Bruising	All included leukaemia patients and controls aged 15-24 years	0.0117 (0.004-0.0343) Cases: 9/143

			Controls: 5/1799
Dommett (2013b)	Fatigue	All included leukaemia patients and controls aged 15-24 years	0.0121 (0.0052-0.0282) Cases: 15/143 Controls: 8/1799
Dommett (2013b)	Lymphadenopathy	All included leukaemia patients and controls aged 15-24 years	0.0151 (0.004-0.0578) Cases: 7/143 Controls: 3/1799
Dommett (2013b)	≥ 3 consultations	All included leukaemia patients and controls aged 15-24 years	0.0038 (0.003-0.0048) Cases: 74/143 Controls: 125/1799
Hallissey (1990)	Dyspepsia	All patients	0.04 (0.002-0.3) 1/2585

The positive predictive values are calculated using Bayesian statistics for Dommett (2013b).

Evidence statement(s):

The positive predictive values of having leukaemia/lymphoma childhood cancer ranged from 0.01% (for fever and abdominal pain) to 0.53% (for bruising) for patients aged 0-14 years old, the positive predictive values of having young adulthood leukaemia ranged from 0.0117% (for bruising) to 0.0151% (for lymphadenopathy) for patients aged 15-24 years (1 study, N = 30855), and the positive predictive value of having adulthood leukaemia was 0.04% (for dyspepsia) for patients aged > 40 years (1 study, N = 2585) . Both studies were associated with 1 bias/applicability concern (see also Tables 1-2).

Evidence tables

Dommett (2013a,b)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Population-based nested case-control study using data from the General Practice Research Database (GPRD)
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: 1267 children; aged 0-4 years: N = 436; aged 5-14 years: N = 831; 703 males/564 females. Cancer type: Leukemia: N = 368; brain: N = 270; lymphoma: N = 142; bone: N = 107; soft tissue sarcoma: N = 91; renal: N = 82; neuroblastoma: N = 75;

	other ICD codes: N = 132. 1064 teenagers and young adults (TYA): 15-24 years: Gender not reported. Cancer type: Leukemia: N = 143; brain: N = 154; lymphoma: N = 270; bone: N = 96; soft tissue sarcoma: N = 100; other ICD codes: N = 301 (including testis: N = 60; skin: N = 49; ovary: N = 20 and thyroid: N = 17). Controls: 15318 children; aged 0-4 years: N = 4802; aged 5-14 years: N = 10516; 8461 males/6857 females. 13206 TYA. Gender not reported Inclusion criteria: The sample comprised all children and TYU aged 0–24 years, inclusive, drawn from all general practices contributing research-standard data to the GPRD between 1 January 1988 and 31 December 2010. To be included, the practices had to have been contributing research-standard data for a minimum of 1 year before each child's date of cancer diagnosis or the index date (see below) for matched controls. Cases: Patients diagnosed with the following cancers: leukaemia, lymphoma, neuroblastoma, soft tissue sarcoma, hepatic, renal, bone and central nervous system tumours, using pre-defined medical codes used in the GPRD. The date of diagnosis for cases was defined as the date of pathological diagnosis, but if this was unavailable, the date of the first cancer code entered in the GPRD was used. Controls: Up to 13 controls (children with no diagnosis of cancer at any time) were selected per case, using a computer-generated random sequence, matched on age (within 1 year), sex and practice, and had to be currently registered on the date of diagnosis of their matched case (the index date). Exclusion criteria: None listed Clinical setting: Primary care, UK.
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	The GPRD uses just over 100 000 medical codes to encompass all primary care events, including both symptoms and diagnoses. From this list, libraries of codes were assembled representing individual alert symptoms derived from the NICE referral guidelines for suspected cancer in children. *No more information reported.*
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	

Reference standard(s)	Cancer diagnosis in the UK's General Practice Research Database.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	This study is published in three papers.

Hallissey (1990)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Propective consecutive patient series from a group of 10 general practices in England.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 2585 aged > 40 years. No other information reported. The patient group was equally divided between new patients with dyspepsia, old patients with uninvestigated dyspepsia, and and old patients with investigated dyspepsia. Inclusion criteria: All patients over 40 years making their first attendance during the study period (4 years and 9 months) with any degree of dyspepsia Exclusion criteria: None listed. Clinical setting: Primary care, England.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Dyspepsia of any degree
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**

Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Upper gastrointestinal endoscopy within 4 weeks and follow up.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	2659 patients were seen and 2585 attended for investigation
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	Malignancy was detected in 115 patients: Gastric adenocarcinoma (57), gastric lymphoma (1; added to the gastric adenocarcinoma data in the PPV), oesophageal cancer (15), colorectal (14), pancreatic (6), bronchial (8), prostatic (2), duodenal (1, also added to the gastric carcinoma data in the PPV), liver (1), gall bladder (1), carcinoid (1), uterine (1), leukaemia (1), circinomatosis of unknown primary (7).

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Review question:
Which investigations of symptoms of suspected leukemia should be done with clinical responsibility retained by primary care?

Results

Literature search

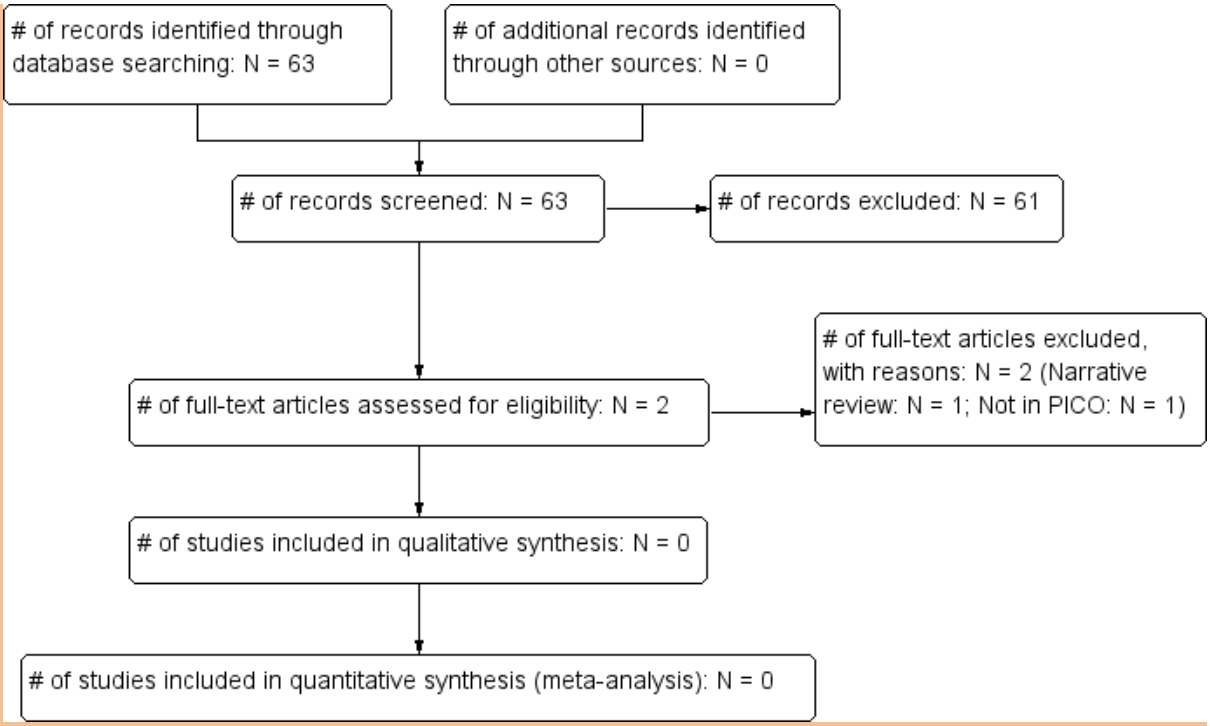
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-2013	239	34	18/04/2013
Premedline	1980-2013	28	8	18/04/2013
Embase	1980-2013	261	21	18/04/2013
Cochrane Library	1980-2013	7	0	18/04/2013
Psychinfo	1980-2013	2	0	18/04/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2013	57	5	18/04/2013

Total References retrieved (after de-duplication): 57

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	4/2013-18/08/2014	10	2	18/08/2014
Premedline	4/2013-18/08/2014	30	2	18/08/2014
Embase	4/2013-18/08/2014	51	3	18/08/2014
Cochrane Library	4/2013-18/08/2014	11	0	18/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	4/2013-18/08/2014	11	1	18/08/2014

Total References retrieved (after de-duplication): 6



Study results

No evidence was identified pertaining to the diagnostic accuracy of white blood cell count in patients with suspected leukaemia where the clinical responsibility was retained by primary care.

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Included studies

None

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MYELOMA

Review question:

What is the risk of myeloma in patients presenting in primary care with symptom(s)?

Results

Literature search results

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-2013	565	16	09/04/2013
Premedline	1980--2013	74	9	10/04/2013
Embase	1980--2013	773	35	11/04/2013
Cochrane Library	1980--2013	684	0	10/04/2013
Psychinfo	1980--2013	21	3	11/04/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980--2013	545	7	12/04/2013

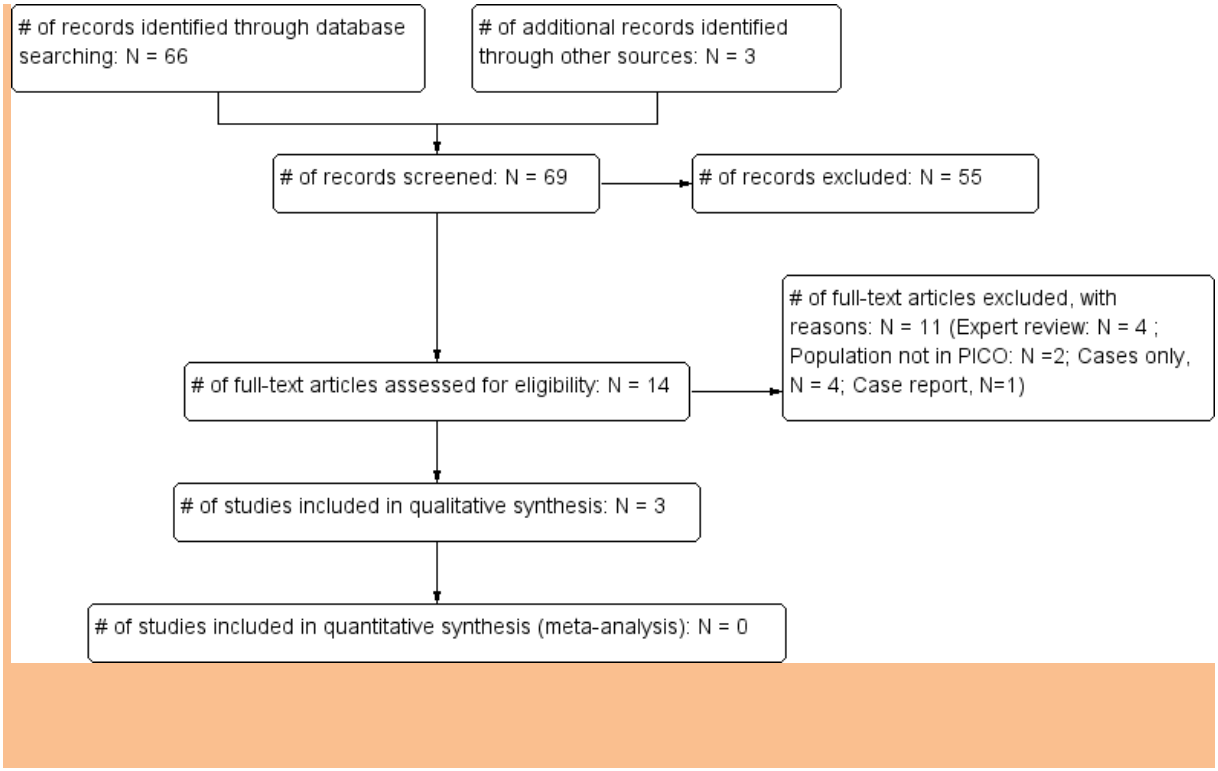
Total references retrieved (after de-duplication): 60

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	4/2013-19/08/2014	20	0	19/08/2014
Premedline	4/2013-19/08/2014	40	3	19/08/2014
Embase	4/2013-19/08/2014	38	3	19/08/2014
Cochrane Library	4/2013-19/08/2014	349	0	19/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	4/2013-19/08/2014	44	2	19/08/2014

Total References retrieved (after de-duplication): 6

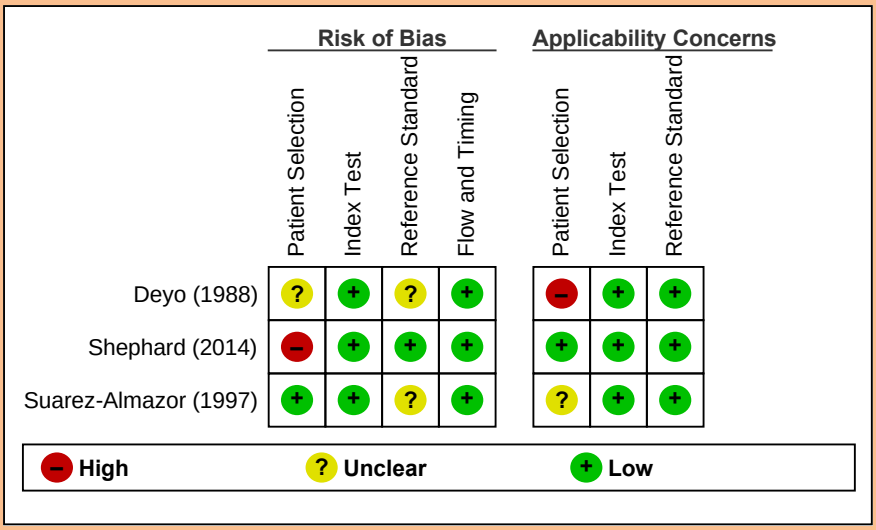
Study flow diagram


# of records identified through database searching: N = 66
# of additional records identified through other sources: N = 3
# of records screened: N = 69
# of records excluded: N = 55
# of full-text articles assessed for eligibility: N = 14
# of full-text articles excluded, with reasons: N = 11 (Expert review: N = 4 ; Population not in PICO: N =2; Cases only, N = 4; Case report, N=1)
# of studies included in qualitative synthesis: N = 3
# of studies included in quantitative synthesis (meta-analysis): N = 0

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issues to note are (1) that two of the studies employed samples of patients that are not directly representative of an unselected symptomatic population of patients presenting to the UK-based GP, and (2) that two of the studies employed patient selection methods that were not clearly consecutive or random in nature, which, in turn, may result in inflated estimates of the positive predictive values. However, the statistics employed by Shephard (2014) may have gone some way in counteracting this influence.

Risk of bias summary



Study results

Table 1: Myeloma: Positive predictive values of individual symptoms for myeloma in patients aged > 14-15 years

Study	Symptom(s)	Patient group	PPV % (95% CI) for myeloma; prevalence of myeloma
Deyo (1988)	Back pain	All included patients	0.05 (0.003-0.3); 1/1975
Suarez-Almazor (1997)	Acute low back pain	All included patients	0 (0-0.5) or 0.21 (0.04-0.83) 0-2/963 Unclear if diagnosis was prior to symptom
Shephard (2014)	Joint pain	Patients ≥ 60 years	0.05 (0.04-0.06)
Shephard (2014)	Shortness of breath	Patients ≥ 60 years	0.06 (0.05-0.06)
Shephard (2014)	Chest infection	Patients ≥ 60 years	0.06 (0.05-0.06)
Shephard (2014)	Chest pain	Patients ≥ 60 years	0.1 (0.09-0.11)
Shephard (2014)	Fracture	Patients ≥ 60 years	0.1 (0.08-0.12)
Shephard (2014)	Nausea	Patients ≥ 60 years	0.1 (0.08-0.12)

Shephard (2014)	Combined bone pain	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2014)	Nosebleeds	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2014)	Back pain	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2014)	Weight loss	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2014)	Rib pain	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2014)	Low haemoglobin	Patients ≥ 60 years	0.17 (0.16-0.19)
Shephard (2014)	Leucopenia	Patients ≥ 60 years	0.3 (0.2-0.3)
Shephard (2014)	Low platelets	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2014)	Raised inflammatory markers	Patients ≥ 60 years	0.2 (0.18-0.22)
Shephard (2014)	Raised creatinine	Patients ≥ 60 years	0.08 (0.08-0.09)
Shephard (2014)	Raised MVC	Patients ≥ 60 years	0.18 (0.16-0.22)
Shephard (2014)	Hypercalcaemia	Patients ≥ 60 years	0.7 (0.5-1)

Abbreviations: CI, confidence interval; FP, False positives; PPV, positive predictive value; TP, True positives; NR, Not reported.

Table 2: Myeloma: Positive predictive value of symptom combinations for myeloma in patients aged > 14-15 years

Study	Symptom(s)	Patient group	PPV % (95% CI) for myeloma; prevalence of myeloma
Shephard (2014)	Joint pain and shortness of breath	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2014)	Joint pain and chest infection	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Joint pain and chest pain	Patients ≥ 60 years	0.1 (NR)
Shephard (2014)	Joint pain and fracture	Patients ≥ 60 years	0.1 (NR)
Shephard (2014)	Joint pain and nausea	Patients ≥ 60 years	0.1 (NR)
Shephard (2014)	Joint pain and combined bone pain	Patients ≥ 60 years	0.1 (NR)
Shephard (2014)	Joint pain and nosebleeds	Patients ≥ 60 years	Non-calculable
Shephard (2014)	Joint pain and back pain	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2014)	Joint pain and	Patients ≥ 60	Non-calculable

	weight loss	years	
Shephard (2014)	Joint pain and rib pain	Patients ≥ 60 years	0.7 (NR)
Shephard (2014)	Shortness of breath and chest infection	Patients ≥ 60 years	0.1 (NR)
Shephard (2014)	Shortness of breath and chest pain	Patients ≥ 60 years	0.1 (0.05-0.1)
Shephard (2014)	Shortness of breath and fracture	Patients ≥ 60 years	0.1 (0.1-0.3)
Shephard (2014)	Shortness of breath and nausea	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2014)	Shortness of breath and combined bone pain	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2014)	Shortness of breath and nosebleeds	Patients ≥ 60 years	0.1 (NR)
Shephard (2014)	Shortness of breath and back pain	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2014)	Shortness of breath and weight loss	Patients ≥ 60 years	0.1 (0.1-0.3)
Shephard (2014)	Shortness of breath and rib pain	Patients ≥ 60 years	0.2 (NR)
Shephard (2014)	Chest infection and chest pain	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2014)	Chest infection and fracture	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2014)	Chest infection and nausea	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2014)	Chest infection and combined bone pain	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Chest infection and nosebleeds	Patients ≥ 60 years	0.1 (NR)
Shephard (2014)	Chest infection and back pain	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2014)	Chest infection and weight loss	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Chest infection and rib pain	Patients ≥ 60 years	0.2 (NR)
Shephard (2014)	Chest pain and fracture	Patients ≥ 60 years	0.3 (0.2-0.6)

Shephard (2014)	Chest pain and nausea	Patients ≥ 60 years	0.3 (0.2-0.4)
Shephard (2014)	Chest pain and combined bone pain	Patients ≥ 60 years	0.2 (0.1-0.4)
Shephard (2014)	Chest pain and nosebleeds	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Chest pain and back pain	Patients ≥ 60 years	0.3 (0.2-0.4)
Shephard (2014)	Chest pain and weight loss	Patients ≥ 60 years	0.1 (NR)
Shephard (2014)	Chest pain and rib pain	Patients ≥ 60 years	0.9 (NR)
Shephard (2014)	Fracture and nausea	Patients ≥ 60 years	0.2 (0.1-0.4)
Shephard (2014)	Fracture and combined bone pain	Patients ≥ 60 years	0.8 (NR)
Shephard (2014)	Fracture and nosebleeds	Patients ≥ 60 years	Non-calculable
Shephard (2014)	Fracture and back pain	Patients ≥ 60 years	0.5 (0.3-0.9)
Shephard (2014)	Fracture and weight loss	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Fracture and rib pain	Patients ≥ 60 years	0.7 (NR)
Shephard (2014)	Nausea and combined bone pain	Patients ≥ 60 years	0.6 (NR)
Shephard (2014)	Nausea and nosebleeds	Patients ≥ 60 years	Non-calculable
Shephard (2014)	Nausea and back pain	Patients ≥ 60 years	0.4 (0.2-0.6)
Shephard (2014)	Nausea and weight loss	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Nausea and rib pain	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Combined bone pain and nosebleeds	Patients ≥ 60 years	Non-calculable
Shephard (2014)	Combined bone pain and back pain	Patients ≥ 60 years	0.5 (0.3-0.8)
Shephard (2014)	Combined bone pain and weight loss	Patients ≥ 60 years	Non-calculable
Shephard (2014)	Combined bone pain and rib pain	Patients ≥ 60 years	0.5 (NR)
Shephard (2014)	Nosebleeds and back pain	Patients ≥ 60 years	1.5 (NR)

Shephard (2014)	Nosebleeds and weight loss	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Nosebleeds and rib pain	Patients ≥ 60 years	Non-calculable
Shephard (2014)	Back pain and weight loss	Patients ≥ 60 years	0.5 (NR)
Shephard (2014)	Back pain and rib pain	Patients ≥ 60 years	1.1 (NR)
Shephard (2014)	Weight loss and rib pain	Patients ≥ 60 years	Non-calculable
Shephard (2014)	Back pain first episode and low haemoglobin	Patients ≥ 60 years	0.5 (0.4-0.7)
Shephard (2014)	Back pain first episode and leucopenia	Patients ≥ 60 years	0.6 (0.4-1.2)
Shephard (2014)	Back pain first episode and low platelets	Patients ≥ 60 years	0.7 (0.4-1.3)
Shephard (2014)	Back pain first episode and raised inflammatory markers	Patients ≥ 60 years	0.6 (0.4-0.7)
Shephard (2014)	Back pain first episode and raised creatinine	Patients ≥ 60 years	0.3 (0.2-0.4)
Shephard (2014)	Back pain first episode and raised MCV	Patients ≥ 60 years	0.4 (0.3-0.6)
Shephard (2014)	Back pain first episode and hypercalcaemia	Patients ≥ 60 years	4 (NR)
Shephard (2014)	Back pain second episode and low haemoglobin	Patients ≥ 60 years	0.9 (0.6-1.3)
Shephard (2014)	Back pain second episode and leucopenia	Patients ≥ 60 years	2 (NR)
Shephard (2014)	Back pain second episode and low platelets	Patients ≥ 60 years	0.7 (NR)
Shephard (2014)	Back pain second episode and raised inflammatory markers	Patients ≥ 60 years	1.1 (0.7-1.6)
Shephard (2014)	Back pain	Patients ≥ 60	0.5 (0.3-0.7)

	second episode and raised creatinine	years	
Shephard (2014)	Back pain second episode and raised MCV	Patients ≥ 60 years	0.8 (0.4-1.6)
Shephard (2014)	Back pain second episode and hypercalcaemia	Patients ≥ 60 years	>10 (NR)
Shephard (2014)	Shortness of breath and low haemoglobin	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2014)	Shortness of breath and leucopenia	Patients ≥ 60 years	0.3 (0.2-0.6)
Shephard (2014)	Shortness of breath and low platelets	Patients ≥ 60 years	0.3 (0.1-0.5)
Shephard (2014)	Shortness of breath and raised inflammatory markers	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2014)	Shortness of breath and raised creatinine	Patients ≥ 60 years	0.1 (0.07-0.11)
Shephard (2014)	Shortness of breath and raised MCV	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2014)	Shortness of breath and hypercalcaemia	Patients ≥ 60 years	1.5 (NR)
Shephard (2014)	Chest pain and low haemoglobin	Patients ≥ 60 years	0.3 (0.2-0.4)
Shephard (2014)	Chest pain and leucopenia	Patients ≥ 60 years	0.3 (0.1-0.6)
Shephard (2014)	Chest pain and low platelets	Patients ≥ 60 years	0.3 (0.2-0.6)
Shephard (2014)	Chest pain and raised inflammatory markers	Patients ≥ 60 years	0.5 (0.3-0.6)
Shephard (2014)	Chest pain and raised creatinine	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2014)	Chest pain and raised MCV	Patients ≥ 60 years	0.3 (0.2-0.6)
Shephard (2014)	Chest pain and	Patients ≥ 60	1.9 (NR)

	hypercalcaemia	years	
Shephard (2014)	Chest infection and low haemoglobin	Patients ≥ 60 years	0.2 (0.2-0.3)
Shephard (2014)	Chest infection and leucopenia	Patients ≥ 60 years	0.3 (0.1-0.5)
Shephard (2014)	Chest infection and low platelets	Patients ≥ 60 years	0.2 (0.1-0.4)
Shephard (2014)	Chest infection and raised inflammatory markers	Patients ≥ 60 years	0.3 (0.2-0.4)
Shephard (2014)	Chest infection and raised creatinine	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2014)	Chest infection and raised MCV	Patients ≥ 60 years	0.3 (0.2-0.4)
Shephard (2014)	Chest infection and hypercalcaemia	Patients ≥ 60 years	2 (NR)
Shephard (2014)	Nosebleeds and low haemoglobin	Patients ≥ 60 years	0.4 (0.2-0.8)
Shephard (2014)	Nosebleeds and leucopenia	Patients ≥ 60 years	> 10 (NR)
Shephard (2014)	Nosebleeds and low platelets	Patients ≥ 60 years	1.2 (NR)
Shephard (2014)	Nosebleeds and raised inflammatory markers	Patients ≥ 60 years	0.9 (NR)
Shephard (2014)	Nosebleeds and raised creatinine	Patients ≥ 60 years	0.2 (0.1-0.4)
Shephard (2014)	Nosebleeds and raised MCV	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Nosebleeds and hypercalcaemia	Patients ≥ 60 years	NR
Shephard (2014)	Fracture and low haemoglobin	Patients ≥ 60 years	0.3 (0.2-0.4)
Shephard (2014)	Fracture and leucopenia	Patients ≥ 60 years	> 10 (NR)
Shephard (2014)	Fracture and low platelets	Patients ≥ 60 years	0.1 (NR)
Shephard (2014)	Fracture and raised inflammatory markers	Patients ≥ 60 years	0.4 (0.2-0.6)
Shephard (2014)	Fracture and	Patients ≥ 60	0.2 (0.1-0.4)

	raised creatinine	years	
Shephard (2014)	Fracture and raised MCV	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Fracture and hypercalcaemia	Patients ≥ 60 years	> 10 (NR)
Shephard (2014)	Nausea and low haemoglobin	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2014)	Nausea and leucopenia	Patients ≥ 60 years	0.4 (NR)
Shephard (2014)	Nausea and low platelets	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Nausea and raised inflammatory markers	Patients ≥ 60 years	0.3 (0.2-0.5)
Shephard (2014)	Nausea and raised creatinine	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2014)	Nausea and raised MCV	Patients ≥ 60 years	0.3 (0.2-0.7)
Shephard (2014)	Nausea and hypercalcaemia	Patients ≥ 60 years	1 (NR)
Shephard (2014)	Combined bone pain and low haemoglobin	Patients ≥ 60 years	0.5 (0.3-1)
Shephard (2014)	Combined bone pain and leucopenia	Patients ≥ 60 years	> 5 (NR)
Shephard (2014)	Combined bone pain and low platelets	Patients ≥ 60 years	0.1 (NR)
Shephard (2014)	Combined bone pain and raised inflammatory markers	Patients ≥ 60 years	0.5 (0.3-0.9)
Shephard (2014)	Combined bone pain and raised creatinine	Patients ≥ 60 years	0.2 (0.1-0.4)
Shephard (2014)	Combined bone pain and raised MCV	Patients ≥ 60 years	0.5 (NR)
Shephard (2014)	Combined bone pain and hypercalcaemia	Patients ≥ 60 years	1.4 (NR)
Shephard (2014)	Joint pain and low haemoglobin	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2014)	Joint pain and leucopenia	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Joint pain and	Patients ≥ 60	0.2 (NR)

	low platelets	years	
Shephard (2014)	Joint pain and raised inflammatory markers	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2014)	Joint pain and raised creatinine	Patients ≥ 60 years	0.1 (0.05-0.13)
Shephard (2014)	Joint pain and raised MCV	Patients ≥ 60 years	0.2 (NR)
Shephard (2014)	Joint pain and hypercalcaemia	Patients ≥ 60 years	> 10 (NR)
Shephard (2014)	Rib pain and low haemoglobin	Patients ≥ 60 years	0.9 (NR)
Shephard (2014)	Rib pain and leucopenia	Patients ≥ 60 years	0.5 (NR)
Shephard (2014)	Rib pain and low platelets	Patients ≥ 60 years	NR
Shephard (2014)	Rib pain and raised inflammatory markers	Patients ≥ 60 years	0.4 (0.2-0.8)
Shephard (2014)	Rib pain and raised creatinine	Patients ≥ 60 years	0.8 (NR)
Shephard (2014)	Rib pain and raised MCV	Patients ≥ 60 years	1.1 (NR)
Shephard (2014)	Rib pain and hypercalcaemia	Patients ≥ 60 years	> 10 (NR)
Shephard (2014)	Weight loss and low haemoglobin	Patients ≥ 60 years	0.4 (0.?-0.7)
Shephard (2014)	Weight loss and leucopenia	Patients ≥ 60 years	0.5 (NR)
Shephard (2014)	Weight loss and low platelets	Patients ≥ 60 years	0.5 (NR)
Shephard (2014)	Weight loss and raised inflammatory markers	Patients ≥ 60 years	0.6 (0.3-1.1)
Shephard (2014)	Weight loss and raised creatinine	Patients ≥ 60 years	0.5 (NR)
Shephard (2014)	Weight loss and raised MCV	Patients ≥ 60 years	0.6 (NR)
Shephard (2014)	Weight loss and hypercalcaemia	Patients ≥ 60 years	0.5 (NR)

Abbreviations: CI, confidence interval; FP, False positives; PPV, positive predictive value; TP, True positives, NR, Not reported. Shepard (2014) reports that PPVs were not calculated if < 5 cases had the feature(s) and CIs were omitted where < 10 cases or controls had the combined features.

Evidence statements:

The positive predictive values for myeloma of single symptoms presenting in a primary care setting ranged from 0% (for 'acute low back pain') to 0.7% (for hypercalcaemia in patients aged ≥ 60 years; 3 studies, N = 17798). The studies were subject to 1-3 bias or applicability concerns (See also Table 1).

The positive predictive values for myeloma of symptom pairs presenting in a primary care setting ranged from 0.1% (for raised creatinine with 'shortness of breath'/ chest infection / joint pain, and for joint pain with 'raised inflammatory markers'/back pain/ 'combined bone pain'/ nausea/fracture/chest pain/ 'shortness of breath', and for 'shortness of breath' with chest infection / chest pain/ fracture/ nausea/ nosebleeds/ back pain/ weight loss, and for chest infection with nosebleeds/nausea, and for chest pain with weight loss; all in patients aged ≥ 60 years) to > 10% (for hypercalcaemia with 'back pain second episode'/ fracture / joint pain/rib pain, and for leucopenia with nosebleeds/fracture; all in patients aged ≥ 60 years; 1 study, N = 14860). The study was subject to 1 bias concern (see also Table 2).

Evidence tables

Deyo (1988)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective consecutive? patient series
Was a consecutive or random sample of patients enrolled?	**Unclear**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes (probably)**
Could the selection of patients have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 1975, mean (SD; range) age = 39.5 (15.4; 15-86) years, 62% females. 54% of the patients were seeking medical care for back pain for the first time and 76% of the patients had had back pain for < 3 months. 3% had a history of back pain surgery. Maximal back pain in the low back (84%) or in the upper back (16%). Inclusion criteria: Patients who sought treatment between March 1982 and September 1984 in the walk-in clinic of a public hospital where virtually all patients are self-referred. In each case back pain was part of the chief complaint. Exclusion criteria: Neck pain. Clinical setting: Walk-in clinic of a public hospital; this clinic is a source of primary care for indigent persons in a county in the USA with a population of approximately 1 million.
Are there concerns that the included patients and setting do not match the review question?	**High concern**
INDEX TEST	
A. Risk of bias	
Index test	Back pain; not further specified.

Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	The reference standard consisted of a search on each patient name in the institutional tumour registry ≥ 6 months after the index visit. The registry included every patient with a histological diagnosis of cancer made in the authors' hospital system regardless of site of care. The authors point out that "while this method might fail to identify cancer patients who sought care elsewhere, it is likely that most patients sought follow-up for a particular illness at the same facility.
Is the reference standard likely to correctly classify the target condition?	**Unclear**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No (but all patients had a positive index test)**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All the patients are accounted for in the results.
Was there an appropriate interval between index test and reference standard?	**Yes (probably)**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	It is a concern that some patients with cancer might have been missed due to the choice of reference standard because this would result in an underestimation of the positive predictive value. 38/1975 patients were found in the tumour registry. Of those 38, 13 patients had tumours that were probable causes of back pain, and 4 of these 13 patients already had a diagnosis of cancer at presentation. The 9/1975 patients who had undiagnosed cancer that the back pain could be attributed to had: Lymphoma (NOS; 2), cancer of unknown primary (1), prostate cancer (1), retroperitoneal liposarcoma (1), lung cancer (1), renal cell (1), multiple myeloma (1), mucinous adenocarcinoma (of gallbladder?; 1)

Shephard (2014)

PATIENT SELECTION	
A. risk of bias	

Patient sampling	Matched case-control study using patients in the UK's Clinical Practice Research Database (CPRD).
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: N = 2703, 1449 males/ 1254 females, median age at diagnosis = 73 (IQR = 64-80) years; median number of consultations in the year before diagnosis = 16 (IQR = 10-25); UK. Controls: N = 12157; 6359 males/ 5798 females; median age at matched-case diagnosis = 73 (IQR = 65-80) years median number of consultations in the year before diagnosis = 8 (IQR = 4-14); UK. Inclusion criteria: Cases: Patients aged ≥ 40 years with one of 23 myeloma diagnostic codes in the CPRD between January 2000 and December 2009, with min. 1 year of data before diagnosis. The first instance of a myeloma cancer code was assigned the data of diagnosis/index date. Controls: Up to 5 controls per case, matched on sex, general practice, and to 1 year of age of the case. The index date was the index date of the matched case. Exclusion criteria: Any case or control with less than 1 year of data before the index date; cases without controls; controls with myeloma; controls with only one line consisting of incomplete data (suggestion they had not sought medical care after registration). Clinical setting: UK primary care
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	**"**Symptoms, diseases and abnormal investigations reported in the myeloma literature and from patient online support groups were studied". "The GPRD contains over 100,000 medical codes; several codes can potentially be associated with each feature. A symptom library of codes was compiled for each feature. Occurrences of features were identified in the year before the index date. Only those features present in ≥2% of cases or controls were retained (this was invariably cases)." "Abnormal investigation results were defined as the patient having a test value falling outside their local laboratory's normal range. Patients with a normal laboratory result were grouped with those who had not been tested." "Some tests were grouped together. The raised inflammatory markers variable was a composite of any

	of abnormal erythrocyte sedimentation rate, plasma viscosity, or C-reactive protein, as different local laboratories had local preferences for the inflammatory marker of choice; similarly abnormal liver function tests reflected a raised value of any of the hepatic enzymes reported by each laboratory. In clinical practice, haemoglobin, white cell count and platelets are normally requested together ('the full blood count'). We used these slightly differently in our analyses; for the multivariable analyses, a composite variable 'cytopenia' was deemed to be positive if any of the haemoglobin, white cell count or platelets was abnormally low; for positive predictive values (see below) the three different cell types were analysed separately. Bone pain codes often had an anatomical descriptor as well as the words 'bone pain'. We retained 'rib pain', 'back pain' and 'joint pain' as separate entities; remaining bone pain codes, such as 'tibial pain' were merged with the generic 'bone pain' code, making a group we called 'combined bone pain'. "
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	One of 23 myeloma diagnostic codes in the CPRD.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	A total of 16233 patients were identified, 13503 controls and 2730 cases. After the exclusion criteria were applied there were 12157 controls and 2703 cases.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**

NOTES	62 symptoms and 22 abnormal test results were considered initially.

Suarez-Almazor (1997)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Retrospective consecutive patient series
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 1550, of whom N = 331 had chronic (> 3 months?) back pain, N = 963 had acute (< 3 months) low back pain, and N = 256 had back pain of unspecified duration. Of the patients with acute low back pain, 442 were males, and it appears that the mean (SD) age = 42.2 (15.6) years for the patients with acute low back pain, 14/963 had a history of cancer Inclusion criteria: All patients aged ≥ 18 years presenting to four family clinics in Edmonton (Alberta, Canada) between January 1 1992 and December 31 1993 with low back pain or leg pain compatible with sciatic pain for which no visit had been made within the past 12 months. Exclusion criteria: Low back pain attributable to visceral pain (e.g., urinary infection, inflammatory pelvic disease), previous diagnosis of ankylosing apondylitis, pregnancy. Clinical setting: Four family clinics in Edmonton (Alberta, Canada), two of which are university-affiliated and hospital-based, with the other two based in the community.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Acute (< 3 months) low back pain; not further specified.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Follow up consisting of chart review after a minimum of 2 years. Patients were considered to have cancer if recorded in the physician notes or in reports from laboratory or diagnostic tests.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No (but all patients had a positive index test)**

Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	The results are only presented for the patients with acute low back pain.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	13/963 patients with acute low back pain had active cancer. 3 of those 13 patients had the cancer diagnosis prior to the index visit; 3/13 patients had tumours that were probable causes of the acute low back pain (spinal infiltrates from multiple myeloma [2] and metastatic bone disease with compression fractures [1]), and 10/13 patients had cancer that was not considered to have caused the acute low back pain (bladder cancer [3], colon [1], breast [1], thyroid [1], lung [1], prostate [1], endometrium [1], oesophagus [1]). However, as it is not reported which of these patients already had a diagnosis of cancer pre-index visit, it is not possible to present the data accurately for the individual cancers.

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Review question:
Which investigations of symptoms of suspected myeloma should be done with clinical responsibility retained by primary care?

Results

Literature search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-2013	618	49	08/04/2013
Premedline	1980-2013	39	11	08/04/2013
Embase	1980-2013	636	54	08/04/2013
Cochrane Library	1980-2013	646	3	09/04/2013
Psychinfo	1980-2013	2	0	08/04/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2013	66	11	09/04/2013

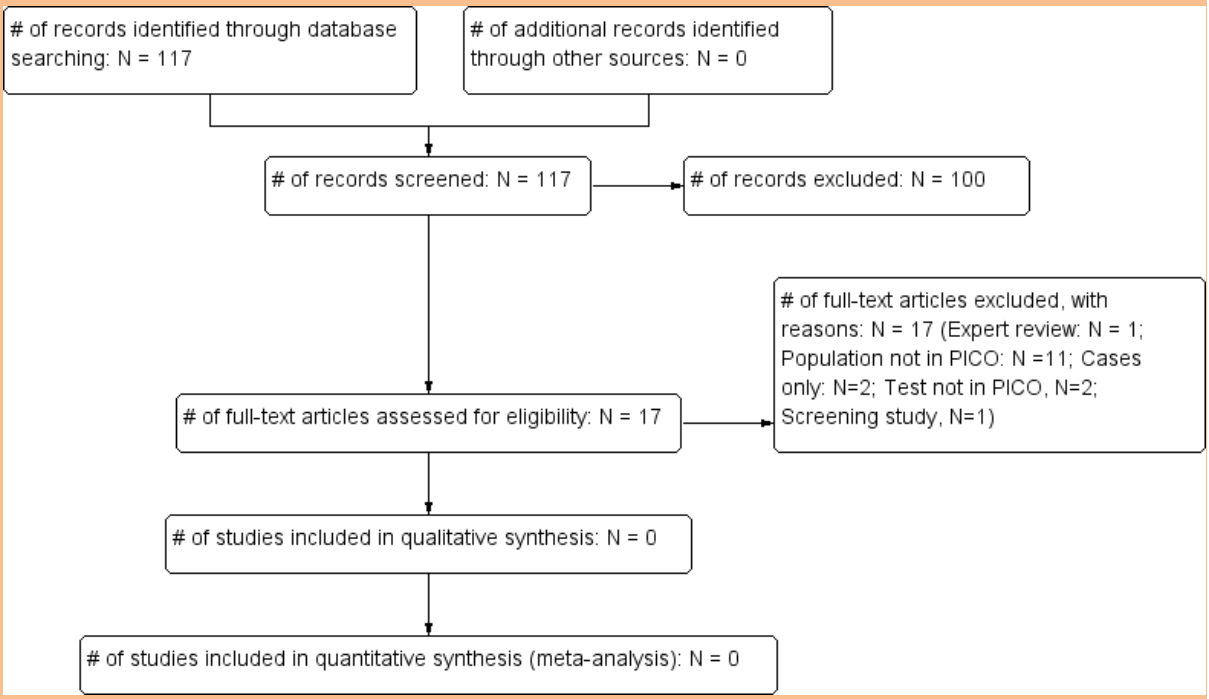
Total References retrieved (after de-duplication): 109

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	4/2013-19/08/2014	15	0	19/08/2014

Premedline	4/2013-19/08/2014	49	5	19/08/2014
Embase	4/2013-19/08/2014	52	4	19/08/2014
Cochrane Library	4/2013-19/08/2014	345	0	19/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	4/2013-19/08/2014	5	1	19/08/2014

Total References retrieved (after de-duplication): 8



Study results

No evidence was identified pertaining to the diagnostic accuracy of paraprotein/serum electrophoresis/Bence-Jones protein tests, ESR, X-ray, viscosity or calcium tests in patients with suspected myeloma cancer where the clinical responsibility was retained by primary care.

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Included studies

None

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Exclusion reason : repeat publication

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Palladini, G., Russo, P., Bosoni, T., Verga, L., Sarais, G., Lavatelli, F., Nuvolone, M., Obici, L., Casarini, S., Donadei, S., Albertini, R., Righetti, G., Marini, M., Graziani, M. S., D'Eril, G. V. M., Moratti, R. & Merlini, G. (2009) Identification of Amyloidogenic Light Chains Requires the Combination of Serum-Free Light Chain Assay with Immunofixation of Serum and Urine. Clinical Chemistry, 55: 499-504.
Exclusion reason : test not in PICO

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Exclusion reason : population not in PICO

Peruzzi, B., Carretti, F., Rondelli, T., Caporale, R., Fanelli, A. & Grazia Gelli, A. M. (2012) Seven-color flow cytometry for evaluation of bone marrow plasma cells disorders: Different aberrant phenotype with different aggressivness. Cytometry Part B - Clinical Cytometry, 82B: 401-402.
Exclusion reason : test not in PICO

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Exclusion reason : test not in PICO

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Exclusion reason : population not in PICO

Rajeswaran, C., Spencer, J., Barth, J. H. & Orme, S. M. (2007) Utility of biochemical screening in the context of evaluating patients with a presumptive diagnosis of osteoporosis. Clinical Rheumatology, 26: 362-365.
Exclusion reason : population not in PICO

Ramon Rodriguez, L. G., Rivera-Keeling, C., Arencibia-Nunez, A., Avila-Cabrera, O. M., Izquierdo-Cano, L., Espinosa-Estrada, E., Gonzalez-Pinedo, L., Quintero-Sierra, Y., Gutierrez-Diaz, A. & Hernandez-Padron, C. (2013) Clinical and laboratory characterization of multiple myeloma at the Institute of Hematology and Immunology. *Revista Cubana de Hematologia, Inmunologia y Hemoterapia,* 29: 382-397.
Exclusion reason : Not in PICO

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Exclusion reason : test not in PICO

Renuga, G., Babu, A. & Arumugam, K. R. (2008) Molecular characterization of plasma proteins to confirm the risk factor for rogression to multiple myeloma. Asian Journal of Microbiology, Biotechnology and Environmental Sciences, 10: 229-234.
Exclusion reason : test not in PICO

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Exclusion reason : test not in PICO
Ross, J. R., Saunders, Y., Edmonds, P. M., Patel, S., Wonderling, D., Normand, C. & Broadley, K. (2004) A systematic review of the role of bisphosphonates in metastatic disease. [Review] [335 refs]. Health Technology Assessment (Winchester, England), 8: 1-176.
Exclusion reason : treatment study
Savini, P., Lanzi, A., Castagnari, B., Gollini, C., Re, G., Musardo, G. & Stefanini, G. F. (2009) Proposal for the management of the MGUS. Haematologica, 94: 244-245.
Exclusion reason : expert review
Schmidt, G. P., Schoenberg, S. O., Reiser, M. F. & Baur-Melnyk, A. (2005) Whole-body MR imaging of bone marrow. [Review] [40 refs]. European Journal of Radiology, 55: 33-40.
Exclusion reason : test not in PICO
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Exclusion reason : test not in PICO
Sethi, B., Butola, K. S. & Kumar, Y. (2012) A Diagnostic Dilemma: Waldenstrom's Macroglobulinemia/Plasma Cell Leukemia. Case Reports in Pathology Print, 2012: 271407.
Exclusion reason : case report
Shaheen, S. P. & Levinson, S. S. (2009) Serum free light chain analysis may miss monoclonal light chains that urine immunofixation electrophoreses would detect. Clinica Chimica Acta, 406: 162-166.
Exclusion reason : population not in PICO
Sharma, A., Tripathi, M., Satyam, A. & Kumar, L. (2009) Study of antioxidant levels in patients with multiple myeloma. Leukemia & Lymphoma, 50: 809-815.
Exclusion reason : test not in PICO
Smellie, W. S. A. & Spickett, G. P. (2006) Cases in primary care laboratory medicine - Paraprotein management. British Medical Journal, 333: 185-187.
Exclusion reason : editorial
Smith, D. B., Harris, M., Gowland, E., Chang, J. & Scarffe, J. H. (1986) Non-secretory multiple myeloma: a report of 13 cases with a review of the literature. Hematological Oncology, 4: 307-313.
Exclusion reason : cases only
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Exclusion reason : Not in PICO
Takemura, Y., Hayashi, K., Miyoshi, K., Mori, S., Kugai, N. & Sekiguchi, S. (1992) [Laboratory tests in primary care medicine: "essential laboratory tests" (2). Usefulness of hematological, biochemical and serological tests in diagnosis of new outpatients]. [Japanese]. Rinsho Byori - Japanese Journal of Clinical Pathology, 40: 403-409.
Exclusion reason : population not in PICO
Talbot, R. W., Bannister, J. J. & Hills, N. H. (1984) A haematuria diagnostic service in a district general hospital. Annals of the Royal College of Surgeons of England, 66: 348-350.
Exclusion reason : population not in PICO
Tate, J., Caldwell, G., Daly, J., Gillis, D., Jenkins, M., Jovanovich, S., Martin, H., Steele, R., Wienholt, L. & Mollee, P. (2012) Recommendations for standardized reporting of protein electrophoresis in Australia and New Zealand. Annals of Clinical Biochemistry, 49: 242-256.

Exclusion reason : expert review

Thakkinstian, A., Tran, H., Reeves, G., Murch, S. & Attia, J. (2008) A clinical decision rule to aid ordering of serum and urine protein electrophoresis for case-finding of paraproteins in hospitalized inpatients. Journal of General Internal Medicine, 23: 1688-1692.

Exclusion reason : not primary care

Van Zaanen, H. C., Lokhorst, H. M., Aarden, L. A., Rensink, H. J., Warnaar, S. O. & Van Oers, M. H. (1998) Blocking interleukin-6 activity with chimeric anti-IL6 monoclonal antibodies in multiple myeloma: effects on soluble IL6 receptor and soluble gp130. Leukemia & Lymphoma, 31: 551-558.

Exclusion reason : test not in PICO

Vardiman, J. (2011) Classification of hematologic neoplasms: Current and future approaches for the myeloid neoplasms. International Journal of Laboratory Hematology, 33: 1-2.

Exclusion reason : expert review

Varshney, R., Deka, M., Bhattacharya, J. & Gogoi, P. K. (2012) Clinico-haematological analysis of haematological malignancy, a hospital based study. Indian Journal of Hematology and Blood Transfusion, 28: 245.

Exclusion reason : not primary care

Vieillard, M. H., Boutry, N., Chastanet, P., Duquesnoy, B., Cotten, A. & Cortet, B. (2005) Contribution of percutaneous biopsy to the definite diagnosis in patients with suspected bone tumor. Joint, Bone, Spine: Revue du Rhumatisme, 72: 53-60.

Exclusion reason : test not in PICO

Vladutiu, A. O. (1987) Prevalence of M-proteins in serum of hospitalized patients. Physicians' response to finding M-proteins in serum protein electrophoresis. Annals of Clinical & Laboratory Science, 17: 157-161.

Exclusion reason : test not in PICO

Wahane, R. N., Lele, V. R. & Bobhate, S. K. (2007) Fine needle aspiration cytology of bone tumors. Acta Cytologica, 51: 711-720.

Exclusion reason : test not in PICO

Waldmann, A., Barragan, B., Cursaru, V., Heberlein, C., Hrianka, M., Richter, F. & Sadzuga, R. (2010) Detecting myeloma-ways to shortening an often painful and tedious patient odyssey: Results from an international survey conducted by myeloma euronet, The European network of myeloma patient groups. Haematologica, 95: 389.

Exclusion reason : cases only

Watanaboonyongcharoen, P., Nakorn, T. N., Rojnuckarin, P., Lawasut, P. & Intragumtornchai, T. (2012) Prevalence of monoclonal gammopathy of undetermined significance in Thailand. International Journal of Hematology, 95: 176-181.

Exclusion reason : screening study

Wei, A. & Juneja, S. (2003) Bone marrow immunohistology of plasma cell neoplasms. Journal of Clinical Pathology, 56: 406-411.

Exclusion reason : test not in PICO

Wilson, A. B., Prout, M. N., Neogi, T. & Jick, S. (2012) The role of surveillance bias in the incidence of the myelodysplastic syndromes and chronic myeloproliferative disorders. Pharmacoepidemiology and Drug Safety, 21: 336.

Exclusion reason : test not in PICO

Zagroda, M., Prystupa, A. & Mosiewicz, J. (2013) Diverse clinical presentation in the course of multiple myeloma. *Family Medicine and Primary Care Review,* 15: 423-425.

Exclusion reason : Not in PICO

Zhang, H., Zhang, L., Wang, J., Ma, Y., Zhang, J., Mo, F., Zhang, W., Yan, S., Yang, G. & Lin, B. (2009) Proteomic analysis of bone tissues of patients with osteonecrosis of the femoral head. Omics a Journal of Integrative Biology, 13: 453-466.

Exclusion reason : test not in PICO

Zhang, L., Li, J., Yang, H., Luo, Z. & Zou, J. (2012) Histological evaluation of bone biopsy results during PVP or PKP of vertebral compression fractures. Oncology Letters, 5: 135-138.
Exclusion reason : test not in PICO

Zhang, S., Suvannasankha, A., Crean, C. D., White, V. L., Chen, C. S. & Farag, S. S. (2011) The novel histone deacetylase inhibitor, AR-42, inhibits gp130/Stat3 pathway and induces apoptosis and cell cycle arrest in multiple myeloma cells. International Journal of Cancer, 129: 204-213.
Exclusion reason : test not in PICO

Zima, T., Spicka, I., Stipek, S., Crkovska, J., Platenik, J., Merta, M. & Tesar, V. (1996) Antioxidant enzymes and lipid peroxidation in patients with multiple myeloma. Neoplasma, 43: 69-73.
Exclusion reason : population not in PICO

NON-HODGKIN'S LYMPHOMA

Review question:
What is the risk of Non-Hodgkin's lymphoma in patients presenting in primary care with symptom(s)?

Results

Literature search

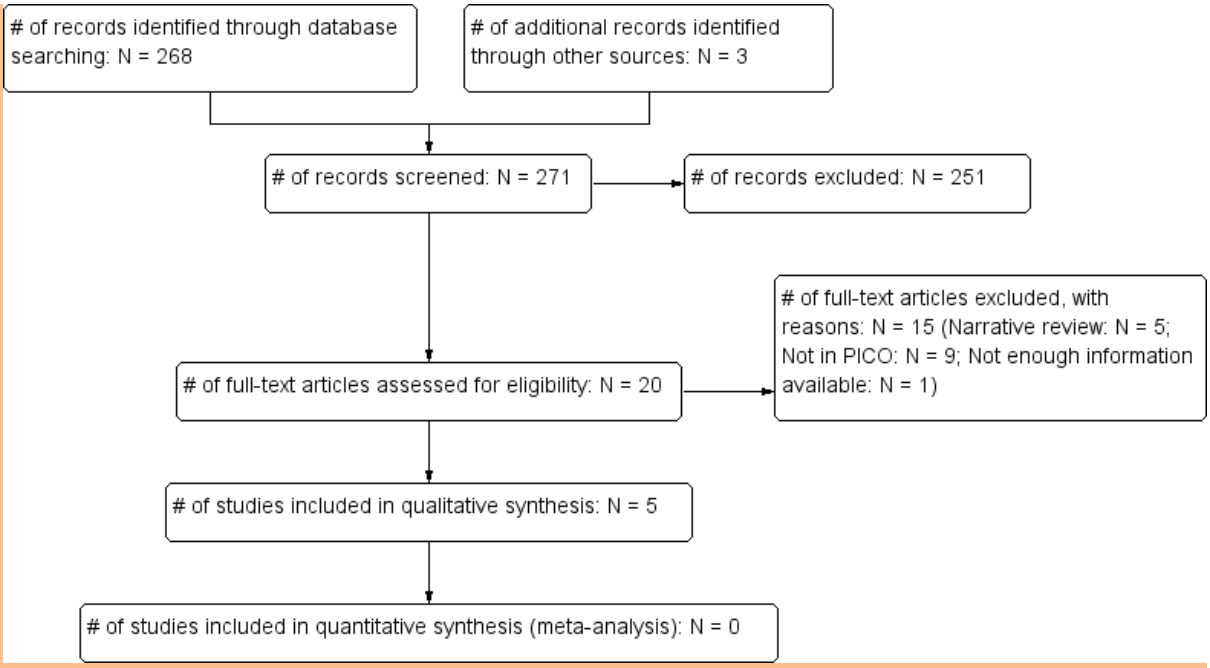
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2012	1184	141	16/10/12
Premedline	All-2012	18	5	16/10/12
Embase	All-2012	856	102	18/10/12
Cochrane Library	All-2012	89	0	18/10/12
Psychinfo	All-2012	4	1	16/10/12
Web of Science (SCI & SSCI) and ISI Proceedings	All-2012	71	26	18/10/12
Biomed Central	All-2012	244	9	18/10/.12

Total References retrieved (after de-duplication): 256

Update Search

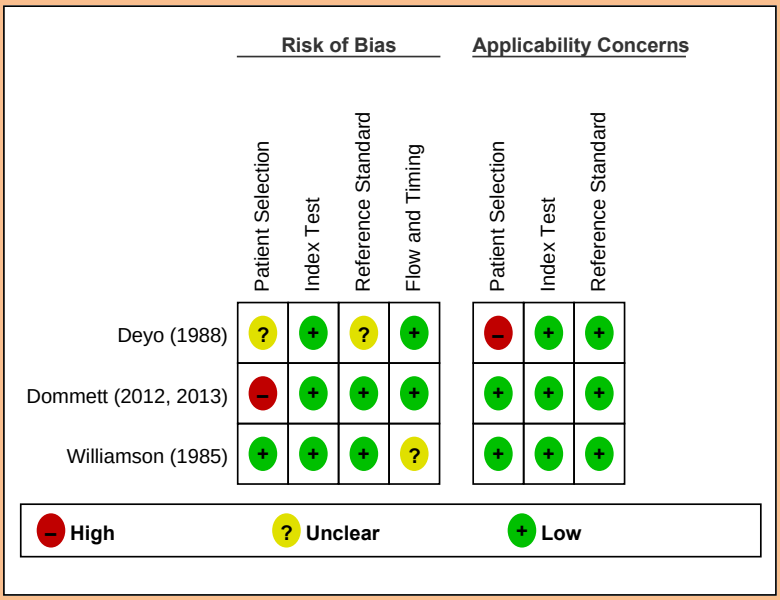
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	10/2012-20/08/2014	48	2	20/08/2014
Premedline	10/2012-20/08/2014	44	7	20/08/2014
Embase	10/2012-20/08/2014	93	3	20/08/2014
Cochrane Library	10/2012-20/08/2014	78	0	20/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	10/2012-20/08/2014	12	0	20/08/2014

Total References retrieved (after de-duplication): 12



Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issue to note is that 2/3 studies employed samples of patients that are not directly representative of an unselected symptomatic population of patients presenting to the UK-based GP, and that there was some uncertainty about the verification of the outcome for some of the patients. Dommett (2012; 2013a,b) employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence.



Study results

Table 1: Non-Hodgkin's lymphoma: Adult and mixed age populations

Study	Symptom(s)	Patient group	Result
Deyo (1988)	Back pain	All included patients	0.1 (0.02-0.41) 2/1975 7 had other types of cancer: lymphoma (NOS): N = 2, unknown primary: N = 1, Prostate: N = 1, retroperitoneal liposarcoma: N = 1, lung cancer: N = 1, renal cell: N = 1, multiple myeloma: N = 1, mucinous adenocarcinoma (of gallbladder?): N = 1
Williamson (1985)	Lymphadenopathy	All included patients	0.8 (0.1-3.2) TP = 2, FP = 247 Cancer: Hodgkin's: N = 1 Adenocarcinoma: N = 1

TP = True positives, FP = False positives.

Table 2: Non-Hodgkin's lymphoma: Positive predictive values for leukaemia/lymphoma childhood cancer

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013a)	Bruising 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.53 (0.07-3.91)
Dommett (2013a)	Pallor 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.43 (0.06-3.15)
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.35 (0.05-2.65)
Dommett (2013a)	Fatigue 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.07 (0.03-0.15)
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis	All included leukemia/lymphoma	0.06 (0.04-0.11)

		patients and controls aged 0-14 years	
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.05 (0.02-0.13)
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.03 (0.01-0.08)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.03 (0.01-0.06)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.02 (0.01-0.03)
Dommett (2013a)	Fever 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0.01-0.01)
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01(0-0.01)
Dommett (2013a)	≥ 3 consultations	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01(0.01-0.01)

The positive predictive values are calculated using Bayesian statistics.

Table 3: Non-Hodgkin's lymphoma: Positive predictive values for teenage and young adult lymphoma

Study	**Symptom(s)**	**Patient group**	**Positive predictive value (95% CI) Frequency**
Dommett (2013b)	Lump mass swelling head and neck	All included lymphoma patients and controls aged 15-24 years	0.5034 (0.0696-3.68) Cases: 35/270 Controls: 1/3350
Dommett (2013b)	Lump mass swelling below neck excluding abdomen	All included lymphoma patients and controls aged 15-24 years	0.0279 (0.0152-0.0515) Cases: 29/270 Controls: 15/3350
Dommett (2013b)	Lymphadenopathy	All included lymphoma patients and controls aged 15-24 years	0.278 (0.1-0.75) Cases: 77/270 Controls: 4/3350
Dommett (2013b)	'Lump mass swelling head and neck', 'lymphadenopathy' and 'lump mass swelling	All included lymphoma patients and controls aged 15-24 years	0.0903 (0.057-0.1425)

	below neck excluding abdomen' combined as a single symptom		
Dommett (2013b)	≥ 3 consultations	All included lymphoma patients and controls aged 15-24 years	0.0086 (0.0075-0.0099) Cases: 175/270 Controls: 294/3350

The positive predictive values are calculated using Bayesian statistics.

Evidence statement(s):

Adult and mixed age populations

Back pain (1 study, N = 1975) and lymphadenopathy (1 study, N = 249) presenting in a primary care setting do not appear to confer a markedly increased risk of Hodgkin's/Non-Hodgkin's lymphoma, although the study populations are probably not directly representative of the typical unselected symptomatic UK GP population (see also Table 1).

Children and teenagers and young adults

The positive predictive values of having leukaemia/lymphoma childhood cancer ranged from 0.01% (for fever and abdominal pain) to 0.53% (for bruising) for patients aged 0-14 years old, and the positive predictive values of having young adulthood lymphoma ranged from 0.0279% (for 'lump mass swelling below the neck excluding the abdomen') to 0.5034% (for 'lump mass swelling head and neck') for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Tables 2-3).

Evidence tables

Deyo (1988)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective consecutive? patient series
Was a consecutive or random sample of patients enrolled?	**Unclear**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes (probably)**
Could the selection of patients have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 1975, mean (SD; range) age = 39.5 (15.4; 15-86) years, 62% females. 54% of the patients were seeking medical care for back pain for the first time and 76% of the patients had had back pain for < 3 months. 3% had a history of back pain surgery. Maximal back pain in the low back (84%) or in the upper back (16%). Inclusion criteria: Patients who sought treatment between March 1982 and September 1984 in the walk-in clinic of a public hospital where virtually all patients are self-referred. In each case back pain was part of the chief complaint. Exclusion criteria: Neck pain. Clinical setting: Walk-in clinic of a public hospital; this clinic is a source of primary care for indigent persons in a county in the USA with a population of

	approximately 1 million.	
Are there concerns that the included patients and setting do not match the review question?		**High concern**
INDEX TEST		
A. Risk of bias		
Index test	Back pain; not further specified.	
Were the index test results interpreted without knowledge of the results of the reference standard?		**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?		**Yes**
Could the conduct or interpretation of the index test have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		**Low concern**
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	The reference standard consisted of a search on each patient name in the institutional tumour registry ≥ 6 months after the index visit. The registry included every patient with a histological diagnosis of cancer made in the authors' hospital system regardless of site of care. The authors point out that "while this method might fail to identify cancer patients who sought care elsewhere, it is likely that most patients sought follow-up for a particular illness at the same facility.	
Is the reference standard likely to correctly classify the target condition?		**Unclear**
Were the reference standard results interpreted without knowledge of the results of the index tests?		**No (but all patients had a positive index test)**
Could the reference standard, its conduct, or its interpretation have introduced bias?		**Unclear risk**
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		**Low concern**
FLOW AND TIMING		
A. risk of bias		
Flow and timing	All the patients are accounted for in the results.	
Was there an appropriate interval between index test and reference standard?		**Yes (probably)**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**Yes**
Could the patient flow have introduced bias?		**Low risk**
NOTES	It is a concern that some patients with cancer might have been missed due to the choice of reference standard because this would result in an underestimation of the positive predictive value. 38/1975 patients were found in the tumour registry. Of those 38, 13 patients had tumours that were probable causes of back pain, and 4 of these 13	

	patients already had a diagnosis of cancer at presentation. The 9/1975 patients who had undiagnosed cancer that the back pain could be attributed to had: Lymphoma (NOS; 2), cancer of unknown primary (1), prostate cancer (1), retroperitoneal liposarcoma (1), lung cancer (1), renal cell (1), multiple myeloma (1), mucinous adenocarcinoma (of gallbladder?; 1)

Dommett (2012; 2013a,b)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Population-based nested case-control study using data from the General Practice Research Database (GPRD)
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: 1267 children; aged 0-4 years: N = 436; aged 5-14 years: N = 831; 703 males/564 females. Cancer type: Leukemia: N = 368; brain: N = 270; lymphoma: N = 142; bone: N = 107; soft tissue sarcoma: N = 91; renal: N = 82; neuroblastoma: N = 75; other ICD codes: N = 132. 1064 teenagers and young adults (TYA): 15-24 years: Gender not reported. Cancer type: Leukemia: N = 143; brain: N = 154; lymphoma: N = 270; bone: N = 96; soft tissue sarcoma: N = 100; other ICD codes: N = 301 (including testis: N = 60; skin: N = 49; ovary: N = 20 and thyroid: N = 17). Controls: 15318 children; aged 0-4 years: N = 4802; aged 5-14 years: N = 10516; 8461 males/6857 females. 13206 TYA. Gender not reported Inclusion criteria: The sample comprised all children and TYU aged 0–24 years, inclusive, drawn from all general practices contributing research-standard data to the GPRD between 1 January 1988 and 31 December 2010. To be included, the practices had to have been contributing research-standard data for a minimum of 1 year before each child's date of cancer diagnosis or the index date (see below) for matched controls. Cases: Patients diagnosed with the following cancers: leukaemia, lymphoma, neuroblastoma, soft tissue sarcoma, hepatic, renal, bone and central nervous system tumours, using pre-defined medical codes used in the GPRD. The date of diagnosis for cases was defined as the date of pathological diagnosis, but if this was unavailable, the date of the first cancer code entered in the GPRD was used.

	Controls: Up to 13 controls (children with no diagnosis of cancer at any time) were selected per case, using a computer-generated random sequence, matched on age (within 1 year), sex and practice, and had to be currently registered on the date of diagnosis of their matched case (the index date). Exclusion criteria: None listed Clinical setting: Primary care, UK.
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	The GPRD uses just over 100 000 medical codes to encompass all primary care events, including both symptoms and diagnoses. From this list, libraries of codes were assembled representing individual alert symptoms derived from the NICE referral guidelines for suspected cancer in children. *No more information reported.*
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Cancer diagnosis in the UK's General Practice Research Database.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	This study is published in three papers.

Williamson (1985)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Retrospective consecutive patient series
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes (probably)**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 249, mean age = 24 years, 26% were < 15 years; 58% females. Inclusion criteria: Patients seen at the Family Medical Care Centre of the University of Missouri-Columbia, between July 1 19978 and June 30 1983 whose diagnoses were coded as "enlarged lymph nodes, not infected" (ICHPPC 266) and "lymphadenitis, acute" (ICHPPC 209). Exclusion criteria: None listed Clinical setting: Family Medical Care Centre of the University of Missouri-Columbia.
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	Diagnoses coded as "enlarged lymph nodes, not infected" (ICHPPC 266) and "lymphadenitis, acute" (ICHPPC 209).
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Diagnoses were accepted if verified by history, physical examination or laboratory tests. Outcomes were determined, where possible, from the medical record. Follow up was considered adequate to determine an adverse outcome if one of four criteria were met: 1) A definite diagnosis was made, 2) The nodes were documented to be resolving, 3) There was at least one chart entry for any condition at least 6 months after the index visit for lymphadenopathy, or 4) The patient was reached by telephone and determined to have a favourable outcome.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No (but all patients had a positive index test)**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	11/249 patients did not fit the criteria for adequate follow up: 3/11 had return visits showing no increase in the size of the nodes, 6/11 had nodes < 1 cm in size and were told to come back if the nodes did not resolve, 2/11 presented with cervical lymph nodes described as 1 cm in size and follow up examination was not recommended. None of these 11 patients could be reached by phone.
Was there an appropriate interval between index test and reference standard?	**Yes (probably)**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Unclear**
Could the patient flow have introduced bias?	**Unclear risk**
NOTES	The author note that the study would not have included all the patients presenting with enlarged lymph nodes during the study period because not all such patients would have the diagnosis noted as required for study entry, e.g., a diagnosis of infectious mononucleosis made on the first visit would probably have been coded as such and not as enlarged lymph nodes.

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Review question:
Which investigations of symptoms of suspected Non-Hodgkin's lymphoma cancer should be done with clinical responsibility retained by primary care?

Results

Literature search

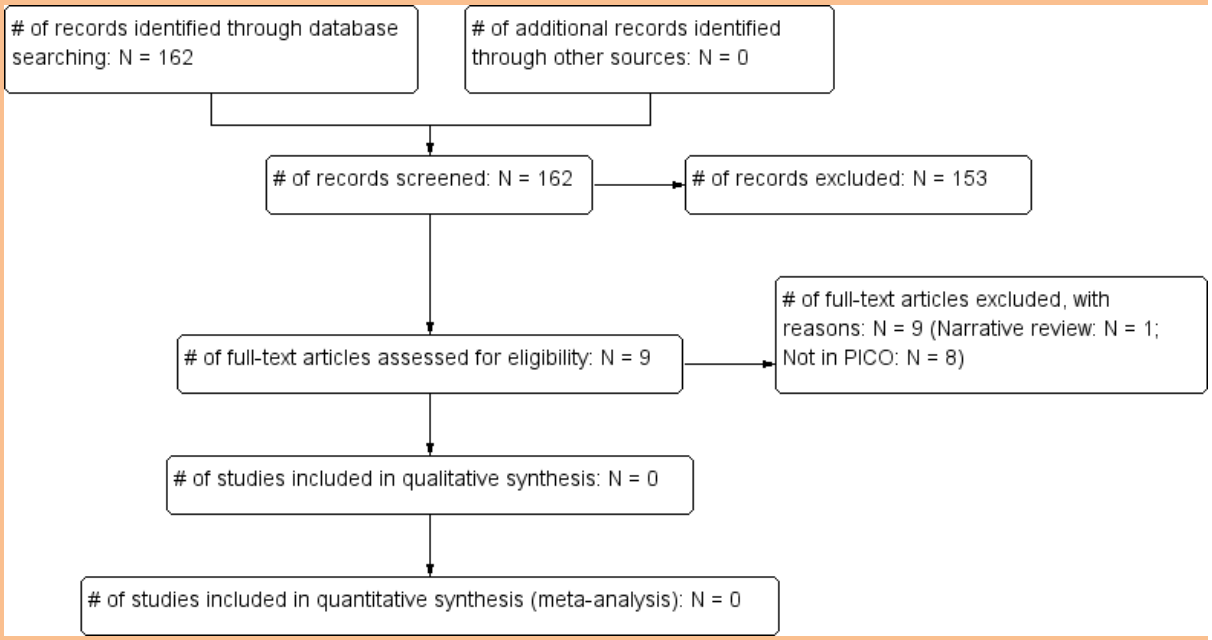
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-2012	320	102	20/12/2012
Premedline	1980-2012	3	1	07/01/2013
Embase	1980-2012	331	64	20/12/2012
Cochrane Library	1980-2012	31	0	07/01/2013
Psychinfo	1980-2012	0	0	07/01/2013
Web of Science (SCI & SSCI) and ISI Proceedings	19802012	31	2	07/01/2013
Biomed Central	1980-2012	312	1	07/01/2013

Total References retrieved (after de-duplication): 140

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2013-20/08/2014	19	5	20/08/2014
Premedline	2013-20/08/2014	5	4	20/08/2014
Embase	2013-20/08/2014	87	16	20/08/2014
Cochrane Library	2013-20/08/2014	19	0	20/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	2013-20/08/2014	3	0	20/08/2014

Total References retrieved (after de-duplication): 22



Study results

No evidence was identified pertaining to the diagnostic accuracy of CT scan, ultrasound, chest X-ray or LDH in patients with suspected non-hodgkin's lymphoma cell cancer where the clinical responsibility was retained by primary care.

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Included studies

None

Excluded studies

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HODGKIN'S LYMPHOMA

Review question:

What is the risk of Hodgkin's lymphoma in patients presenting in primary care with symptom(s)?

Results

Literature search

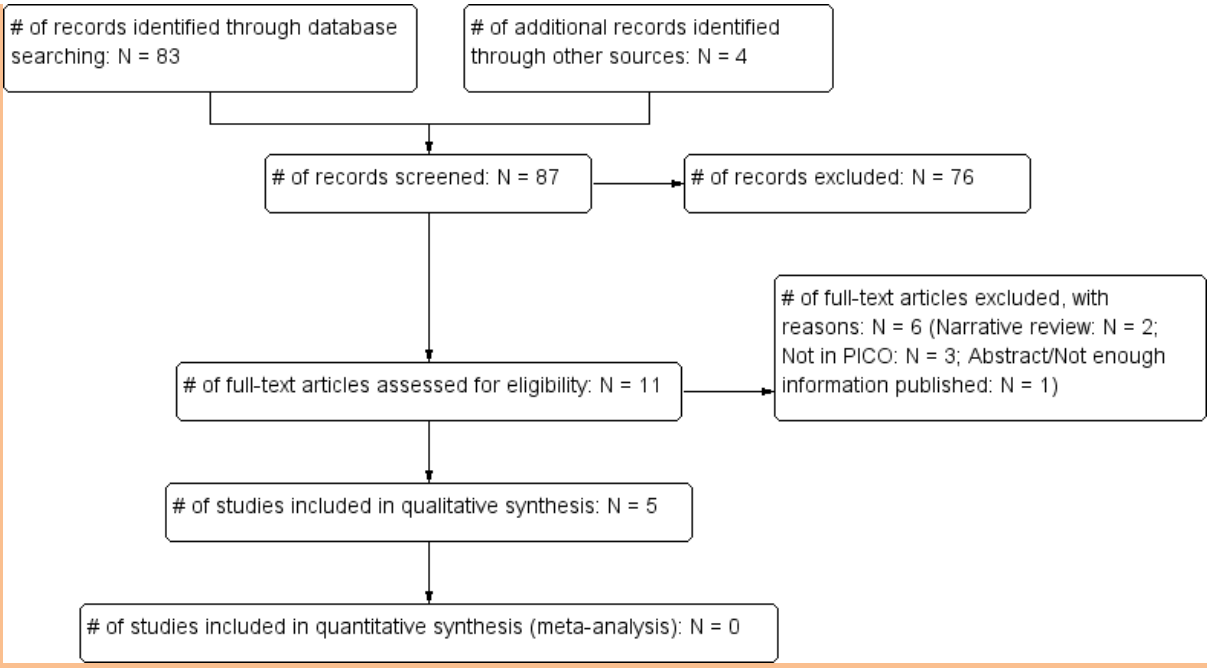
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2012	356	35	25/10/2012
Premedline	All-2012	8	0	25/10/2012
Embase	All-2012	587	49	25/10/2012
Cochrane Library	All-2012	124	0	25/10/2012
Psychinfo	All-2012	8	0	25/10/2012
Web of Science (SCI & SSCI) and ISI Proceedings	All-2012	184	6	25/10/2012
Biomed Central	All-2012	279	2	25/10/2012

Total References retrieved (after de-duplication): 83

Update Search

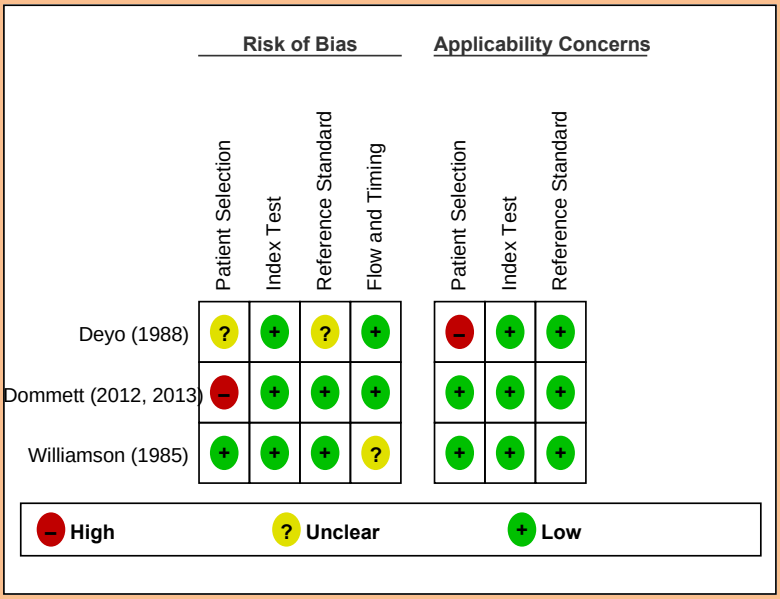
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	10/2012-26/08/2014	12	0	26/08/2014
Premedline	10/2012-26/08/2014	27	0	26/08/2014
Embase	10/2012-26/08/2014	224	0	26/08/2014
Cochrane Library	10/2012-26/08/2014	37	0	26/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	10/2012-26/08/2014	42	0	26/08/2014

Total References retrieved (after de-duplication): 0



Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issue to note is that 2/3 studies employed samples of patients that are not directly representative of an unselected symptomatic population of patients presenting to the UK-based GP, and that there was some uncertainty about the verification of the outcome for some of the patients. Dommett (2012; 2013a,b) employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence.



Study results

Table 1: Hodgkin's lymphoma: Adult and mixed age populations

Study	Symptom(s)	Patient group	PPVs (95% CI)
Deyo (1988)	Back pain	All included patients	0.1 (0.02-0.41) 2/1975 7 had other types of cancer: lymphoma (NOS): N = 2, unknown primary: N = 1, Prostate: N = 1, retroperitoneal liposarcoma: N = 1, lung cancer: N = 1, renal cell: N = 1, multiple myeloma: N = 1, mucinous adenocarcinoma (of gallbladder?): N = 1
Williamson (1985)	Lymphadenopathy	All included patients	0.8 (0.1-3.2) TP = 2, FP = 247 Cancer: Hodgkin's: N = 1 Adenocarcinoma: N = 1

TP = True positives, FP = False positives.

Table 2: Hodgkin's lymphoma: Positive predictive values for leukaemia/lymphoma childhood cancer

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013a)	Bruising 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.53 (0.07-3.91)
Dommett (2013a)	Pallor 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.43 (0.06-3.15)
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.35 (0.05-2.65)
Dommett (2013a)	Fatigue 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.07 (0.03-0.15)
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.06 (0.04-0.11)

Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.05 (0.02-0.13)
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.03 (0.01-0.08)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.03 (0.01-0.06)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.02 (0.01-0.03)
Dommett (2013a)	Fever 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0.01-0.01)
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01(0-0.01)
Dommett (2013a)	≥ 3 consultations	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01(0.01-0.01)

The positive predictive values are calculated using Bayesian statistics.

Table 3: Hodgkin's lymphoma: Positive predictive values for teenage and young adult lymphoma

Study	**Symptom(s)**	**Patient group**	**Positive predictive value (95% CI) Frequency**
Dommett (2013b)	Lump mass swelling head and neck	All included lymphoma patients and controls aged 15-24 years	0.5034 (0.0696-3.68) Cases: 35/270 Controls: 1/3350
Dommett (2013b)	Lump mass swelling below neck excluding abdomen	All included lymphoma patients and controls aged 15-24 years	0.0279 (0.0152-0.0515) Cases: 29/270 Controls: 15/3350
Dommett (2013b)	Lymphadenopathy	All included lymphoma patients and controls aged 15-24 years	0.278 (0.1-0.75) Cases: 77/270 Controls: 4/3350
Dommett (2013b)	'Lump mass swelling head and neck', 'lymphadenopathy' and 'lump mass swelling below neck excluding abdomen' combined as a single symptom	All included lymphoma patients and controls aged 15-24 years	0.0903 (0.057-0.1425)

Dommett (2013b)	≥ 3 consultations	All included lymphoma patients and controls aged 15-24 years	0.0086 (0.0075-0.0099) Cases: 175/270 Controls: 294/3350

The positive predictive values are calculated using Bayesian statistics.

Evidence statement(s):

Adult and mixed age populations

Back pain (1 study, N = 1975) and lymphadenopathy (1 study, N = 249) presenting in a primary care setting do not appear to confer a markedly increased risk of Hodgkin's/Non-Hodgkin's lymphoma, although the study populations are probably not directly representative of the typical unselected symptomatic UK GP population (see also Table 1).

Children and teenagers and young adults

The positive predictive values of having leukaemia/lymphoma childhood cancer ranged from 0.01% (for fever and abdominal pain) to 0.53% (for bruising) for patients aged 0-14 years old, and the positive predictive values of having young adulthood lymphoma ranged from 0.0279% (for 'lump mass swelling below the neck excluding the abdomen') to 0.5034% (for 'lump mass swelling head and neck') for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Tables 2-3).

Evidence tables

Deyo (1988)

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Prospective consecutive? patient series	
Was a consecutive or random sample of patients enrolled?		**Unclear**
Was a case-control design avoided?		**Yes**
Did the study avoid inappropriate exclusions?		**Yes (probably)**
Could the selection of patients have introduced bias?		**Unclear risk**
B. Concerns regarding applicability		
Patient characteristics and setting	N = 1975, mean (SD; range) age = 39.5 (15.4; 15-86) years, 62% females. 54% of the patients were seeking medical care for back pain for the first time and 76% of the patients had had back pain for < 3 months. 3% had a history of back pain surgery. Maximal back pain in the low back (84%) or in the upper back (16%). Inclusion criteria: Patients who sought treatment between March 1982 and September 1984 in the walk-in clinic of a public hospital where virtually all patients are self-referred. In each case back pain was part of the chief complaint. Exclusion criteria: Neck pain. Clinical setting: Walk-in clinic of a public hospital; this clinic is a source of primary care for indigent persons in a county in the USA with a population of approximately 1 million.	
Are there concerns that the included patients and setting do not match the review question?		**High concern**

INDEX TEST		
A. Risk of bias		
Index test	Back pain; not further specified.	
Were the index test results interpreted without knowledge of the results of the reference standard?		**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?		**Yes**
Could the conduct or interpretation of the index test have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		**Low concern**
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	The reference standard consisted of a search on each patient name in the institutional tumour registry ≥ 6 months after the index visit. The registry included every patient with a histological diagnosis of cancer made in the authors' hospital system regardless of site of care. The authors point out that "while this method might fail to identify cancer patients who sought care elsewhere, it is likely that most patients sought follow-up for a particular illness at the same facility.	
Is the reference standard likely to correctly classify the target condition?		**Unclear**
Were the reference standard results interpreted without knowledge of the results of the index tests?		**No (but all patients had a positive index test)**
Could the reference standard, its conduct, or its interpretation have introduced bias?		**Unclear risk**
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		**Low concern**
FLOW AND TIMING		
A. risk of bias		
Flow and timing	All the patients are accounted for in the results.	
Was there an appropriate interval between index test and reference standard?		**Yes (probably)**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**Yes**
Could the patient flow have introduced bias?		**Low risk**
NOTES	It is a concern that some patients with cancer might have been missed due to the choice of reference standard because this would result in an underestimation of the positive predictive value. 38/1975 patients were found in the tumour registry. Of those 38, 13 patients had tumours that were probable causes of back pain, and 4 of these 13 patients already had a diagnosis of cancer at presentation. The 9/1975 patients who had undiagnosed cancer that the back pain could be attributed to had: Lymphoma (NOS; 2), cancer of unknown primary (1), prostate cancer	

	(1), retroperitoneal liposarcoma (1), lung cancer (1), renal cell (1), multiple myeloma (1), mucinous adenocarcinoma (of gallbladder?; 1)

Dommett (2012; 2013a,b)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Population-based nested case-control study using data from the General Practice Research Database (GPRD)
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: 1267 children; aged 0-4 years: N = 436; aged 5-14 years: N = 831; 703 males/564 females. Cancer type: Leukemia: N = 368; brain: N = 270; lymphoma: N = 142; bone: N = 107; soft tissue sarcoma: N = 91; renal: N = 82; neuroblastoma: N = 75; other ICD codes: N = 132. 1064 teenagers and young adults (TYA): 15-24 years: Gender not reported. Cancer type: Leukemia: N = 143; brain: N = 154; lymphoma: N = 270; bone: N = 96; soft tissue sarcoma: N = 100; other ICD codes: N = 301 (including testis: N = 60; skin: N = 49; ovary: N = 20 and thyroid: N = 17). Controls: 15318 children; aged 0-4 years: N = 4802; aged 5-14 years: N = 10516; 8461 males/6857 females. 13206 TYA. Gender not reported Inclusion criteria: The sample comprised all children and TYU aged 0–24 years, inclusive, drawn from all general practices contributing research-standard data to the GPRD between 1 January 1988 and 31 December 2010. To be included, the practices had to have been contributing research-standard data for a minimum of 1 year before each child's date of cancer diagnosis or the index date (see below) for matched controls. Cases: Patients diagnosed with the following cancers: leukaemia, lymphoma, neuroblastoma, soft tissue sarcoma, hepatic, renal, bone and central nervous system tumours, using pre-defined medical codes used in the GPRD. The date of diagnosis for cases was defined as the date of pathological diagnosis, but if this was unavailable, the date of the first cancer code entered in the GPRD was used. Controls: Up to 13 controls (children with no diagnosis of cancer at any time) were selected per case, using a computer-generated random sequence, matched on age (within 1 year), sex and practice, and had to be currently

	registered on the date of diagnosis of their matched case (the index date). Exclusion criteria: None listed Clinical setting: Primary care, UK.
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	The GPRD uses just over 100 000 medical codes to encompass all primary care events, including both symptoms and diagnoses. From this list, libraries of codes were assembled representing individual alert symptoms derived from the NICE referral guidelines for suspected cancer in children. *No more information reported.*
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Cancer diagnosis in the UK's General Practice Research Database.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	This study is published in three papers.

Williamson (1985)

PATIENT SELECTION

A. risk of bias	
Patient sampling	Retrospective consecutive patient series
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes (probably)**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 249, mean age = 24 years, 26% were < 15 years; 58% females. Inclusion criteria: Patients seen at the Family Medical Care Centre of the University of Missouri-Columbia, between July 1 19978 and June 30 1983 whose diagnoses were coded as "enlarged lymph nodes, not infected" (ICHPPC 266) and "lymphadenitis, acute" (ICHPPC 209). Exclusion criteria: None listed Clinical setting: Family Medical Care Centre of the University of Missouri-Columbia.
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	Diagnoses coded as "enlarged lymph nodes, not infected" (ICHPPC 266) and "lymphadenitis, acute" (ICHPPC 209).
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Diagnoses were accepted if verified by history, physical examination or laboratory tests. Outcomes were determined, where possible, from the medical record. Follow up was considered adequate to determine an adverse outcome if one of four criteria were met: 1) A definite diagnosis was made, 2) The nodes were documented to be resolving, 3) There was at least one chart entry for any condition at least 6 months after the index visit for lymphadenopathy, or 4) The patient was reached by telephone and determined to have a favourable outcome.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No (but all patients had a positive index test)**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined	**Low concern**

by the reference standard does not match the question?		
FLOW AND TIMING		
A. risk of bias		
Flow and timing	11/249 patients did not fit the criteria for adequate follow up: 3/11 had return visits showing no increase in the size of the nodes, 6/11 had nodes < 1 cm in size and were told to come back if the nodes did not resolve, 2/11 presented with cervical lymph nodes described as 1 cm in size and follow up examination was not recommended. None of these 11 patients could be reached by phone.	
Was there an appropriate interval between index test and reference standard?		**Yes (probably)**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**Unclear**
Could the patient flow have introduced bias?		**Unclear risk**
NOTES	The author note that the study would not have included all the patients presenting with enlarged lymph nodes during the study period because not all such patients would have the diagnosis noted as required for study entry, e.g., a diagnosis of infectious mononucleosis made on the first visit would probably have been coded as such and not as enlarged lymph nodes.	

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Review question:

Which investigations of symptoms of suspected Hodgkin's lymphoma should be done with clinical responsibility retained by primary care?

Results

Literature search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-2013	89	20	14/05/2013

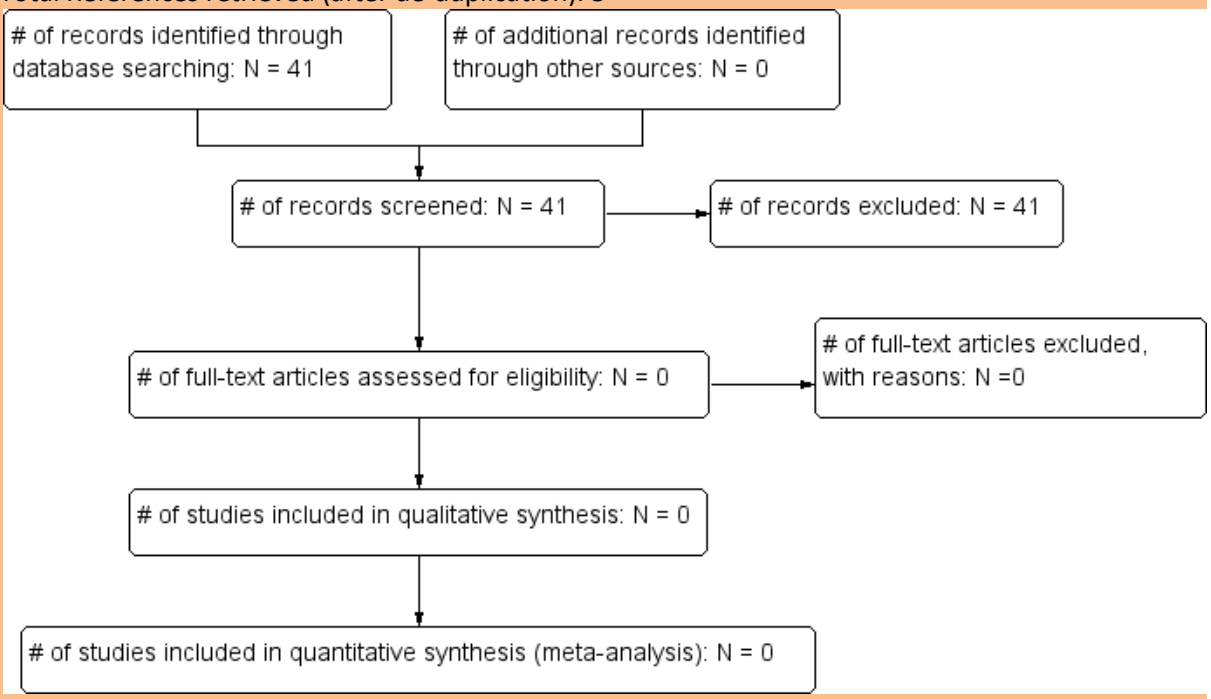
Premedline	1980-2013	5	2	14/05/2013
Embase	1980-2013	71	19	14/05/2013
Cochrane Library	1980-2013	31	1	14/05/2013
Psychinfo	1980-2013	2	0	14/05/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2013	8	3	14/05/2013

Total References retrieved (after de-duplication): 38

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	5/2013-26/08/2014	6	0	26/08/2014
Premedline	5/2013-26/08/2014	7	2	26/08/2014
Embase	5/2013-26/08/2014	17	1	26/08/2014
Cochrane Library	5/2013-26/08/2014	4	0	26/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	5/2013-26/08/2014	2	0	26/08/2014

Total References retrieved (after de-duplication): 3



Study results

No evidence was identified pertaining to the diagnostic accuracy of chest x-ray, CT scan, ultrasound or LDH in patients with suspected Hodgkin's lymphoma where the clinical responsibility was retained by primary care.

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Included studies

None

Excluded studies (with excl reason)

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SARCOMAS

BONE SARCOMA

Review question:
What is the risk of bone sarcoma in patients presenting in primary care with symptom(s)?

Results

Literature search

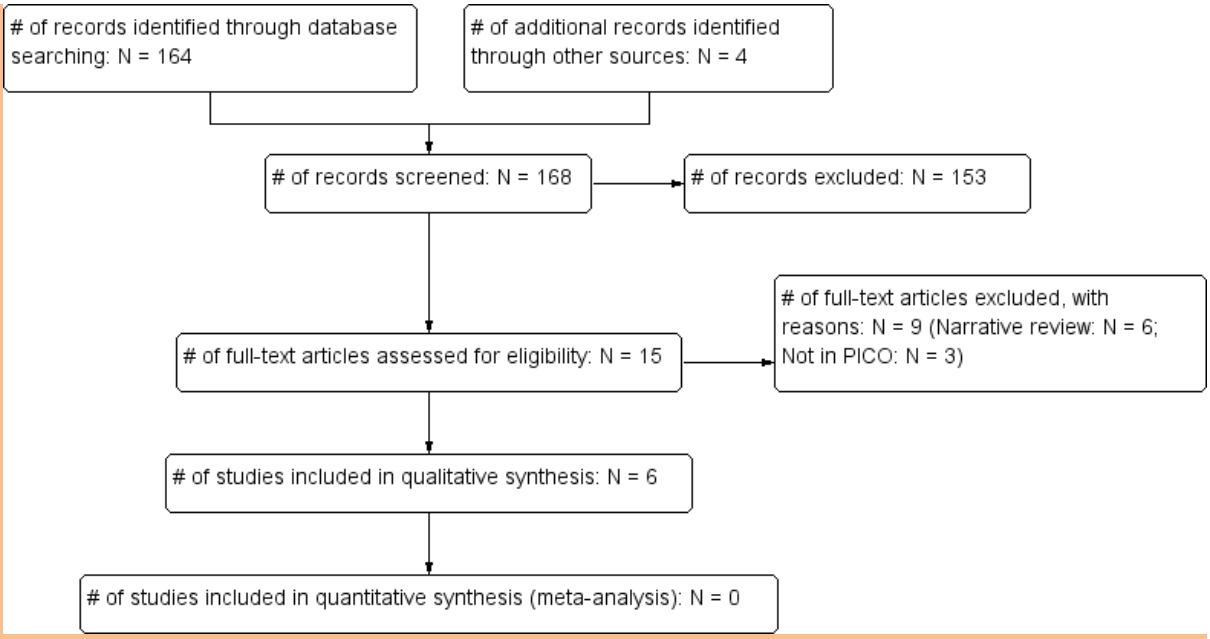
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2012	2069	78	11/10/12
Premedline	All-2012	57	8	11/10/12
Embase	All-2012	2009	76	11/10/12
Cochrane Library	All-2012	407	2	15/10/12
Psychinfo	All-2012	10	1	11/10/12
Web of Science (SCI & SSCI) and ISI Proceedings	All-2012	706	14	15/10/12
Biomed Central	All-2012	138	5	15/10/12

Total References retrieved (after de-duplication): 155

Update Search

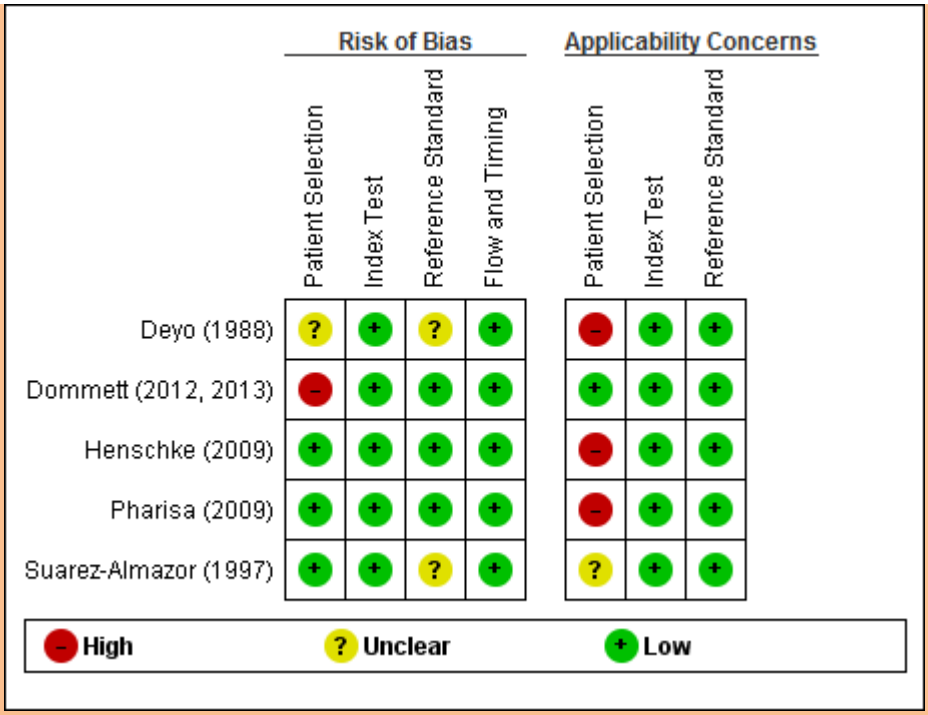
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	10/2012-26/08/2014	85	1	26/08/2014
Premedline	10/2012-26/08/2014	60	4	26/08/2014
Embase	10/2012-26/08/2014	258	6	26/08/2014
Cochrane Library	10/2012-26/08/2014	262	0	26/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	10/2012-26/08/2014	134	0	26/08/2014

Total References retrieved (after de-duplication): 9



Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issue to note is that 4/5 studies employed samples of patients that are not directly representative of an unselected symptomatic population of patients presenting to the UK-based GP. In the case of Pharisa (2009) whose sample consisted of patients presenting as emergencies, the symptom spectrum is likely to be of the more severe kind than those typically seen by a GP in the UK, but in the other cases (e.g., presentations to physiotherapists, chiropractors and hospital-based walk-in and family clinics) it is unclear how the patients differ from those of primary current interest. Dommett (2012, 2013a,b) only presented results for bone and soft tissue sarcoma in combination and also employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence. Finally, two studies employed reference standards that are at some (unknown level of) risk of failing to identify all patients with cancer, which means that the relevant PPVs may be underestimated (to the extent that the reference standards have failed to identify patients with cancer).



Study results

Table 1: Bone sarcoma: Patients aged > 14-15 years

Study	Symptom(s)	Patient group	PPVs (95% CI); prevalence
Deyo (1988)	Back pain	All included patients	0 (0-0.2) 0/1975 None had bone sarcoma, but N = 9 had other types of cancer
Suarez-Almazor (1997)	Acute low back pain	All included patients	TP = 0-1, FP = 962-963 Unclear if diagnosis prior to symptom
Henschke (2009)	Acute low back pain	All included patients	0 (0-0.4) 0/1172 None had cancer
Henschke (2009)	Acute low back pain + age at onset < 20 years or > 55 years	Subgroup with both symptoms	0 (0-1.7) 0/281 None had cancer
Henschke (2009)	Acute low back pain + previous history of cancer	Subgroup with both symptoms	0 (0-9.6) 0/46 None had cancer
Henschke (2009)	Acute low back pain + tried bed rest, but no relief	Subgroup with both symptoms	0 (0-2.4) 0/192 None had cancer
Henschke (2009)	Acute low back pain + unexplained weight loss	Subgroup with both symptoms	0 (0-69) 0/3

			None had cancer
Henschke (2009)	Acute low back pain + insidious onset	Subgroup with both symptoms	0 (0-2.3) 0/202 None had cancer
Henschke (2009)	Acute low back pain + systemically unwell	Subgroup with both symptoms	0 (0-15.5) 0/27 None had cancer
Henschke (2009)	Acute low back pain + constant progressive non-mechanical pain	Subgroup with both symptoms	0 (0-13) 0/33 None had cancer
Henschke (2009)	Acute low back pain + sensory level altered from trunk down	Subgroup with both symptoms	0 (0-20.9) 0/19 None had cancer

TP = True positives, FP = False positives.

Table 2: Bone sarcoma: Positive predictive values for child- or young adulthood bone tumour/soft tissue sarcoma

Study	**Symptom(s)**	**Patient group**	**Positive predictive value (95% CI) Frequency**
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included bone tumour/soft tissue sarcoma patients and controls aged 0-14 years	0.03 (0.01-0.14)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included bone tumour/soft tissue sarcoma patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013a)	Trauma 0-3 months before diagnosis	All included bone tumour/soft tissue sarcoma patients and controls aged 0-14 years	0 (0-0)
Dommett (2013a)	≥ 3 consultations	All included bone tumour/soft tissue sarcoma patients and controls aged 0-14 years	0 (0-0)
Dommett (2013b)	Lump mass swelling	All included bone tumour/soft tissue sarcoma patients and controls aged 15-24 years	0.0415 (0.0124-0.1392) Cases: 19/196 Controls: 3/2438
Dommett (2013b)	Musculoskeletal symptoms	All included bone tumour/soft tissue sarcoma patients and controls aged 15	0.0093 (0.0058-0.0151) Cases: 37/196 Controls: 26/2438
Dommett (2013b)	Chest pain	All included bone tumour/soft tissue	0.0027 (0.001-0.0077)

		sarcoma patients and controls aged 15	Cases: 5/196 Controls: 12/2438
Dommett (2013b)	≥ 3 consultations	All included bone tumour/soft tissue sarcoma patients and controls aged 15	0.003 (0.0024-0.0037) Cases: 86/196 Controls: 189/2438
Pharisa (2009)	Neck pain	Children ≤ 16 years	TP = 0, FP = 170 None had cancer

The positive predictive values are calculated using Bayesian statistics. TP = true positives, FP = false positives

Evidence statement(s):

Adult patients

Acute low back pain alone (2 studies, N = 2135) or in combination with other single risk factors/symptoms (1 study, N = 19-281), and back pain (1 study, N = 1975) presenting in a primary care setting do not appear to confer an increased risk of bone sarcoma, although the study populations are probably not directly representative of the typical unselected symptomatic UK GP population (see also Table 1).

Children, teenage and young adult patients

The positive predictive values of having childhood or young adulthood bone sarcoma tumour/soft tissue sarcoma ranged from 0% (for trauma) to 0.03% (for 'lump mass swelling below neck excluding abdomen') for patients aged 0-14 years old, and from 0.0027% (for chest pain) to 0.0415% (for 'lump mass swelling') for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 2).

Neck pain (1 study, N = 170) presenting in a primary care setting does not appear to confer an increased risk of bone sarcoma, although the study population is not directly representative of the typical unselected symptomatic UK GP population (see also Table 2).

Evidence tables

Deyo (1988)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective consecutive? patient series
Was a consecutive or random sample of patients enrolled?	**Unclear**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes (probably)**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Patient	N = 1975, mean (SD; range) age = 39.5 (15.4; 15-86) years, 62% females. 54%

characteristics and setting	of the patients were seeking medical care for back pain for the first time and 76% of the patients had had back pain for < 3 months. 3% had a history of back pain surgery. Maximal back pain in the low back (84%) or in the upper back (16%). Inclusion criteria: Patients who sought treatment between March 1982 and September 1984 in the walk-in clinic of a public hospital where virtually all patients are self-referred. In each case back pain was part of the chief complaint. Exclusion criteria: Neck pain. Clinical setting: Walk-in clinic of a public hospital; this clinic is a source of primary care for indigent persons in a county in the USA with a population of approximately 1 million.
Are there concerns that the included patients and setting do not match the review question?	**High concern**
INDEX TEST	
A. Risk of bias	
Index test	Back pain; not further specified.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	The reference standard consisted of a search on each patient name in the institutional tumour registry ≥ 6 months after the index visit. The registry included every patient with a histological diagnosis of cancer made in the authors' hospital system regardless of site of care. The authors point out that "while this method might fail to identify cancer patients who sought care elsewhere, it is likely that most patients sought follow-up for a particular illness at the same facility.
Is the reference standard likely to correctly classify the target condition?	**Unclear**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No (but all patients had a positive index test)**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	

Flow and timing	All the patients are accounted for in the results.
Was there an appropriate interval between index test and reference standard?	**Yes (probably)**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	It is a concern that some patients with cancer might have been missed due to the choice of reference standard because this would result in an underestimation of the positive predictive value. 38/1975 patients were found in the tumour registry. Of those 38, 13 patients had tumours that were probable causes of back pain, and 4 of these 13 patients already had a diagnosis of cancer at presentation. The 9/1975 patients who had undiagnosed cancer that the back pain could be attributed to had: Lymphoma (NOS; 2), cancer of unknown primary (1), prostate cancer (1), retroperitoneal liposarcoma (1), lung cancer (1), renal cell (1), multiple myeloma (1), mucinous adenocarcinoma (of gallbladder?; 1)

Dommett (2012; 2013a,b)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Population-based nested case-control study using data from the General Practice Research Database (GPRD)
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: 1267 children; aged 0-4 years: N = 436; aged 5-14 years: N = 831; 703 males/564 females. Cancer type: Leukemia: N = 368; brain: N = 270; lymphoma: N = 142; bone: N = 107; soft tissue sarcoma: N = 91; renal: N = 82; neuroblastoma: N = 75; other ICD codes: N = 132. 1064 teenagers and young adults (TYA): 15-24 years: Gender not reported. Cancer type: Leukemia: N = 143; brain: N = 154; lymphoma: N = 270; bone: N = 96; soft tissue sarcoma: N = 100; other ICD codes: N = 301 (including testis: N = 60; skin: N = 49; ovary: N = 20 and thyroid: N = 17). Controls: 15318 children; aged 0-4 years: N = 4802; aged 5-14 years: N = 10516; 8461 males/6857 females. 13206 TYA. Gender not reported Inclusion criteria:

	The sample comprised all children and TYU aged 0–24 years, inclusive, drawn from all general practices contributing research-standard data to the GPRD between 1 January 1988 and 31 December 2010. To be included, the practices had to have been contributing research-standard data for a minimum of 1 year before each child's date of cancer diagnosis or the index date (see below) for matched controls. Cases: Patients diagnosed with the following cancers: leukaemia, lymphoma, neuroblastoma, soft tissue sarcoma, hepatic, renal, bone and central nervous system tumours, using pre-defined medical codes used in the GPRD. The date of diagnosis for cases was defined as the date of pathological diagnosis, but if this was unavailable, the date of the first cancer code entered in the GPRD was used. Controls: Up to 13 controls (children with no diagnosis of cancer at any time) were selected per case, using a computer-generated random sequence, matched on age (within 1 year), sex and practice, and had to be currently registered on the date of diagnosis of their matched case (the index date). Exclusion criteria: None listed Clinical setting: Primary care, UK.
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	The GPRD uses just over 100 000 medical codes to encompass all primary care events, including both symptoms and diagnoses. From this list, libraries of codes were assembled representing individual alert symptoms derived from the NICE referral guidelines for suspected cancer in children. *No more information reported.*
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Cancer diagnosis in the UK's General Practice Research Database.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	

Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	This study is published in three papers.

Henschke (2009)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective consecutive patient series
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 1172, mean (SD) age = 43.97 (15.1) years, 626 males/546 females; Primary care physician consulted: Medical practitioner (N = 267), physiotherapist (N = 851), chiropractor (N = 54); Previous episode of low back pain (N = 888); Duration of low back pain: < 1 week (N = 696), 1-2 weeks (N = 145), 2-3 weeks (N =174), 3-4 weeks (N = 73), 4-5 weeks (N = 30), 5-6 weeks (N = 54). Inclusion criteria: Consecutive English-speaking (and writing) patients aged ≥ 14 years with acute low back pain who presented for a first consultation to participating primary care providers in the Sydney region of Australia. *Please note that in Australia, the majority of primary care management for low back pain is provided by general medical practitioners, physiotherapists and chiropractors.* Exclusion criteria: Diagnosis of serious pathology prior to the consultation, which was considered to be the cause of the current episode of low back pain. Clinical setting: Primary care (including physiotherapy and chiropractice)
Are there concerns that the included patients and setting do not match the review question?	**High concern**
INDEX TEST	
A. Risk of bias	
Index test	An episode of acute low back pain was defined as pain in the area bounded superiorly by T12 and inferiorly by the buttock crease, lasting for more than 24 hours but less than 6 weeks, and preceded by a period of at least 1 month without back pain. Patients remained eligible if they also had pain that referred beyond this region.
Were the index test results interpreted without knowledge	**Yes**

of the results of the reference standard?	
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	The reference standard consisted of close follow up for 12 months. Participants were contacted by telephone 6 weeks, 3 months, and 12 months after the initial consultation. At each follow up contact, participants were asked the following question: "Low back pain is occasionally the result of a fracture, infection, arthritis, or cancer. Has a health care provider said that your back pain is caused by one of these rare diseases?" Participants were also prompted to provide any further details of a diagnosis or explanation for their low back pain that had been provided to them. All patients with potentially serious pathology were subsequently examined by a study rheumatologist. At each follow up contact, participants were also questioned to establish whether they had recovered from the episode of low back pain. Recovery was defined as 1 month with no pain, no interference with function due to pain, and return to previous work status for 1 month. Patients suspected by their primary care clinician of having a serious spinal pathology and those who reported having a serious spinal pathology during the follow up period were referred immediately to 1 of 2 study rheumatologists for a clinical assessment. Within 2 weeks from the time of referral, the rheumatologists examined each patient in their clinics and were additionally provided with the complete medical histories and all test results.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No (but all patients had a positive index test)**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for in the results
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	Please note that the primary care physician consulted were: Medical practitioner: N = 267, physiotherapist: N = 851, chiropractor: N = 54

Pharisa (2009)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Retrospective consecutive patient series
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 170 (61 females/109 males), mean age = 9.05 years, median age = 9 years (range = 7 weeks to 16 years). A history of trauma was clearly reported in 106 of the children and clinical examination revealed restricted neck movements in 48 of these patients and painful movements without restriction in 28 of these patients. None of the patients had a neurological deficit on initial physical examination. Inclusion criteria: All children aged ≤ 16 years presenting with neck pain and/or restricted neck movements from October 2004 to September 2005. Although any child with a complaint of neck pain was considered for inclusion in the study, only those whose neck pain was confirmed during medical examination were included. Exclusion criteria: Toxic-appearing children with obvious signs of meningitis Clinical setting: Emergency department of the Children's Hospital of Lausanne, Switzerland
Are there concerns that the included patients and setting do not match the review question?	**High concern**
INDEX TEST	
A. Risk of bias	
Index test	"Neck pain confirmed during medical examination"
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Chart review and follow-up, including telephone calls to paediatricians to confirm final diagnosis
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No (but all patients had a positive index test)**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**

B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	Follow up data were obtained by telephone in 134/170 patients, but final diagnoses are presented for all 170 patients.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	

Suarez-Almazor (1997)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Retrospective consecutive patient series
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 1550, of whom N = 331 had chronic (> 3 months?) back pain, N = 963 had acute (< 3 months) low back pain, and N = 256 had back pain of unspecified duration. Of the patients with acute low back pain, 442 were males, and it appears that the mean (SD) age = 42.2 (15.6) years for the patients with acute low back pain, 14/963 had a history of cancer Inclusion criteria: All patients aged ≥ 18 years presenting to four family clinics in Edmonton (Alberta, Canada) between January 1 1992 and December 31 1993 with low back pain or leg pain compatible with sciatic pain for which no visit had been made within the past 12 months. Exclusion criteria: Low back pain attributable to visceral pain (e.g., urinary infection, inflammatory pelvic disease), previous diagnosis of ankylosing apondylitis, pregnancy. Clinical setting: Four family clinics in Edmonton (Alberta, Canada), two of which are university-affiliated and hospital-based, with the other two based in the community.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Acute (< 3 months) low back pain; not further specified.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test	**Low risk**

have introduced bias?	
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Follow up consisting of chart review after a minimum of 2 years. Patients were considered to have cancer if recorded in the physician notes or in reports from laboratory or diagnostic tests.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No (but all patients had a positive index test)**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	The results are only presented for the patients with acute low back pain.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	13/963 patients with acute low back pain had active cancer. 3 of those 13 patients had the cancer diagnosis prior to the index visit; 3/13 patients had tumours that were probable causes of the acute low back pain (spinal infiltrates from multiple myeloma [2] and metastatic bone disease with compression fractures [1]), and 10/13 patients had cancer that was not considered to have caused the acute low back pain (bladder cancer [3], colon [1], breast [1], thyroid [1], lung [1], prostate [1], endometrium [1], oesophagus [1]). However, as it is not reported which of these patients already had a diagnosis of cancer pre-index visit, it is not possible to present the data accurately for the individual cancers.

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Review question:
Which investigations of symptoms of suspected bone sarcoma should be done with clinical responsibility retained by primary care?

Results

Literature search

Database name	Dates	No of references	No of references	Finish date of

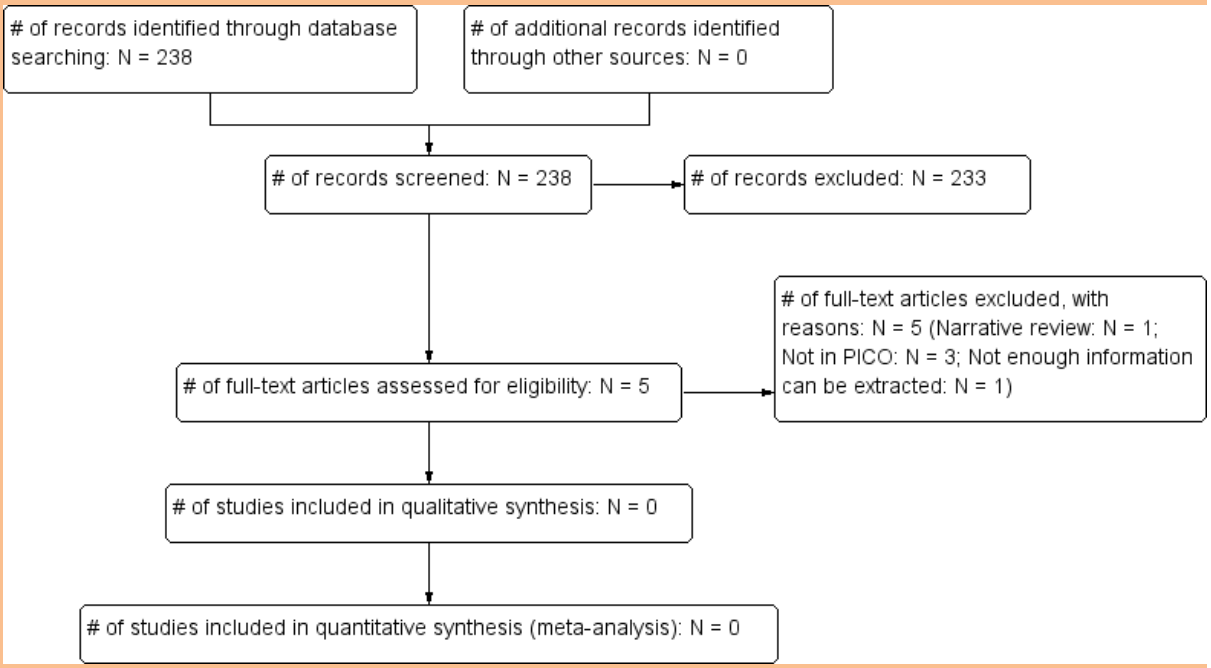
	Covered	found	retrieved	search
Medline	1980-2013	1289	104	25/03/2013
Premedline	1980-2013	100	16	25/03/2013
Embase	1980-2013	1277	125	27/03/2013
Cochrane Library	1980-2013	158	6	27/03/2013
Psychinfo	1980-2013	10	0	27/03/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2013	166	9	27/03/2013

Total References retrieved (after de-duplication): 219

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	3/2013-26/08/2014	60	7	26/08/2014
Premedline	3/2013-26/08/2014	98	11	26/08/2014
Embase	3/2013-26/08/2014	104	9	26/08/2014
Cochrane Library	3/2013-26/08/2014	116	0	26/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	3/2013-26/08/2014	26	0	26/08/2014

Total References retrieved (after de-duplication): 19



Study results

No evidence was identified pertaining to the diagnostic accuracy of x-ray, calcium or alkaline phosphatase in patients with suspected bone sarcoma where the clinical responsibility was retained by primary care.

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Included studies

None

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SOFT TISSUE SARCOMA

Review question:
What is the risk of soft tissue sarcoma in patients presenting in primary care with symptom(s)?

Results

Literature search

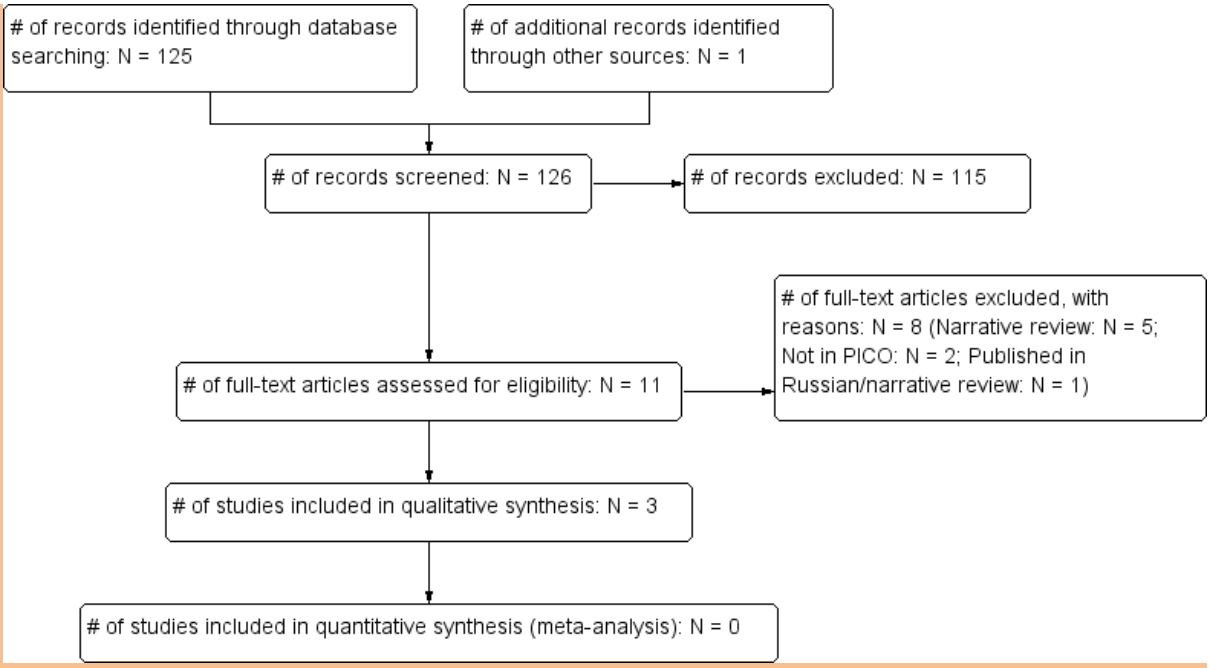
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2012	389	66	08/11/2012
Premedline	All-2012	26	6	08/11/2012
Embase	All-2012	287	63	08/11/2012
Cochrane Library	All-2012	82	0	08/11/2012
Psychinfo	All-2012	20	2	08/11/2012
Web of Science (SCI & SSCI) and ISI Proceedings	All-2012	192	6	08/11/2012
Biomed Central	All-2012	128	4	08/11/2012

Total References retrieved (after de-duplication): 118

Update Search

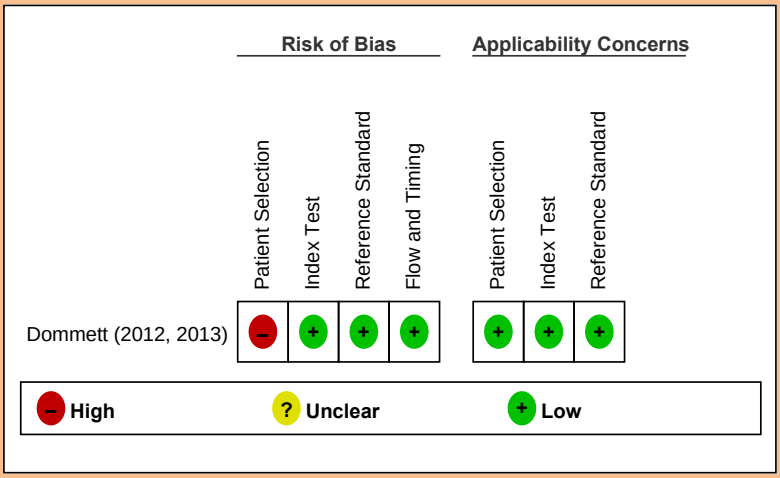
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	11/2012-26/08/2014	61	2	26/08/2014
Premedline	11/2012-26/08/2014	56	4	26/08/2014
Embase	11/2012-26/08/2014	23	2	26/08/2014
Cochrane Library	11/2012-26/08/2014	27	0	26/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	11/2012-26/08/2014	25	0	26/08/2014

Total References retrieved (after de-duplication): 7



Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included study in the figure below. The main issue to note is that the study only presented results for bone and soft tissue sarcoma in combination and also employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting the influence of the latter.



Study results

Table 1: Soft tissue sarcoma: Positive predictive values for child- or young adulthood bone cancer tumour/soft tissue sarcoma

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013a)	Lump mass swelling below neck excluding	All included bone cancer tumour/soft	0.03 (0.01-0.14)

	abdomen 0-3 months before diagnosis	tissue sarcoma patients and controls aged 0-14 years	
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013a)	Trauma 0-3 months before diagnosis	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0 (0-0)
Dommett (2013a)	≥ 3 consultations	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0 (0-0)
Dommett (2013b)	Lump mass swelling	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 15-24 years	0.0415 (0.0124-0.1392) Cases: 19/196 Controls: 3/2438
Dommett (2013b)	Musculoskeletal symptoms	All included lymphoma patients and controls aged 15-24 years	0.0093 (0.0058-0.0151) Cases: 37/196 Controls: 26/2438
Dommett (2013b)	Chest pain	All included lymphoma patients and controls aged 15-24 years	0.0027 (0.001-0.0077) Cases: 5/196 Controls: 12/2438
Dommett (2013b)	≥ 3 consultations	All included lymphoma patients and controls aged 15-24 years	0.003 (0.0024-0.0037) Cases: 86/196 Controls: 189/2438

The positive predictive values are calculated using Bayesian statistics.

Evidence statement(s):

The positive predictive values of having childhood or young adulthood bone cancer tumour/soft tissue sarcoma ranged from 0% (for trauma) to 0.03% (for 'lump mass swelling below neck excluding abdomen') for patients aged 0-14 years old, and from 0.0027% (for chest pain) to 0.0415% (for ‘lump mass swelling’) for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 1).

Evidence tables

Dommett (2012; 2013a,b)

PATIENT SELECTION
A. risk of bias

Patient sampling	Population-based nested case-control study using data from the General Practice Research Database (GPRD)
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: 1267 children; aged 0-4 years: N = 436; aged 5-14 years: N = 831; 703 males/564 females. Cancer type: Leukemia: N = 368; brain: N = 270; lymphoma: N = 142; bone: N = 107; soft tissue sarcoma: N = 91; renal: N = 82; neuroblastoma: N = 75; other ICD codes: N = 132. 1064 teenagers and young adults (TYA): 15-24 years: Gender not reported. Cancer type: Leukemia: N = 143; brain: N = 154; lymphoma: N = 270; bone: N = 96; soft tissue sarcoma: N = 100; other ICD codes: N = 301 (including testis: N = 60; skin: N = 49; ovary: N = 20 and thyroid: N = 17). Controls: 15318 children; aged 0-4 years: N = 4802; aged 5-14years: N = 10516; 8461 males/6857 females. 13206 TYA. Gender not reported Inclusion criteria: The sample comprised all children and TYU aged 0–24 years, inclusive, drawn from all general practices contributing research-standard data to the GPRD between 1 January 1988 and 31 December 2010. To be included, the practices had to have been contributing research-standard data for a minimum of 1 year before each child's date of cancer diagnosis or the index date (see below) for matched controls. Cases: Patients diagnosed with the following cancers: leukaemia, lymphoma, neuroblastoma, soft tissue sarcoma, hepatic, renal, bone and central nervous system tumours, using pre-defined medical codes used in the GPRD. The date of diagnosis for cases was defined as the date of pathological diagnosis, but if this was unavailable, the date of the first cancer code entered in the GPRD was used. Controls: Up to 13 controls (children with no diagnosis of cancer at any time) were selected per case, using a computer-generated random sequence, matched on age (within 1 year), sex and practice, and had to be currently registered on the date of diagnosis of their matched case (the index date). Exclusion criteria: None listed Clinical setting: Primary care, UK.
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	

A. Risk of bias		
Index test	The GPRD uses just over 100 000 medical codes to encompass all primary care events, including both symptoms and diagnoses. From this list, libraries of codes were assembled representing individual alert symptoms derived from the NICE referral guidelines for suspected cancer in children. *No more information reported.*	
Were the index test results interpreted without knowledge of the results of the reference standard?		**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?		**Yes**
Could the conduct or interpretation of the index test have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		**Low concern**
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	Cancer diagnosis in the UK's General Practice Research Database.	
Is the reference standard likely to correctly classify the target condition?		**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?		**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		**Low concern**
FLOW AND TIMING		
A. risk of bias		
Flow and timing	All patients appear to be accounted for.	
Was there an appropriate interval between index test and reference standard?		**Yes**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**Yes**
Could the patient flow have introduced bias?		**Low risk**
NOTES	This study is published in three papers.	

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Ref Type: Generic
Ref ID: 114
Reprint: Not in File
Abstract: (from the chapter) present basic medical information about childhood cancer / [present] an overview of the characteristics, manifestations, and current thought regarding etiology / [present] information about establishing and explaining the diagnosis and treatment plans to the family / [discuss] the course and general principles of cancer treatment / [discuss] the most common pediatric malignancies [e.g., acute lymphoblastic and nonlymphoblastic leukemia, brain tumors, lymphomas, Wilms' tumor, neuroblastoma, bone tumors and soft tissue sarcomas, and retinoblastoma] / [summarize the] late effects of treatment (PsycINFO Database Record (c) 2012 APA, all rights reserved)
Notes: DB - PsycINFO
AN - Book: 1994-98308-001
SO - Bearison, David J [Ed]; Mulhern, Raymond K [Ed]. (1994). Pediatric psychooncology: Psychological perspectives on children with cancer. (pp. 9-34). xvi, 247 pp. New York, NY, US: Oxford University Press; US

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Ref Type: Generic
Ref ID: 113
Reprint: Not in File
Abstract: (from the chapter) Bone and soft tissue sarcomas are a heterogeneous group of cancers that arise from primitive mesenchymal cells throughout the body. Population-based data suggest that these cancers account for approximately 0.9% of cancer cases overall, but 13% of cancers in pediatric patients. Aggressive multimodality therapy, including various combinations of surgery, chemotherapy, and radiotherapy, is generally necessary for cure. Currently, the overall 5-year survival rate of patients with bone and soft tissue sarcomas is about two-thirds of that of the general population. Thus, sarcomas produce considerable morbidity as well as mortality. This chapter reviews the major clinical features, treatment, and outcomes of bone and soft tissue sarcomas, and addresses the major psychological issues facing individuals affected by these rare tumors. (PsycINFO Database Record (c) 2012 APA, all rights reserved)
Notes: DB - PsycINFO
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SO - Holland, Jimmie C [Ed]; Breitbart, William S [Ed]; Jacobsen, Paul B [Ed]; Lederberg, Marguerite S [Ed]; Loscalzo, Matthew J [Ed]; McCorkle, Ruth [Ed]. (2010). Psycho-oncology (2nd ed.). (pp. 187-190). xxv, 685 pp. New York, NY, US: Oxford University Press; US

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Review question:
Which investigations of symptoms of suspected soft tissue sarcoma should be done with clinical responsibility retained by primary care?

Results

Literature search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-2013	164	33	20/06/2013
Premedline	1980-2013	14	3	24/06/2013
Embase	1980-2013	145	51	24/06/2013
Cochrane Library	1980-2013	34	3	24/06/2013
Psychinfo	1980-2013	0	0	24/06/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2013	47	10	24/06/2013

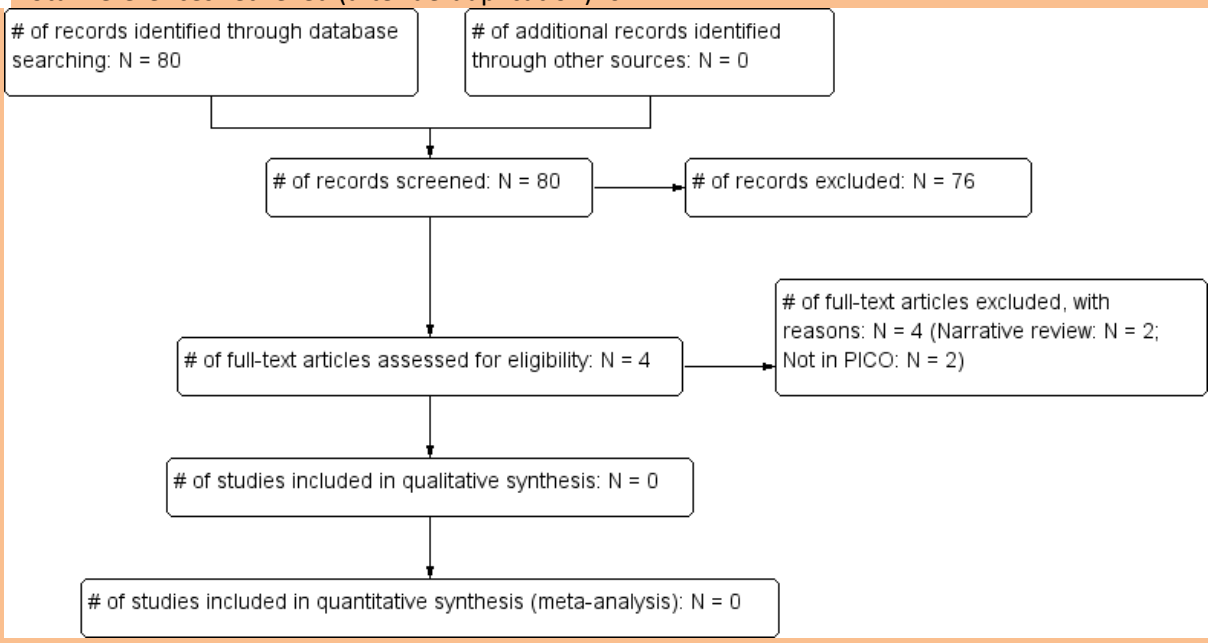
Total References retrieved (after de-duplication): 74

Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	6/2013-26/08/2014	3	0	26/08/2014
Premedline	6/2013-26/08/2014	17	2	26/08/2014
Embase	6/2013-26/08/2014	21	3	26/08/2014
Cochrane Library	6/2013-26/08/2014	10	0	26/08/2014

Web of Science (SCI & SSCI) and ISI Proceedings	6/2013-26/08/2014	11	1	26/08/2014

Total References retrieved (after de-duplication): 6



Study results

No evidence was identified pertaining to the diagnostic accuracy of ultrasound in patients with suspected soft tissue sarcoma where the clinical responsibility was retained by primary care.

References

Included studies

None

Excluded studies (with excl reason)

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Narrative review

CHILDHOOD CANCERS

NEUROBLASTOMA, RETINOBLASTOMA, WILM'S TUMOUR

Review question:
What is the risk of neuroblastoma, retinoblastoma and Wilm's tumour in children presenting in primary care with symptom(s)?

Results

Literature search

Neuroblastoma:

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2012	384	29	14/11/2012
Premedline	All-2012	19	0	14/11/2012
Embase	All-2012	198	28	14/11/2012
Cochrane Library	All-2012	59	1	14/11/2012
Psychinfo	All-2012	14	0	14/11/2012
Web of Science (SCI & SSCI) and ISI Proceedings	All-2012	33	5	14/11/2012
Biomed Central	All-2012	166	1	14/11/2012

Total References retrieved (after de-duplication): 45

Neuroblastoma: Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	11/2012-27/08/2014	8	1	27/08/2014
Premedline	11/2012-27/08/2014	49	1	27/08/2014
Embase	11/2012-27/08/2014	62	2	27/08/2014
Cochrane Library	11/2012-27/08/2014	21	0	27/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	11/2012-27/08/2014	6	1	27/08/2014

Total References retrieved (after de-duplication): 5

Retinoblastoma:

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2012	576	62	15/11/2012
Premedline	All-2012	13	3	14/11/2012
Embase	All-2012	386	62	15/11/2012
Cochrane Library	All-2012	67	0	15/11/2012
Psychinfo	All-2012	1	0	15/11/2012
Web of Science (SCI	All-2012	30	8	15/11/2012

& SSCI) and ISI Proceedings				
Biomed Central	All-2012	75	0	15/11/2012

Total References retrieved (after de-duplication): 83

Retinoblastoma: Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	11/2012-27/08/2014	28	4	27/08/2014
Premedline	11/2012-27/08/2014	31	1	27/08/2014
Embase	11/2012-27/08/2014	51	2	27/08/2014
Cochrane Library	11/2012-27/08/2014	64	1	27/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	11/2012-27/08/2014	10	0	27/08/2014

Total References retrieved (after de-duplication): 4

Wilm's tumour:

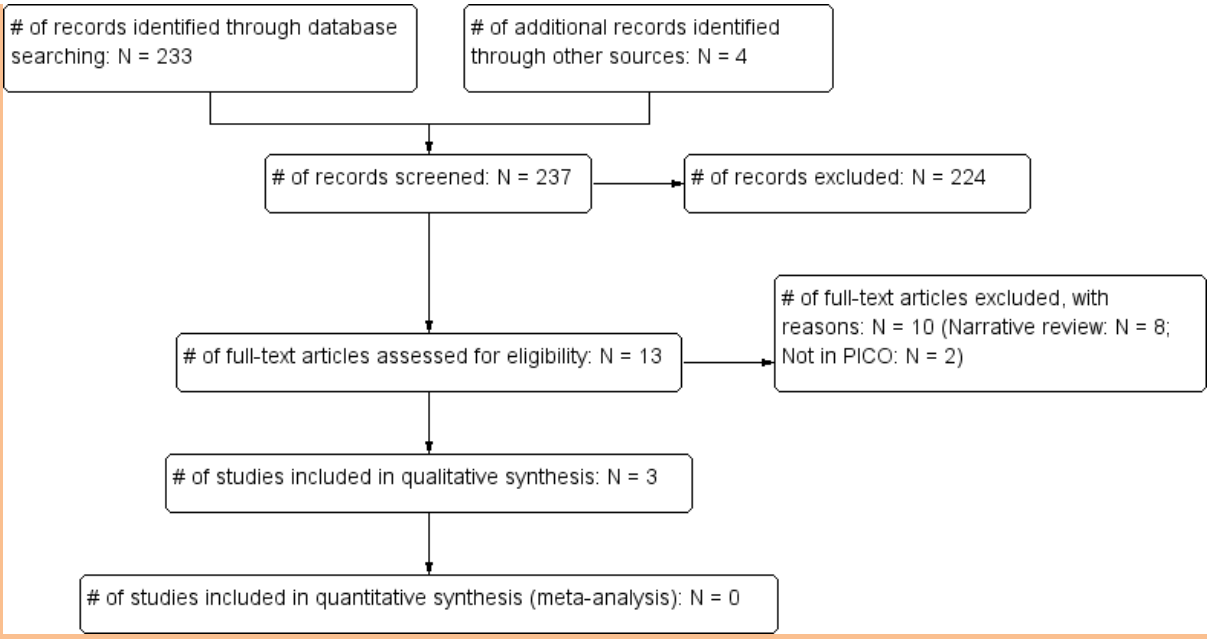
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2012	281	53	13/11/2012
Premedline	All-2012	20	3	13/11/2012
Embase	All-2012	311	55	14/11/2012
Cochrane Library	All-2012	34	0	14/11/2012
Psychinfo	All-2012	0	0	13/11/2012
Web of Science (SCI & SSCI) and ISI Proceedings	All-2012	7	3	14/11/2012
Biomed Central	All-2012	4	0	14/11/2012

Total References retrieved (after de-duplication): 93

Wilm's tumour: Update Search

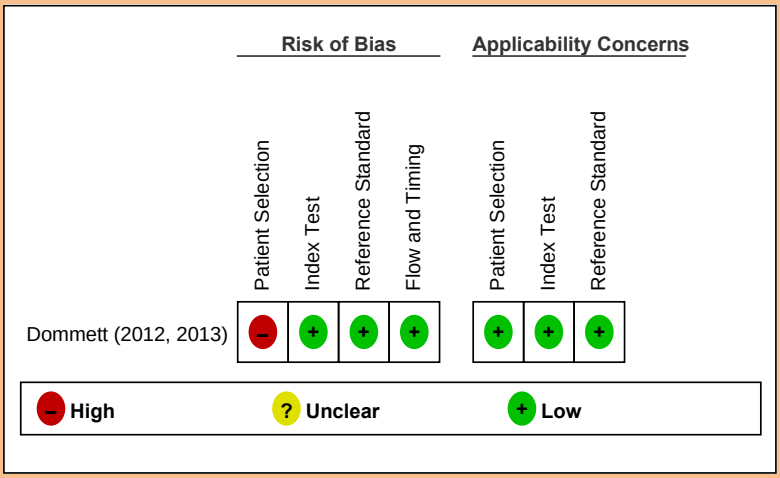
Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	11/2012-27/08/2014	20	3	27/08/2014
Premedline	11/2012-27/08/2014	45	2	27/08/2014
Embase	11/2012-27/08/2014	33	0	27/08/2014
Cochrane Library	11/2012-27/08/2014	22	0	27/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	11/2012-27/08/2014	2	0	27/08/2014

Total References retrieved (after de-duplication): 3



Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included study in the figure below. The main issue to note is that the study employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence.



Study results

Table 1: Childhood cancers (neuroblastoma, retinoblastoma, Wilm's tumour): Positive predictive values for any childhood cancer: Patients aged 0-14 years

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	All included patients	0.055 (0.047-0.065) Cases: 342/1267 Control: 211/15318
Dommett (2012)	Any NICE alert symptom 0-12 months before	All included patients	0.07 (0.064-0.078) Cases: 427/1267

	diagnosis		Control: 829/15318
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	All included patients	0.083 (0.067-0.105) Cases: 108/1267 Control: 207/15318
Dommett (2012)	Headache 0-12 months before diagnosis	All included patients	0.064 (0.051-0.082) Cases: 90/1267 Control: 224/15318
Dommett (2013a)	Headache 0-3 months before diagnosis	All included patients	0.06 (0.04-0.08) Cases: 73/1267 Control: 55/15318
Dommett (2013a)	Headache 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.13 (0.08-0.22)
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	All included patients	0.096 (0.074-0.126) Cases: 82/1267 Control: 136/15318
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis	All included patients	0.09 (0.06-0.13) Cases: 69/1267 Control: 33/15318
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.2 (0.1-0.39)
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	All included patients	0.172 (0.119-0.25) Cases: 56/1267 Control: 52/15318
Dommett (2013a)	Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis	All included patients	0.11 (0.06-0.2) Cases: 42/1267 Control: 16/15318
Dommett (2013a)	Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.3 (0.09-0.99)
Dommett (2012)	Fatigue 0-12 months before diagnosis	All included patients	0.085 (0.06-0.121) Cases: 47/1267 Control: 88/15318
Dommett (2013a)	Fatigue 0-12 months before diagnosis	All included patients	0.07 (0.04-0.12) Cases: 42/1267 Control: 24/15318
Dommett (2013a)	Fatigue 0-12 months before diagnosis and ≥ 3 consultations	All included patients	0.12 (0.06-0.23)
Dommett (2012)	Back pain 0-12 months before diagnosis	All included patients	0.088 (0.06-0.128) Cases: 40/1267 Control: 73/15318
Dommett (2012)	Bruising 0-12 months before diagnosis	All included patients	0.08 (0.054-0.118) Cases: 38/1267 Control: 76/15318
Dommett (2013a)	Bruising 0-3 months before diagnosis	All included patients	0.08 (0.05-0.13) Cases: 33/1267

			Control: 18/15318
Dommett (2013a)	Bruising 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.38 (0.09-1.64)
Dommett (2013a)	Pallor 0-3 months before diagnosis	All included patients	0.41 (0.12-1.34) Cases: 33/1267 Control: 18/15318
Dommett (2013a)	Pallor 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.76 (0.1-5.7)
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis	All included patients	0.3 (0.1-0.84) Cases: 28/1267 Control: 4/15318
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.76 (0.1-5.7)
Dommett (2013a)	Abnormal movement 0-3 months before diagnosis	All included patients	0.08 (0.04-0.14) Cases: 49/1267 Control: 26/15318
Dommett (2013a)	Abnormal movement 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.15 (0.07-0.32)
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included patients	0.06 (0.03-0.1) Cases: 28/1267 Control: 21/15318
Dommett (2013a)	Bleeding 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.11 (0.04-0.31)
Dommett (2013a)	Visual symptoms 0-3 months before diagnosis	All included patients	0.06 (0.03-0.1) Cases: 28/1267 Control: 21/15318
Dommett (2013a)	Visual symptoms 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.23 (0.07-0.77)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included patients	0.04 (0.03-0.06) Cases: 42/1267 Control: 41/15318
Dommett (2013a)	Pain 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.14 (0.07-0.31)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included patients	0.04 (0.03-0.07) Cases: 107/1267 Control: 102/15318
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.13 (0.08-0.19)
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	All included patients	0.266 (0.117-0.609) Cases: 15/1267

			Control: 9/15318
Dommett (2013a)	≥ 3 consultations	All included patients	0.02
Dommett (2013a)	Childhood infection 0-3 months before diagnosis	All included patients	Cases: 54/1267 Control: 236/15318
Dommett (2013a)	Upper respiratory tract infection 0-3 months before diagnosis	All included patients	Cases: 143/1267 Control: 942/15318
Dommett (2013a)	Vomiting 0-3 months before diagnosis	All included patients	Cases: 86/1267 Control: 105/15318
Dommett (2013a)	Cough 0-3 months before diagnosis	All included patients	Cases: 77/1267 Control: 654/15318
Dommett (2013a)	Rash 0-3 months before diagnosis	All included patients	Cases: 63/1267 Control: 555/15318
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included patients	Cases: 60/1267 Control: 137/15318
Dommett (2013a)	Abdominal mass 0-3 months before diagnosis	All included patients	Cases: 48/1267 Control: 0/15318
Dommett (2013a)	Fever 0-3 months before diagnosis	All included patients	Cases: 49/1267 Control: 166/15318
Dommett (2013a)	Eye swelling 0-3 months before diagnosis	All included patients	Cases: 39/1267 Control: 238/15318
Dommett (2013a)	Shortness of breath 0-3 months before diagnosis	All included patients	Cases: 35/1267 Control: 221/15318
Dommett (2013a)	Constipation 0-3 months before diagnosis	All included patients	Cases: 26/1267 Control: 61/15318
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	All included patients	2.19 (0.295-17.034) Cases: 14/1267 Control: 1/15318

The positive predictive values are calculated using Bayesian statistics.

Table 2: Childhood cancers (neuroblastoma, retinoblastoma, Wilm's tumour): Positive predictive values for any childhood cancer: Patients aged 0-4 years

Study	**Symptom(s)**	**Patient group**	**Positive predictive value (95% CI) Frequency**
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	Patients aged 0-4 years	0.081 (0.059-0.112) Cases: 96/436 Control: 55/4802
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	Patients aged 0-4 years	0.093 (0.077-0.113) Cases: 124/436 Control: 248/4802
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	Patients aged 0-4 years	0.076 (0.054-0.107) Cases: 43/436 Control: 105/4802
Dommett (2012)	Headache 0-12 months before diagnosis	Patients aged 0-4 years	0.135 (0.055-0.335) Cases: 8/436 Control: 11/4802
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	Patients aged 0-4 years	0.061 (0.037-0.1) Cases: 20/436 Control: 61/4802
Dommett (2012)	Lump/mass/swelling 0-	Patients aged 0-4 years	0.198 (0.099-0.399)

	12 months before diagnosis		Cases: 16/436 Control: 15/4802
Dommett (2012)	Fatigue 0-12 months before diagnosis	Patients aged 0-4 years	0.087 (0.048-0.16) Cases: 15/436 Control: 32/4802
Dommett (2012)	Back pain 0-12 months before diagnosis	Patients aged 0-4 years	0.186 (0.047-0.742) Cases: 4/436 Control: 4/4802
Dommett (2012)	Bruising 0-12 months before diagnosis	Patients aged 0-4 years	0.155 (0.086-0.279) Cases: 20/436 Control: 24/4802
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	Patients aged 0-4 years	0.739 (0.159-3.496) Cases: 8/436 Control: 2/4802
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	Patients aged 0-4 years	1.286 (0.161-10.569) Cases: 7/436 Control: 1/4802

The positive predictive values are calculated using Bayesian statistics.

Table 3: Childhood cancers (neuroblastoma, retinoblastoma, Wilm's tumour): Positive predictive values for any childhood cancer: Patients aged 5-14 years

Study	**Symptom(s)**	**Patient group**	**Positive predictive value (95% CI) Frequency**
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	Patients aged 5-14 years	0.056 (0.047-0.068) Cases: 246/831 Control: 156/10516
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	Patients aged 5-14 years	0.075 (0.066-0.084) Cases: 303/831 Control: 581/10561
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	Patients aged 5-14 years	0.091 (0.067-0.123) Cases: 65/831 Control: 102/10516
Dommett (2012)	Headache 0-12 months before diagnosis	Patients aged 5-14 years	0.055 (0.043-0.07) Cases: 82/831 Control: 213/10516
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	Patients aged 5-14 years	0.118 (0.085-0.164) Cases: 62/831 Control: 75/10516
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	Patients aged 5-14 years	0.154 (0.099-0.24) Cases: 40/831 Control: 37/10516
Dommett (2012)	Fatigue 0-12 months before diagnosis	Patients aged 5-14 years	0.082 (0.053-0.125) Cases: 32/831 Control: 56/10516
Dommett (2012)	Back pain 0-12 months before diagnosis	Patients aged 5-14 years	0.075 (0.05-0.111) Cases: 36/831 Control: 69/10516
Dommett (2012)	Bruising 0-12 months before diagnosis	Patients aged 5-14 years	0.049 (0.029-0.084) Cases: 18/831 Control: 52/10516

Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	Patients aged 5-14 years	0.143 (0.05-0.407) Cases: 7/831 Control: 7/10516
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	Patients aged 5-14 years	Cases: 7/831 Control: 0/10516

The positive predictive values are calculated using Bayesian statistics.

Table 4: Childhood cancers (neuroblastoma, retinoblastoma, Wilm's tumour): Positive predictive values for leukaemia/lymphoma childhood cancer

Study	**Symptom(s)**	**Patient group**	**Positive predictive value (95% CI)**
Dommett (2013a)	Bruising 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.53 (0.07-3.91)
Dommett (2013a)	Pallor 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.43 (0.06-3.15)
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.35 (0.05-2.65)
Dommett (2013a)	Fatigue 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.07 (0.03-0.15)
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.06 (0.04-0.11)
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.05 (0.02-0.13)
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.03 (0.01-0.08)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.03 (0.01-0.06)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.02 (0.01-0.03)
Dommett (2013a)	Fever 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls	0.01 (0.01-0.01)

		aged 0-14 years	
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013a)	≥ 3 consultations	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0.01-0.01)

The positive predictive values are calculated using Bayesian statistics.

Table 5: Childhood cancers (neuroblastoma, retinoblastoma, Wilm's tumour): Positive predictive values for teenage and young adult leukaemia

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013b)	Bruising	All included leukaemia patients and controls aged 15-24 years	0.0117 (0.004-0.0343) Cases: 9/143 Controls: 5/1799
Dommett (2013b)	Fatigue	All included leukaemia patients and controls aged 15-24 years	0.0121 (0.0052-0.0282) Cases: 15/143 Controls: 8/1799
Dommett (2013b)	Lymphadenopathy	All included leukaemia patients and controls aged 15-24 years	0.0151 (0.004-0.0578) Cases: 7/143 Controls: 3/1799
Dommett (2013b)	≥ 3 consultations	All included leukaemia patients and controls aged 15-24 years	0.0038 (0.003-0.0048) Cases: 74/143 Controls: 125/1799

The positive predictive values are calculated using Bayesian statistics.

Table 6: Childhood cancers (neuroblastoma, retinoblastoma, Wilm's tumour): Positive predictive values for teenage and young adult lymphoma

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013b)	Lump mass swelling head and neck	All included lymphoma patients and controls aged 15-24 years	0.5034 (0.0696-3.68) Cases: 35/270 Controls: 1/3350
Dommett (2013b)	Lump mass swelling below neck excluding abdomen	All included lymphoma patients and controls aged 15-24 years	0.0279 (0.0152-0.0515) Cases: 29/270 Controls: 15/3350
Dommett (2013b)	Lymphadenopathy	All included lymphoma patients and controls aged 15-24 years	0.278 (0.1-0.75) Cases: 77/270 Controls: 4/3350
Dommett (2013b)	'Lump mass swelling head and neck', 'lymphadenopathy' and	All included lymphoma patients and controls aged 15-24 years	0.0903 (0.057-0.1425)

	'lump mass swelling below neck excluding abdomen' combined as a single symptom		
Dommett (2013b)	≥ 3 consultations	All included lymphoma patients and controls aged 15-24 years	0.0086 (0.0075-0.0099) Cases: 175/270 Controls: 294/3350

The positive predictive values are calculated using Bayesian statistics.

Table 7: Childhood cancers (neuroblastoma, retinoblastoma, Wilm's tumour): Positive predictive values for central nervous system (CNS) child- or young adulthood cancer tumour

Study	**Symptom(s)**	**Patient group**	**Positive predictive value (95% CI) Frequency**
Dommett (2013a)	Abnormal movement 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.11 (0.03-0.35)
Dommett (2013a)	Visual symptoms 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.07 (0.02-0.24)
Dommett (2013a)	Vomiting 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.04 (0.02-0.07)
Dommett (2013a)	Headache 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.03 (0.02-0.06)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.03 (0.01-0.08)
Dommett (2013a)	Seizure 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.02 (0.01-0.06)
Dommett (2013a)	≥ 3 consultations	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013b)	Seizure	All included CNS	0.0238 (0.0082-

		patients and controls aged 15-24 years	0.0695) Cases: 18/154 Controls: 4/1906
Dommett (2013b)	Headache	All included CNS patients and controls aged 15-24 years	0.0145 (0.0077-0.0276) Cases: 33/154 Controls: 12/1906
Dommett (2013b)	Vomiting	All included CNS patients and controls aged 15-24 years	0.0116 (0.0041-0.031) Cases: 11/154 Controls: 5/1906
Dommett (2013b)	Pain	All included CNS patients and controls aged 15-24 years	0.0029 (0.0014-0.006) Cases: 11/154 Controls: 20/1906
Dommett (2013b)	Visual symptoms	All included CNS patients and controls aged 15-24 years	Cases: 8.4% Controls: 0%
Dommett (2013b)	≥ 3 consultations	All included CNS patients and controls aged 15-24 years	0.0023 (0.0019-0.0029) Cases: 73/154 Controls: 165/1906

The positive predictive values are calculated using Bayesian statistics.

Table 8: Childhood cancers (neuroblastoma, retinoblastoma, Wilm's tumour): Positive predictive values for child- or young adulthood bone cancer tumour/soft tissue sarcoma

Study	**Symptom(s)**	**Patient group**	**Positive predictive value (95% CI) Frequency**
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0.03 (0.01-0.14)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013a)	Trauma 0-3 months before diagnosis	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0 (0-0)
Dommett (2013a)	≥ 3 consultations	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0 (0-0)
Dommett (2013b)	Lump mass swelling	All included bone	0.0415 (0.0124-

		cancer tumour/soft tissue sarcoma patients and controls aged 15-24 years	0.1392) Cases: 19/196 Controls: 3/2438
Dommett (2013b)	Musculoskeletal symptoms	All included lymphoma patients and controls aged 15-24 years	0.0093 (0.0058-0.0151) Cases: 37/196 Controls: 26/2438
Dommett (2013b)	Chest pain	All included lymphoma patients and controls aged 15-24 years	0.0027 (0.001-0.0077) Cases: 5/196 Controls: 12/2438
Dommett (2013b)	≥ 3 consultations	All included lymphoma patients and controls aged 15-24 years	0.003 (0.0024-0.0037) Cases: 86/196 Controls: 189/2438

The positive predictive values are calculated using Bayesian statistics.

Table 9: Childhood cancers (neuroblastoma, retinoblastoma, Wilm's tumour): Positive predictive values for childhood abdominal cancer tumour

Study	**Symptom(s)**	**Patient group**	**Positive predictive value (95% CI)**
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.03 (0.01-0.12)
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.03 (0.00-0.23)
Dommett (2013a)	Weight loss 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.02 (0.00-0.1)
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.01 (0.01-0.02)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.01 (0.00-0.01)
Dommett (2013a)	Childhood infection 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0 (0-0)
Dommett (2013a)	≥ 3 consultations	All included abdominal cancer patients and controls aged 0-14 years	0 (0-0)

Evidence statement(s):

The positive predictive values of having any childhood cancer ranged from 0.04% (for pain and musculoskeletal symptoms) to 2.19% (for hepatosplenomegaly) in all included patients aged 0-14 years, and from 0.061% (for lymphadenopathy) to 1.286% (for hepatosplenomegaly) for patients aged 0-4 years old, and from 0.049% (for bruising) to 0.154% (for 'lump/mass/swelling' [the PPV for hepatosplenomegaly could not be calculated as none of the controls experienced this symptom]) for patients aged 5-14 years old (all from 1 study, N = 16585). The evidence quality is somewhat compromised by the case-control design of the study (see also Tables 1-3).

The positive predictive values of having leukaemia/lymphoma childhood cancer ranged from 0.01% (for fever and abdominal pain) to 0.53% (for bruising) for patients aged 0-14 years old; the positive predictive values of having young adulthood leukaemia ranged from 0.0117% (for bruising) to 0.0151% (for lymphadenopathy) for patients aged 15-24 years; and the positive predictive values of having young adulthood lymphoma ranged from 0.0279% (for 'lump mass swelling below the neck excluding the abdomen') to 0.5034% (for 'lump mass swelling head and neck') for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Tables 4-6).

The positive predictive values of having central nervous system childhood or young adulthood cancer tumours ranged from 0.02% (for seizure) to 0.11 (for abnormal movement) for patients aged 0-14 years old , and from 0.0029% (for pain) to 0.0238% (for seizure) for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 7).

The positive predictive values of having childhood or young adulthood bone cancer tumour/soft tissue sarcoma ranged from 0% (for trauma) to 0.03% (for 'lump mass swelling below neck excluding abdomen') for patients aged 0-14 years old, and from 0.0027% (for chest pain) to 0.0415% (for 'lump mass swelling') for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 8).

The positive predictive values of having childhood abdominal cancer tumours ranged from 0% (for childhood infection) to 0.03% (for bleeding and 'lump mass swelling below neck excluding abdomen') for patients aged 0-15 years old (1 study, N = 16585). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 9).

Evidence tables

Dommett (2012; 2013a,b)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Population-based nested case-control study using data from the General Practice Research Database (GPRD)
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to	**Yes**

balance the comparison groups for potential confounders?	
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: 1267 children; aged 0-4 years: N = 436; aged 5-14 years: N = 831; 703 males/564 females. Cancer type: Leukemia: N = 368; brain: N = 270; lymphoma: N = 142; bone: N = 107; soft tissue sarcoma: N = 91; renal: N = 82; neuroblastoma: N = 75; other ICD codes: N = 132. 1064 teenagers and young adults (TYA): 15-24 years: Gender not reported. Cancer type: Leukemia: N = 143; brain: N = 154; lymphoma: N = 270; bone: N = 96; soft tissue sarcoma: N = 100; other ICD codes: N = 301 (including testis: N = 60; skin: N = 49; ovary: N = 20 and thyroid: N = 17). Controls: 15318 children; aged 0-4 years: N = 4802; aged 5-14 years: N = 10516; 8461 males/6857 females. 13206 TYA. Gender not reported Inclusion criteria: The sample comprised all children and TYU aged 0–24 years, inclusive, drawn from all general practices contributing research-standard data to the GPRD between 1 January 1988 and 31 December 2010. To be included, the practices had to have been contributing research-standard data for a minimum of 1 year before each child's date of cancer diagnosis or the index date (see below) for matched controls. Cases: Patients diagnosed with the following cancers: leukaemia, lymphoma, neuroblastoma, soft tissue sarcoma, hepatic, renal, bone and central nervous system tumours, using pre-defined medical codes used in the GPRD. The date of diagnosis for cases was defined as the date of pathological diagnosis, but if this was unavailable, the date of the first cancer code entered in the GPRD was used. Controls: Up to 13 controls (children with no diagnosis of cancer at any time) were selected per case, using a computer-generated random sequence, matched on age (within 1 year), sex and practice, and had to be currently registered on the date of diagnosis of their matched case (the index date). Exclusion criteria: None listed Clinical setting: Primary care, UK.
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	The GPRD uses just over 100 000 medical codes to encompass all primary care events, including both symptoms and diagnoses. From this list, libraries of codes were assembled representing individual alert symptoms derived from the NICE referral guidelines for suspected cancer in children. *No more information reported.*
Were the index test results interpreted without knowledge	**Yes**

of the results of the reference standard?	
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Cancer diagnosis in the UK's General Practice Research Database.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	This study is published in three papers.

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Included studies

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Review question:
Which investigations of symptoms of suspected retinoblastoma, neuroblastoma and Wilm's tumour in children should be done with clinical responsibility retained by primary care?

Results

Literature search

Retinoblastoma:

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-2013	341	42	26/06/2013
Premedline	1980-2013	15	2	26/06/2013
Embase	1980-2013	240	21	26/06/2013
Cochrane Library	1980-2013	19	0	26/06/2013
Psychinfo	1980-2013	1	0	26/06/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2013	34	9	26/06/2013

Total References retrieved (after de-duplication): 66

Retinoblastoma: Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	6/2013-27/08/2014	8	1	27/08/2014
Premedline	6/2013-27/08/2014	11	1	27/08/2014
Embase	6/2013-27/08/2014	11	2	27/08/2014
Cochrane Library	6/2013-27/08/2014	7	0	27/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	6/2013-27/08/2014	8	0	27/08/2014

Total References retrieved (after de-duplication): 2

Neuroblastoma:

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search

Medline	1980-2013	220	16	25/06/2013
Premedline	1980-2013	21	5	25/06/2013
Embase	1980-2013	135	14	25/06/2013
Cochrane Library	1980-2013	4	1	25/06/2013
Psychinfo	1980-2013	4	0	25/06/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2013	26	2	25/06/2013

Total References retrieved (after de-duplication): 33

Neuroblastoma: Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	6/2013-27/08/2014	6	0	27/08/2014
Premedline	6/2013-27/08/2014	26	4	27/08/2014
Embase	6/2013-27/08/2014	18	2	27/08/2014
Cochrane Library	62013-27/08/2014	17	0	27/08/2014
Web of Science (SCI & SSCI) and ISI Proceedings	6/2013-27/08/2014	5	0	27/08/2014

Total References retrieved (after de-duplication): 6

Wilm's tumour:

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1980-2013	266	23	26/06/2013
Premedline	1980-2013	22	2	26/06/2013
Embase	1980-2013	219	11	26/06/2013
Cochrane Library	1980-2013	40	0	26/06/2013
Psychinfo	1980-2013	1	0	26/06/2013
Web of Science (SCI & SSCI) and ISI Proceedings	1980-2013	5	1	26/06/2013

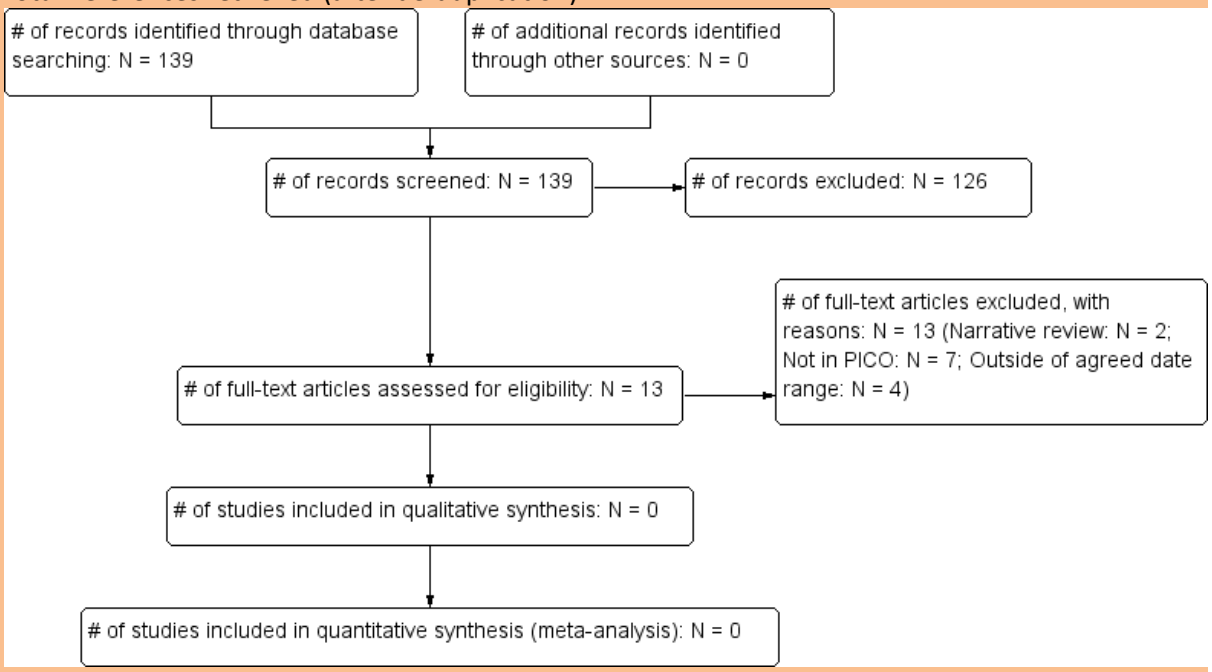
Total References retrieved (after de-duplication): 28

Wilm's tumour: Update Search

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	6/2013-27/08/2014	9	1	27/08/2014
Premedline	6/2013-27/08/2014	28	2	27/08/2014
Embase	6/2013-27/08/2014	29	3	27/08/2014
Cochrane Library	6/2013-27/08/2014	13	0	27/08/2014
Web of Science (SCI &	6/2013-	1	0	27/08/2014

SSCI) and ISI Proceedings	27/08/2014			

Total References retrieved (after de-duplication): 4



Study results

No evidence was identified pertaining to the diagnostic accuracy of tests in children with suspected retinoblastoma, neuroblastoma and Wilm's tumour where the clinical responsibility was retained by primary care.

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Included studies

None

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NON-SITE SPECIFIC SYMPTOMS

ABDOMINAL PAIN

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main validity issues to note is that patient sampling was not clearly consecutive or random in some of the studies, with some studies also conducted in populations that are not clearly directly relevant to the current question and the quality of others suffering from missing data. Studies employing non-consecutive/random sampling are at risk of bias because, for example, case-control studies have been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection. Studies conducted in other settings than UK-based primary care are only applicable to the extent that the study populations and settings are comparable to a UK GP population as defined for the current purposes. Other issues to note concern missing data, the influence of which on the results is difficult to determine.

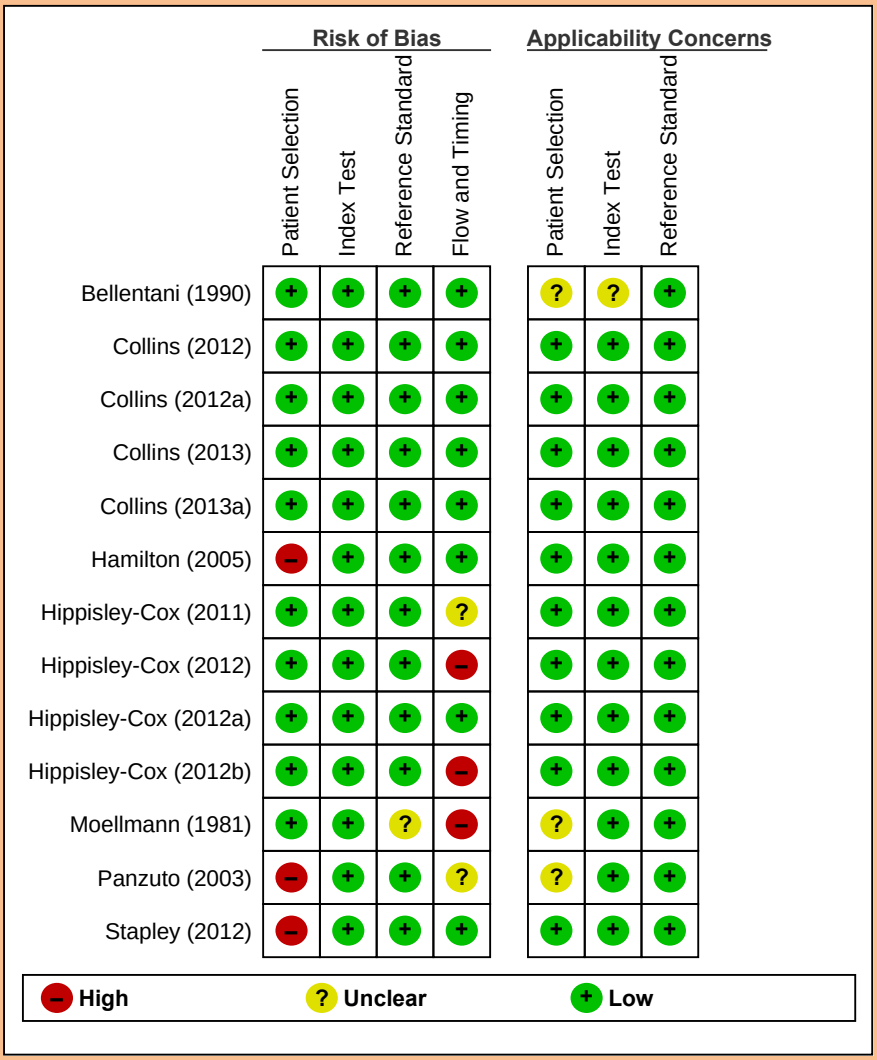

Table 1: Non-site specific symptoms of concern: Calculation of overall positive predictive value of abdominal pain for cancer

Cancer site	Study	Lower age limit	Upper age limit	PPV (95% CI), prevalence
Bladder/renal	Hippisley-Cox (2012)	30	84	0.2 (0.2-0.2)
Colorectal	Various*	30	84	1.524
Oesophagus/ stomach	Meta-analysis	varied	varied	0.34 (0.16-0.71)
Pancreatic	Hippisley-Cox (2012)	30	84	0.3 (0.3-0.4)
Sum				2.364

* Not sure which one to pick, so used average.

Table 2: Non-site specific symptoms of concern: Positive predictive values for abdominal pain

Cancer site	Comment/relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
Bladder/renal		Collins (2013)	Abdominal pain	All patients	0.11 (0.1-0.13)	both	30	84
Bladder/renal		Collins (2013)	Abdominal pain	Men	0.2 (0.2-0.21)	men	30	84
Bladder/renal		Collins (2013)	Abdominal pain	Women	0.1 (0.1-0.1)	women	30	84
Bladder/renal		Hippisley-Cox (2012)	Abdominal pain	All patients	0.2 (0.2-0.2)	both	30	84
Colorectal		Hamilton (2005)	Abdominal pain (reported once)	All patients	1.1 (0.9-1.3) Cases: 148/349 Controls: 163/1744	both	40	no upper limit
Colorectal		Hamilton (2005)	Abdominal pain	Patients 40-69 years	0.65 (NR)	both	40	69
Colorectal		Hamilton (2005)	Abdominal pain	Patients ≥ 70 years	2 (NR)	both	70	no upper limit
Colorectal		Hamilton (2005)	Abdominal pain (reporte	All patients	3 (1.8-5.2)	both	40	no upper limit

			d twice)					
Colorectal		Hamilton (2005)	Abdominal pain and abdominal tenderness	All patients	1.4 (0.3-2.2)	both	40	no upper limit
Colorectal		Hamilton (2005)	Abdominal tenderness (reported once)	All patients	1.1 (0.8-1.5) Cases: 62/349 Controls: 67/1744	both	40	no upper limit
Pancreatic		Collins (2013a)	Abdominal pain	All patients	0.14 (0.12-0.15)	both	30	84
Pancreatic		Collins (2013a)	Abdominal pain	Women	0.1 (0.09-0.12)	women	30	84
Pancreatic		Collins (2013a)	Abdominal pain	Men	0.19 (0.16-0.22)	men	30	84
Pancreatic		Hippisley-Cox (2012b)	Abdominal pain	All patients	0.3 (0.3-0.4)	both	30	84
Pancreatic		Stapley (2012)	Abdominal pain	All patients	0.2 (0.19-0.22)	both	40	no upper limit
Pancreatic		Stapley (2012)	Abdominal pain	Patients ≥ 60 years	0.3 (0.3-0.4)	both	60	no upper limit
Pancreatic		Stapley (2012)	Abdominal pain (attended ≥ twice)	Patients ≥ 60 years	1 (0.8-1.2)	both	60	no upper limit
META-ANALYSES (1) Colorectal								
Colorectal		Meta-analysis	Abdominal pain	N = 371703 patients/4 studies	2.04 (0.53-7.55)	both	2 studies 30-84, 1 study 18-87, 1 study NR Individual study details provided below	
Colorectal		Meta-analysis	Abdominal pain	N = 371480; w/o Panzuto	1.02 (0.38-2.69)	both	2 studies 30-84, 1 study NR Individual study details provided below	

				(2003)				
The 4 studies below are those included in the meta-analysis reported in the cells above:								
Colorectal		Bellentani (1990)	Abdominal pain	All patients (N = 254)	3.9 (2-7.3)	both	NR	NR
Colorectal		Collins (2012)	Abdominal pain	All patients (N = 245989)	0.5 (0.5-0.5)	both	30	84
Colorectal		Hippisley-Cox (2012a)	Abdominal pain	All patients (N = 125237)	0.7 (0.6-0.7)	both	30	84
Colorectal		Panzuto (2003)	Abdominal pain	All patients (N = 223)	13.5 (9.4-18.8)	both	18	87
The following results are any extra analyses reported by the studies included in the above meta-analysis:								
Colorectal		Collins (2012)	Abdominal pain	Men 30-84 years	0.6 (0.6-0.7)	men	30	84
Colorectal		Collins (2012)	Abdominal pain	Women 30-84 years	0.4 (0.4-0.5)	women	30	84
META-ANALYSES (2) Oesophageal								
Oesophagus/stomach	2 combining gastro-oesophageal and 1 reporting on osephageal cancer separately	Meta-analysis	Abdominal pain	N = 3389979/3 studies	0.23 (0.14-0.36)	both	2 studies 30-84, 1 study 40- >90 Individual study details provided below.	
The 3 studies below are those included in the meta-analysis reported in the cell above (Please note the same data from Collins (2012a) and Hippisley-Cox (2011) appear both here and under stomach, avoid double counting it):								
Oesophageal/stom		Collins (2012a)	Abdominal pain	All patients	0.2 (0.2-0.2) 437/2469	both	30	84

ach					98			
Oesophageal/stomach		Hippisley-Cox (2011)	Abdominal pain	All patients	0.3 (0.3-0.4) 309/91627	both	30	84
Oesophageal		Møllmann (1981)	Upper abdominal pain > 2 weeks	All patients	0 (0-0.8) 0/577	both	40	>90
The following results are any extra analyses reported by the studies included in the above meta-analysis:								
Oesophageal/stomach		Collins (2012a)	Abdominal pain	Women	0.1 (0.1-0.1) 139/144266	women	30	84
Oesophageal/stomach		Collins (2012a)	Abdominal pain	Men	0.3 (0.3-0.3) 298/102732	men	30	84
META-ANALYSES (3) Stomach								
Oesophagus/stomach	2 combining gastro-oesophageal and 1 reporting on stomach cancer separately	Meta-analysis	Abdominal pain	N = 3389979/3 studies	0.34 (0.16-0.71)	both	2 studies 30-84, 1 study 40- >90	
The 3 studies below are those included in the meta-analysis reported in the cell above (Please note the same data from Collins (2012a) and Hippisley-Cox (2011) appear both here and under oesophageal, avoid double counting it):								
Oesophageal/stomach		Collins (2012)	Abdominal pain	All patients	0.2 (0.2-0.2) 437/246998	both	30	84
Oesophageal/stomach		Hippisley-Cox (2011)	Abdominal pain	All patients	0.3 (0.3-0.4) 309/91627	both	30	84
Stomach		Møllmann (1981)	Upper abdominal pain > 2 weeks	All patients	1 (0.4-2.4) 6/577	both	40	>90

Evidence statement(s):

Abdominal pain (9 studies, N = 6248014) presenting in a primary care setting is associated with an overall positive predictive value of 2.364% for cancer. The studies were associated with 0-3 bias/applicability concerns (see also Table 1).

Evidence tables

Bellentani (1990)

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Prospective consecutive patient series	
Was a consecutive or random sample of patients enrolled?		**Yes**
Was a case-control design avoided?		**Yes**
Did the study avoid inappropriate exclusions?		**Yes**
Could the selection of patients have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Patient characteristics and setting	N = 254 (103 males/151 females); mean (SD) age of patients = Not reported; N = 140 were studied in primary care, N = 114 were referred to the gastroenterology services. It is unclear from the publication whether the patients who were referred to secondary care were a subset of "254 consecutive patients who presented to their GP during the study period for chronic abdominal pain" or whether they are recruited directly from secondary care (see Inclusion criteria). Inclusion criteria: All consecutive patients consulting 14 GPs of the local health district, taking care of 14000 citizens, or referred to the outpatient clinic of the Gastroenterology Unit, either complaining of recurrent abdominal pain or having intestinal problems (as judges by the GP), between January 1987 and March 1988. Exclusion criteria: Patients with acute abdomen, acute gastroenteritis or a clear cut diagnosis of upper gastrointestinal tract disease (gastritis, oesophagitis, peptic ulcer, or dyspepsia). Clinical setting: Primary/secondary care, Italy.	
Are there concerns that the included patients and setting do not match the review question?		**Unclear concern**
INDEX TEST		
A. Risk of bias		
Index test	Recurrent abdominal pain or intestinal problems (as judges by the GP; not further specified)	
Were the index test results interpreted without knowledge of the results of the reference standard?		**Yes**
Could the conduct or interpretation of the index test have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		**Unclear concern**
REFERENCE STANDARD		

A. risk of bias	
Reference standard(s)	Double-contrast barium enema or colonoscopy no more than 2 months after the enrolment in the study.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear (but all patients had a positive index test)**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients are accounted for in the results but the number of true negatives and false negatives could not be ascertained from the reported results.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	

Collins (2012)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Retrospective patient series using the THIN database.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 2135540 patients were identified from 364 practices. Symptoms: Rectal bleeding (N = 56234; 28423 men, 27811 women), abdominal pain (N = 245989; 102192 men, 143797 women), appetite loss (N = 5776; 2481 men, 3295 women), weight loss (N = 28289; 12891 men, 15398 women), anaemia (N = 18125; 4466 men, 13659 women), change in bowel habit (men only, N = 1670). Incident cases of colorectal cancer during the 2-year follow up period: N = 3712 (2036 men, 1676 women). Inclusion criteria: Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first

	recorded onset within the study period. Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of colorectal cancer at baseline, and patients with a recorded 'red-flag' symptom in the 12 months prior to the study entry date. Clinical setting: Primary care, UK
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms: Rectal bleeding, loss of appetite, weight loss, abdominal pain, change in bowel habit (men only), and anaemia.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	2-year follow up
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients seem to be accounted for
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	The is ***very large, if not complete, overlap*** of the data used in this study with those used in Hamilton (2008 [for anaemia], 2009)

Collins (2012a)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Retrospective patient series using the THIN database.

Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 2135540 patients were identified from 364 practices. Symptoms: Dysphagia (N = 19237; 8846 men, 10391 women), abdominal pain (N = 246998; 102732 men, 144266 women), appetite loss (N = 5838; 2521 men, 3317 women), weight loss (N = 28403; 12938 men, 15465 women), haematemesis (N = 10792; 6162 men, 4630 women), anaemia (N = 18355; 4563 men, 13792 women). Incident cases of gastro-oesophageal cancer during the 2-year follow up period: N = 1766 (1184 men, 582 women; 32% gastric cancer, 68% oesophageal cancer). Inclusion criteria: Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. Exclusion criteria: Patients with a prior diagnosis of gastro-oesophageal cancer, registration with the general practice < 12 months, or with invalid dates. Clinical setting: Primary care, UK
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms: Haematemesis, dysphagia, loss of appetite, weight loss, anaemia, and abdominal pain.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	2-year follow up
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**

B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		**Low concern**
FLOW AND TIMING		
A. risk of bias		
Flow and timing	All patients seem to be accounted for	
Was there an appropriate interval between index test and reference standard?		**Yes**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**Yes**
Could the patient flow have introduced bias?		**Low risk**
NOTES	The study did not distinguish between gastric and oesophageal cancer	

Collins (2013)

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Retrospective patient series using the THIN database.	
Was a consecutive or random sample of patients enrolled?		**Yes**
Was a case-control design avoided?		**Yes**
Did the study avoid inappropriate exclusions?		**Yes**
Could the selection of patients have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Patient characteristics and setting	A total of 2145133 patients (1063355 men, 1081778 women) were identified from 364 practices. Symptoms: Haemoglobin < 11 g/dl recorded in the last year (N = 16961; 3969 men, 12992 women), abdominal pain (N = 253344; 105247 men, 148097 women), appetite loss (N = 6097; 2616 men, 3481 women), weight loss (N = 29369; 13332 men, 16037 women), haematuria (N = 37810; 22810 men, 15000 women), previous diagnosis of cancer apart from renal tract cancer at study entry (N = 49303; 18130 men, 31173 women). Incident cases of renal tract cancer during the 2-year follow up period: N = 2283 (1685 men, 598 women). Inclusion criteria: Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (e.g., haematuria, abdominal pain, weight loss, appetite loss, and anaemia), the date of the first recorded onset within the study period. Exclusion criteria: Patients with a prior diagnosis of renal tract cancer, registered less than 12 months with the general practice, had invalid dates, < 30 years old or ≥ 85 years old. Clinical setting: Primary care, UK	
Are there concerns that the included patients and setting do not match the review question?		**Low concern**
INDEX TEST		

A. Risk of bias	
Index test	'Red-flag' symptoms were defined as symptoms that might alarm the patient and also indicate the presence of renal tract cancer; that is, symptoms of haematuria, loss of appetite, weight loss, or abdominal pain.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Renal tract cancer, which was defined as incident diagnosis of cancer of the bladder, kidney, ureter, or urethra during the 2 years after study entry, recorded either on the patient's GP record using the relevant UK diagnostic Read Codes. Patients without the outcome were censored at the earliest of the date of death, date of leaving the practice study of 2 years of follow up.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients seem to be accounted for
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	It is unclear why no data has been presented for men for the symptoms of appetite loss and weight loss.

Collins (2013a)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Retrospective patient series using the THIN database.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**

B. Concerns regarding applicability	
Patient characteristics and setting	A total of 2150322 patients were identified from 364 practices. Symptoms: Dysphagia (men only: N = 9326), abdominal pain (N = 255058; 106768 men, 148290 women), appetite loss (N = 6102; 2658 men, 3444 women), weight loss (N = 29464; 13484 men, 15980 women), abdominal distension (women only: N = 4457), constipation (men only, N = 5326). Incident cases of pancreatic cancer during the 2-year follow up period: N = 287 (331 men, 287 women). Inclusion criteria: Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. Exclusion criteria: Patients with a prior diagnosis of pancreatic cancer, registration < 12 months with the general practice, or invalid dates. Clinical setting: Primary care, UK
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms: Dysphagia (men only), loss of appetite, weight loss, abdominal pain, abdominal distension (women only), and constipation (men only).
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	2-year follow up
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients seem to be accounted for

Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	

Hamilton (2005)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Population-based matched case-control study involving all 21 general practices in Exeter, Devon, UK.
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: N = 349 (177 males/172 females), age at diagnosis: < 60 years: N = 45, 60-69 years: N = 97, 70-79 years: N = 113, 80+ years: N = 94. 210/349 had tumours at or distal to the splenic flexure, and 126/349 had tumours proximal to the splenic flexure, the remaining 13/349 has tumours in multiple or unknown sites. Duke's staging was known for 305/349: 170/305 were Duke's A or B, and 135/305 were Duke's C or D. Controls: N = 1744 (885 males/859 females), age at diagnosis: < 60 years: N = 225, 60-69 years: N = 487, 70-79 years: N = 555, 80+ years: N = 477. Inclusion criteria: Cases: All patients aged ≥ 40 years with a primary colorectal cancer, diagnosed from 1998 to 2002, were identified from the cancer registry at the Royal Devon and Exeter Hospital combined with computerised searches at every practice in Devon to identify any cases missing from the cancer register. Controls: Five controls were matched to each case on sex, general practice, and age (to 1-year bands if possible, increased in 1-year multiples to a maximum of 5 years). Controls were eligible if they were alive at the time of diagnosis of their case. Exclusion criteria: Cases and controls: Unobtainable records; no consultations in the 2 years before diagnosis; previous colorectal cancer; or residence outside Exeter at the time of diagnosis.

	Clinical setting: Primary care, UK.	
Are there concerns that the included patients and setting do not match the review question?		**Low concern**
INDEX TEST		
A. Risk of bias		
Index test	Anonymised photocopies of the full primary care records for 2 years before diagnosis were coded (blinded to case/control status) for all entries using the International Classification of Primary Care-2. Additional codes were created to incorporate all possible clinical features. Only variables occurring in ≥ 2.5% of cases or controls were analysed.	
Were the index test results interpreted without knowledge of the results of the reference standard?		**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?		**Yes**
Could the conduct or interpretation of the index test have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		**Low concern**
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	Colorectal cancer diagnosis in the cancer registry at the Royal Devon and Exeter Hospital or practice notes.	
Is the reference standard likely to correctly classify the target condition?		**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?		**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		**Low concern**
FLOW AND TIMING		
A. risk of bias		
Flow and timing	All the patients are accounted for.	
Was there an appropriate interval between index test and reference standard?		**Yes**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**Yes**
Could the patient flow have introduced bias?		**Low risk**
NOTES		

Hippisley-Cox (2011)

PATIENT SELECTION	
A. risk of bias	

Patient sampling	Prospective patient series using patients in the QResearch database (version 30).
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 1238971 patients were identified from 189 practices (621478 males, 617493 females), mean (SD) age = 50.1 (15) years, mean (SD) Townsend score = -0.2 (3.6). Symptoms: Current dysphagia (N = 8165), current haematemesis (N = 7119), current abdominal pain (N = 126161), current appetite loss (N = 6133), current weight loss (N = 5377), tiredness in the last year (N = 14119), haemoglobin recorded in the last year (N = 12638, haemoglobin < 11 g/dl in the lasy year (N = 218862. Incident cases of gastro-oseophageal cancer during the 2-year follow up period: N = 1343 (776 oesophageal and 567 gastric). Inclusion criteria: All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000); 12 months after the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. *The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.* Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of gastro-oesophageal cancer at baseline, and patients with a recorded 'red-flag' symptom in the 12 months prior to the study entry date. Clinical setting: Primary care, UK
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms: Incident dysphagia, haematemesis, loss of appetite, weight loss, anaemia, and abdominal pain.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**

REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	2-year follow up	
Is the reference standard likely to correctly classify the target condition?		**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?		**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		**Low concern**
FLOW AND TIMING		
A. risk of bias		
Flow and timing	A total of 1342329 patients were initially identified of whom 103358 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of gastro-oesophageal cancer (N = 538), and ≥ one 'red flag' symptom recorded in the 12 months prior to study entry (N = 31973), leaving 1238971 patients. However, data is presented for 963040/1238971 patients for all symptoms. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.	
Was there an appropriate interval between index test and reference standard?		**Yes**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**No**
Could the patient flow have introduced bias?		**Unclear risk**
NOTES	Results not presented separately for gastric and oesophageal cancer	

Hippisley-Cox (2012)

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Prospective patient series using patients in the QResearch database (version 30).	
Was a consecutive or random sample of patients enrolled?		**Yes**
Was a case-control design avoided?		**Yes**
Did the study avoid inappropriate exclusions?		**Yes**
Could the selection of patients have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Patient characteristics and setting	A total of 1240722 patients were identified from 189 practices (622166 males, 618556 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6). Current symptoms and symptoms in the preceding year: Current haematuria (N = 25553), current abdominal pain (N = 128721), current appetite loss (N = 5531), current weight loss (N = 14464), constipation in the last year (N = 8472), diarrhoea in the last year (N =	

	12171), tiredness in the last year (N = 12669), haemoglobin recoded in the last year (N = 216201), haemoglobin < 11 g/dl in the last year (N = 16169). Incident cases of renal tract cancer during the 2-year follow up period: N = 1622; mean age at diagnosis = 70 years, 1187 males/ 435 females; **Type of cancer: Bladder: N = 1292; Kidney: N = 307; Ureter: N = 21; Urethra: N = 2.** Inclusion criteria: All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000) and 12 months after the patient registered with the practice, ensuring that all patients had ≥ 12 months' registration prior to study entry. For patients with incident haematuria, appetite loss, weight loss, or abdominal pain, the entry date was the date of the first consultation with the symptom within the study period. *The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.* Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of renal tract cancer at baseline, and patients with a recorded 'red-flag' (see "Definition of symptom" below) symptom in the 12 months prior to the study entry date. Clinical setting: Primary care
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms were defined as symptoms that might alarm the patient and also indicate the presence of renal tract cancer; that is, symptoms of haematuria, loss of appetite, weight loss, or abdominal pain.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Renal tract cancer, which was defined as incident diagnosis of cancer of the bladder, kidney, ureter, or urethra during the 2 years after study entry, recorded either on the patient's GP record using the relevant UK diagnostic Read Codes, or their linked Office for National Statistics cause-of-death record, using the relevant ICD-9 codes (188 or 189) or ICD-10 diagnostic codes (C64–67).
Is the reference standard likely to correctly classify the target condition?	**Yes**

Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	A total of 1342329 patients were initially identified of whom 101607 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of renal tract cancer (N = 1506), and ≥ one 'red flag' symptom recorded in the 12 months prior to study entry (N = 29254), leaving 1240722 patients. However, data is presented for 967681 / 1240722 patients. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**No**
Could the patient flow have introduced bias?	**High risk**
NOTES	

Hippisley-Cox (2012a)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective patient series using patients in the QResearch database (version 30).
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 1236601 patients were identified from 189 practices (620240 males, 616361 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6). Symptoms: Current rectal bleeding (N = 29118), current abdominal pain (N = 125816), current appetite loss (N = 5358), current weight loss (N = 14065), recent change in bowel habit (N = 1821). Incident cases of colorectal cancer during the 2-year follow up period: N = 2603 (1562 colon and 1041 rectum). Inclusion criteria: All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset

	and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000); 12 months after the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. *The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.* Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of colorectal cancer at baseline, and patients with a recorded 'red-flag' symptom in the 12 months prior to the study entry date. Clinical setting: Primary care, UK
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms: First onset rectal bleeding, first onset loss of appetite, first onset weight loss, first onset abdominal pain, first onset change in bowel habit (in the past 12 months), and anaemia (recorded haemoglobin < 11 g/dl in the past 12 months).
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	2-year follow up
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	A total of 1342329 patients were initially identified of whom 105728 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of colorectal cancer (N = 2908), and ≥ one 'red flag' symptom recorded in the 12 months prior to study entry (N = 31973), leaving 1236601 patients. However, data is presented for 1235547/1236601 patients for all

	symptoms apart from change in bowel habit, which is only presented for 619651/620240 of the male patients. The missing data does not appear to include any of the cancer cases (although this cannot be ascertained for change in bowel habit), but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**No**
Could the patient flow have introduced bias?	**Low risk**
NOTES	Please note there is some overlap between this patient sample and that of Parker (2007)

Hippisley-Cox (2012b)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective patient series using patients in the QResearch database (version 30).
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 1243740 patients were identified from 189 practices (624352 males, 619388 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6). Current symptoms and symptoms in the preceding year: Current dysphagia (N = 8507), current abdominal pain (N = 129924), current abdominal distension (N = 4929), current appetite loss (N = 5567), current weight loss (N = 14686), constipation in the last year (N = 8476), diarrhoea in the last year (N = 12233), tiredness in the last year (N = 12688), itching in the last year (N = 1454), haemoglobin recoded in the last year (N = 214497), haemoglobin < 11 g/dl in the last year (N = 16172). Incident cases of pancreatic cancer during the 2-year follow up period: N = 781. Inclusion criteria: All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000) and 12 months after the patient registered with the practice, ensuring that all patients had ≥ 12 months' registration prior to study entry. For patients with incident haematuria, appetite loss, weight loss, or abdominal pain, the entry date was the date of the first consultation with the symptom within the study period. *The relevant data for the present purposes*

	is only available for the validation cohort, therefore only information pertaining to these patients will be reported. Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of pancreatic cancer at baseline, and patients with a recorded 'red-flag' (see "Definition of symptom" below) symptom in the 12 months prior to the study entry date. Clinical setting: Primary care	
Are there concerns that the included patients and setting do not match the review question?		**Low concern**
INDEX TEST		
A. Risk of bias		
Index test	'Red-flag' symptoms were defined as symptoms that might alarm the patient and also indicate the presence of pancreatic cancer; that is, symptoms of dysphagia, loss of appetite, weight loss, abdominal distension or abdominal pain.	
Were the index test results interpreted without knowledge of the results of the reference standard?		**Yes**
Could the conduct or interpretation of the index test have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		**Low concern**
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	Pancreatic cancer, which was defined as incident diagnosis of pancreatic cancer during the 2 years after study entry, recorded either on the patient's GP record using the relevant UK diagnostic Read Codes, or their linked Office for National Statistics cause-of-death record, using the relevant ICD-9 code (157) or ICD-10 diagnostic codes (C25).	
Is the reference standard likely to correctly classify the target condition?		**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?		**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		**Low concern**
FLOW AND TIMING		
A. risk of bias		
Flow and timing	A total of 1342329 patients were initially identified of whom 98589 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of pancreatic cancer (N = 96), and ≥ one 'red flag' symptom recorded in the 12 months prior to study entry (N = 27646), leaving 1243740 patients. However, data is presented for 971706 / 1243740 patients. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.	

Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**No**
Could the patient flow have introduced bias?	**High risk**
NOTES	

Møllmann (1981)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective patient series from an open-access gastroscopy clinic in Denmark.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 1480; gender not reported; 40-44 years: N = 144; 45-49 years: N = 186; 50-69 years: N = 882; 70-74 years: N = 130; 75-79 years: N = 83; 80-89 years N = 47: 90- years: N = 8. Inclusion criteria: All patients who, for a 2-year period, presented to their GP with (any of) the following symptoms were referred to the open access gastroscopy clinic: Upper abdominal pain > 2 weeks, nausea and/or vomiting > 2 weeks, weight loss and/or anorexia, gastrointestinal bleeding, and anaemia (i.e., Hb < 80%). Exclusion criteria: Patients who had been examined for any of the above symptoms within the last 6 months. Clinical setting: GPs in Denmark
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Upper abdominal pain > 2 weeks, nausea and/or vomiting > 2 weeks, weight loss and/or anorexia, gastrointestinal bleeding, and anaemia (i.e., Hb < 80%).
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	2-stage process: Gastroscopy with photography, using a gastrocamera, performed with only local anaesthesia of the pharynx. If this investigation disclosed abnormal conditions, the next stage was gastroscopy, possibly with biopsy, using diazepam sedation.

Is the reference standard likely to correctly classify the target condition?	**Unclear**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	177/1480 patients declined endoscopy, 2/1480 did not show up for endoscopy, and it was unsuccessful in a further 24 patients, leaving 1277 patients. However, the paper reports that only 1273 had primary endoscopy, and then reports the results for between 1181 and 1297 patients.
Was there an appropriate interval between index test and reference standard?	**Yes probably**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**No**
Could the patient flow have introduced bias?	**High risk**
NOTES	There were a total of 18 gastric cancers confirmed in the study. No oesophageal cancers were reported. This research was published in 2 papers.

Panzuto (2003)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective 8-week study of patients presenting to 159 primary care physicians (approximately 63600 patient visits during the study period in total) in Italy.
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Unclear**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 280; 120 males, 160 females; median age (range) = 61 (18-87) years. Inclusion criteria: Consecutive patients who consulted their GP "with symptoms considered suspicious for the presence of a colon disease to rule out the presence of colorectal cancer" and who were investigated with a colonoscopy or double-contrast barium enema [The decision of how (colonoscopy or double-contrast barium enema) and when to investigate the colon was made only by the physicians on the basis of the clinical evaluation during the visit]. Exclusion criteria: Patients with previous diagnoses of colorectal disorders or a recent large bowel examination. Clinical setting: Primary care, Italy.

Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Abdominal pain, bloating, constipation, rectal bleeding, diarrhoea, iron-deficiency anaemia (haemoglobin levels < 14 g/dl for males and < 12 g/dl for females, in the presence of ferritin < 30 µg/l and a median corpuscular value < 80 fl), change in bowel habits (onset of diarrhoea or constipation or altered stool in the previous 3 months) and weight loss (decrease of ≥ 3 kg in the 3 months prior to the visit).
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Histology
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	56/332 patients were excluded due to lack of mandatory fields (age, sex, clinical history, presenting symptoms and procedure results) in the database (N = 35) or violation of exclusion criteria (N = 18)
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**No**
Could the patient flow have introduced bias?	**Unclear risk**
NOTES	

Stapley (2012)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Matched case-control study using patients in the UK's General Practice Research Database (GPRD).

Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: N = 3635, 1743 males / 1892 females; median number of consultations = 18 (IQR = 11-27); aged 40-49 years: N = 107; 50-59 years: N = 529; 60-69 years: N = 829; 70-79 years: N = 1212; ≥ 80 years: N = 958; UK. Controls: N = 16459, gender not reported; median number of consultations = 9 (IQR = 4-15); aged 40-49 years: N = 422; 50-59 years: N = 2239; 60-69 years: N = 3755; 70-79 years: N = 5702; ≥ 80 years: N = 4341; UK. Inclusion criteria: Cases: Patients with a record of one of 25 GPRD pancreatic cancer codes between January 2000 and December 2009 inclusive, aged ≥ 40 years, with min. 1 year of data before diagnosis. The first instance of a pancreatic cancer code was assigned the data of diagnosis/index date. Controls: Up to 5 controls were matched to cases on sex, general practice, and to 1 year of age of the case. The index date was the index date of the matched case. Exclusion criteria: Pancreatic cancer (controls), no consultations in the year before diagnosis. Clinical setting: Primary care
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	All symptoms, physical signs or abnormal investigations compiled from the pancreatic cancer literature were studied, and supplemented by discussion with two pancreatic cancer charities. Libraries of codes relating to these were collated. All codes for fractures were also identified, as a test for any recording bias between cases and controls (making the assumption that the fracture rate would be approximately equal). Occurrences of these features in the year before the index date were identified. Features were only retained for further study if they occurred in ≥5% of cases or controls. Repeat attendances with the same symptom were also retained if the subsequent consultation also occurred in ≥5% of cases or controls. New-onset diabetes was defined as a code for diabetes, or a random blood glucose above the local laboratory's normal range, without similar codes more than 1 year before the index date. For laboratory tests, patients without a test were considered to be the same status as those with a normal result, making our binary variable abnormal result/ no abnormal result. Abnormal liver function

	was defined as any liver enzyme above the normal range, and raised inflammatory markers as either abnormal erythrocyte sedimentation rate or C-reactive protein, as there were too few plasma viscosity results.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Pancreatic cancer code in the UK's General Practice Research Database.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	A total of 21624 patients were identified, 17977 controls and 3647 cases. Of the controls the following exclusions were applied: pancreatic cancer (N = 64), case excluded (N = 40), and no data in year pre-index date (N = 1414). Of the cases the following exclusions were applied: No controls (N = 2), and cancer not of pancreatic origin (N = 10).
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	

References

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Stapley, S., Peters, T. J., Neal, R. D., Rose, P. W., Walter, F. M. & Hamilton, W. (2012) The risk of pancreatic cancer in symptomatic patients in primary care: a large case-control study using electronic records. *British Journal of Cancer,* 106: 1940-1944.

APPETITE LOSS

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The body of evidence was generally of high quality. The main validity issues to note is that patient sampling was not clearly consecutive or random in one of the studies, and that some of studies suffered from missing data. Studies employing non-consecutive/random sampling are at risk of bias because, for example, case-control studies have been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection. The statistical analyses employed by this study are however likely to have gone some way in addressing this issue.

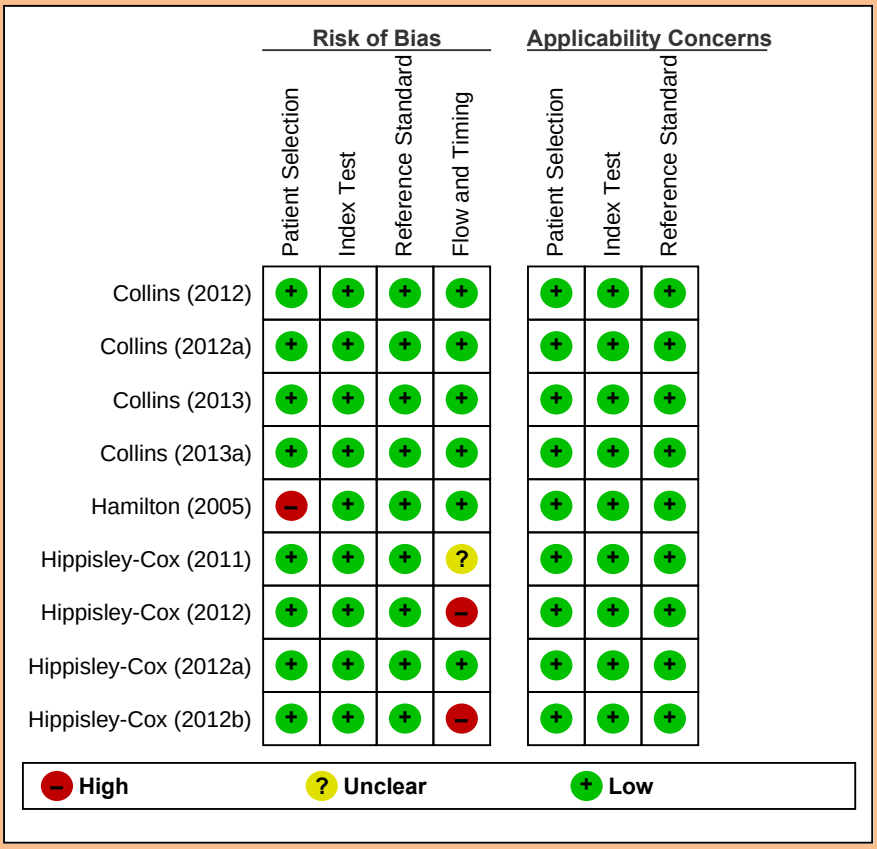

Table 1: Non-site specific symptoms of concern: Calculation of overall positive predictive value of appetite loss for cancer

Cancer site	Study	Lower age limit	Upper age limit	PPV (95% CI), prevalence
Bladder/renal	Hippisley-Cox (2012)	30	84	0.18 (0.07-0.4)
Colorectal	Hippisley-Cox (2012)	30	84	0.9 (0.6-1.2)
Lung	Hamilton* (2005)	40	no upper limit	1.285
Oesophagus/stomach	Hippisley-Cox (2011)	30	84	1.1 (0.8-1.5) 35/3391

Pancreatic	Hippisley-Cox (2012)	30	84	0.8 (0.5-1.2)
Sum				4.65

* Not sure which one to pick, so used average.

Table 2: Non-site specific symptoms of concern: Positive predictive values for appetite loss

Cancer site	Comment/relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
Bladder/renal		Collins (2013)	Appetite loss	Women	0.1 (0.04-0.3)	Women	30	84
Bladder/renal		Hippisley-Cox (2012)	Appetite loss	All patients	0.18 (0.07-0.4)	both	30	84
Colorectal		Hippisley-Cox (2012a)	Loss of appetite	All patients	0.9 (0.6-1.2)	both	30	84
Colorectal		Collins (2012)	Loss of appetite	All patients	0.8 (0.6-1.1)	both	30	84
Colorectal		Collins (2012)	Loss of appetite	Men 30-84 years	1 (0.6-1.5)	men	30	84
Colorectal		Collins (2012)	Loss of appetite	Women 30-84 years	0.6 (0.4-1)	women	30	84
Lung		Hamilton (2005)	Appetite loss	All included patients	0.87 (0.6-1.3)	both	40	No upper limit
Lung		Hamilton (2005)	Appetite loss (reported twice)	All included patients	1.7 (NR)	both	40	No upper limit
Lung		Hamilton (2005)	Appetite loss	Patients 40-69 years	1.1 (NR)	both	40	69
Lung		Hamilton (2005)	Appetite loss	All smokers	1.8 (NR)	both	40	No upper limit

Lung		Hamilton (2005)	Appetite loss (reported twice)	All smokers	2.7 (NR)	both	40	No upper limit
Oesophagus/stomach		Collins (2012a)	Appetite loss	All patients	0.6 (0.5-0.9) 37/5838	both	30	84
Oesophagus/stomach		Collins (2012a)	Appetite loss	Women	0.4 (0.2-0.7) 12/3317	women	30	84
Oesophagus/stomach		Collins (2012a)	Appetite loss	Men	1 (0.7-1.5) 25/2521	men	30	84
Oesophagus/stomach		Hippisley-Cox (2011)	Appetite loss	All patients	1.1 (0.8-1.5) 35/3391	both	30	84
Pancreatic		Collins (2013a)	Appetite loss	All patients	0.39 (0.26-0.59)	both	30	84
Pancreatic		Collins (2013a)	Appetite loss	Women	0.32 (0.17-0.59)	women	30	84
Pancreatic		Collins (2013a)	Appetite loss	Men	0.49 (0.27-0.86)	women	30	84
Pancreatic		Hippisley-Cox (2012b)	Appetite loss	All patients	0.8 (0.5-1.2)	both	30	84

Evidence statement(s):

Appetite loss (5 studies, N = 4961516) presenting in a primary care setting is associated with an overall positive predictive value of 4.65% for cancer. The studies were associated with 0-1 bias/applicability concern (see also Table 1).

Evidence tables

Collins (2012)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Retrospective patient series using the THIN database.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**

B. Concerns regarding applicability	
Patient characteristics and setting	A total of 2135540 patients were identified from 364 practices. Symptoms: Rectal bleeding (N = 56234; 28423 men, 27811 women), abdominal pain (N = 245989; 102192 men, 143797 women), appetite loss (N = 5776; 2481 men, 3295 women), weight loss (N = 28289; 12891 men, 15398 women), anaemia (N = 18125; 4466 men, 13659 women), change in bowel habit (men only, N = 1670). Incident cases of colorectal cancer during the 2-year follow up period: N = 3712 (2036 men, 1676 women). Inclusion criteria: Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of colorectal cancer at baseline, and patients with a recorded 'red-flag' symptom in the 12 months prior to the study entry date. Clinical setting: Primary care, UK
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms: Rectal bleeding, loss of appetite, weight loss, abdominal pain, change in bowel habit (men only), and anaemia.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	2-year follow up
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	

Flow and timing	All patients seem to be accounted for
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	The is ***very large, if not complete, overlap*** of the data used in this study with those used in Hamilton (2008 [for anaemia], 2009)

Collins (2012a)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Retrospective patient series using the THIN database.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 2135540 patients were identified from 364 practices. Symptoms: Dysphagia (N = 19237; 8846 men, 10391 women), abdominal pain (N = 246998; 102732 men, 144266 women), appetite loss (N = 5838; 2521 men, 3317 women), weight loss (N = 28403; 12938 men, 15465 women), haematemesis (N = 10792; 6162 men, 4630 women), anaemia (N = 18355; 4563 men, 13792 women). Incident cases of gastro-oesophageal cancer during the 2-year follow up period: N = 1766 (1184 men, 582 women; 32% gastric cancer, 68% oesophageal cancer). Inclusion criteria: Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. Exclusion criteria: Patients with a prior diagnosis of gastro-oesophageal cancer, registration with the general practice < 12 months, or with invalid dates. Clinical setting: Primary care, UK
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms: Haematemesis, dysphagia, loss of appetite, weight loss, anaemia, and abdominal pain.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test	**Low risk**

have introduced bias?	
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	2-year follow up
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients seem to be accounted for
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	The study did not distinguish between gastric and oesophageal cancer

Collins (2013)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Retrospective patient series using the THIN database.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 2145133 patients (1063355 men, 1081778 women) were identified from 364 practices. Symptoms: Haemoglobin < 11 g/dl recorded in the last year (N = 16961; 3969 men, 12992 women), abdominal pain (N = 253344; 105247 men, 148097 women), appetite loss (N = 6097; 2616 men, 3481 women), weight loss (N = 29369; 13332 men, 16037 women), haematuria (N = 37810; 22810 men, 15000 women), previous diagnosis of cancer apart from renal tract cancer at study entry (N = 49303; 18130 men, 31173 women). Incident cases of renal tract cancer during the 2-year follow up period:

	N = 2283 (1685 men, 598 women). Inclusion criteria: Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (e.g., haematuria, abdominal pain, weight loss, appetite loss, and anaemia), the date of the first recorded onset within the study period. Exclusion criteria: Patients with a prior diagnosis of renal tract cancer, registered less than 12 months with the general practice, had invalid dates, < 30 years old or ≥ 85 years old. Clinical setting: Primary care, UK
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms were defined as symptoms that might alarm the patient and also indicate the presence of renal tract cancer; that is, symptoms of haematuria, loss of appetite, weight loss, or abdominal pain.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Renal tract cancer, which was defined as incident diagnosis of cancer of the bladder, kidney, ureter, or urethra during the 2 years after study entry, recorded either on the patient's GP record using the relevant UK diagnostic Read Codes. Patients without the outcome were censored at the earliest of the date of death, date of leaving the practice study of 2 years of follow up.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients seem to be accounted for
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**

Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	It is unclear why no data has been presented for men for the symptoms of appetite loss and weight loss.

Collins (2013a)

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Retrospective patient series using the THIN database.	
Was a consecutive or random sample of patients enrolled?		**Yes**
Was a case-control design avoided?		**Yes**
Did the study avoid inappropriate exclusions?		**Yes**
Could the selection of patients have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Patient characteristics and setting	A total of 2150322 patients were identified from 364 practices. Symptoms: Dysphagia (men only: N = 9326), abdominal pain (N = 255058; 106768 men, 148290 women), appetite loss (N = 6102; 2658 men, 3444 women), weight loss (N = 29464; 13484 men, 15980 women), abdominal distension (women only: N = 4457), constipation (men only, N = 5326). Incident cases of pancreatic cancer during the 2-year follow up period: N = 287 (331 men, 287 women). Inclusion criteria: Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. Exclusion criteria: Patients with a prior diagnosis of pancreatic cancer, registration < 12 months with the general practice, or invalid dates. Clinical setting: Primary care, UK	
Are there concerns that the included patients and setting do not match the review question?		**Low concern**
INDEX TEST		
A. Risk of bias		
Index test	‘Red-flag’ symptoms: Dysphagia (men only), loss of appetite, weight loss, abdominal pain, abdominal distension (women only), and constipation (men only).	
Were the index test results interpreted without knowledge of the results of the reference standard?		**Yes**
Could the conduct or interpretation of the index test have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		**Low concern**
REFERENCE STANDARD		
A. risk of bias		
Reference	2-year follow up	

standard(s)	
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients seem to be accounted for
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	

Hamilton (2005)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Population-based matched case-control study involving all 21 general practices in Exeter, Devon, UK.
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: N = 247 (170 males/77 females), age at diagnosis: < 60 years: N = 35, 60-69 years: N = 60, 70-79 years: N = 118, 80+ years: N = 34. Controls: N = 1235 (850 males/385 females), age at diagnosis: < 60 years: N = 178, 60-69 years: N = 310, 70-79 years: N = 575, 80+ years: N = 174. Inclusion criteria: Cases: All patients aged ≥ 40 years with a primary lung cancer, diagnosed from 1998 to 2002, were identified from the cancer registry at the Royal Devon and Exeter Hospital combined with computerised searches at every

	practice in Devon to identify any cases missing from the cancer register. Controls: Five controls were matched to each case on sex, general practice, and age. Controls were eligible if they were alive at the time of diagnosis of their case. Exclusion criteria: Cases and controls: Unobtainable records; no consultations in the 2 years before diagnosis; previous lung cancer; or residence outside Exeter at the time of diagnosis. Clinical setting: Primary care, UK.
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	Anonymised photocopies of the full primary care records for 2 years before diagnosis were coded (blinded to case/control status) for all entries using the International Classification of Primary Care-2. Additional codes were created to incorporate all possible clinical features. Only variables occurring in ≥ 2.5% of cases or controls were analysed.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Lung cancer diagnosis in the cancer registry at the Royal Devon and Exeter Hospital or practice notes.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All the patients are accounted for.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**

Could the patient flow have introduced bias?	**Low risk**
NOTES	

Hippisley-Cox (2011)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective patient series using patients in the QResearch database (version 30).
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 1238971 patients were identified from 189 practices (621478 males, 617493 females), mean (SD) age = 50.1 (15) years, mean (SD) Townsend score = -0.2 (3.6). Symptoms: Current dysphagia (N = 8165), current haematemesis (N = 7119), current abdominal pain (N = 126161), current appetite loss (N = 6133), current weight loss (N = 5377), tiredness in the last year (N = 14119), haemoglobin recorded in the last year (N = 12638, haemoglobin < 11 g/dl in the lasy year (N = 218862. Incident cases of gastro-oseophageal cancer during the 2-year follow up period: N = 1343 (776 oesophageal and 567 gastric). Inclusion criteria: All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000); 12 months after the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. *The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.* Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of gastro-oesophageal cancer at baseline, and patients with a recorded 'red-flag' symptom in the 12 months prior to the study entry date. Clinical setting: Primary care, UK
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms: Incident dysphagia, haematemesis, loss of appetite, weight loss, anaemia, and abdominal pain.

Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	2-year follow up
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	A total of 1342329 patients were initially identified of whom 103358 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of gastro-oesophageal cancer (N = 538), and ≥ one 'red flag' symptom recorded in the 12 months prior to study entry (N = 31973), leaving 1238971 patients. However, data is presented for 963040/1238971 patients for all symptoms. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**No**
Could the patient flow have introduced bias?	**Unclear risk**
NOTES	Results not presented separately for gastric and oesophageal cancer

Hippisley-Cox (2012)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective patient series using patients in the QResearch database (version 30).
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**

B. Concerns regarding applicability	
Patient characteristics and setting	A total of 1240722 patients were identified from 189 practices (622166 males, 618556 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6). Current symptoms and symptoms in the preceding year: Current haematuria (N = 25553), current abdominal pain (N = 128721), current appetite loss (N = 5531), current weight loss (N = 14464), constipation in the last year (N = 8472), diarrhoea in the last year (N = 12171), tiredness in the last year (N = 12669), haemoglobin recoded in the last year (N = 216201), haemoglobin < 11 g/dl in the last year (N = 16169). Incident cases of renal tract cancer during the 2-year follow up period: N = 1622; mean age at diagnosis = 70 years, 1187 males/ 435 females; **Type of cancer: Bladder: N = 1292; Kidney: N = 307; Ureter: N = 21; Urethra: N = 2.** Inclusion criteria: All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000) and 12 months after the patient registered with the practice, ensuring that all patients had ≥ 12 months' registration prior to study entry. For patients with incident haematuria, appetite loss, weight loss, or abdominal pain, the entry date was the date of the first consultation with the symptom within the study period. *The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.* Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of renal tract cancer at baseline, and patients with a recorded 'red-flag' (see "Definition of symptom" below) symptom in the 12 months prior to the study entry date. Clinical setting: Primary care
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms were defined as symptoms that might alarm the patient and also indicate the presence of renal tract cancer; that is, symptoms of haematuria, loss of appetite, weight loss, or abdominal pain.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	

Reference standard(s)	Renal tract cancer, which was defined as incident diagnosis of cancer of the bladder, kidney, ureter, or urethra during the 2 years after study entry, recorded either on the patient's GP record using the relevant UK diagnostic Read Codes, or their linked Office for National Statistics cause-of-death record, using the relevant ICD-9 codes (188 or 189) or ICD-10 diagnostic codes (C64–67).

Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	

Flow and timing	A total of 1342329 patients were initially identified of whom 101607 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of renal tract cancer (N = 1506), and ≥ one 'red flag' symptom recorded in the 12 months prior to study entry (N = 29254), leaving 1240722 patients. However, data is presented for 967681 / 1240722 patients. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.

Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**No**
Could the patient flow have introduced bias?	**High risk**
NOTES	

Hippisley-Cox (2012a)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective patient series using patients in the QResearch database (version 30).
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 1236601 patients were identified from 189 practices (620240 males, 616361 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6). Symptoms: Current rectal bleeding (N = 29118), current abdominal pain (N = 125816),

	current appetite loss (N = 5358), current weight loss (N = 14065), recent change in bowel habit (N = 1821). Incident cases of colorectal cancer during the 2-year follow up period: N = 2603 (1562 colon and 1041 rectum). Inclusion criteria: All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000); 12 months after the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. *The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.* Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of colorectal cancer at baseline, and patients with a recorded 'red-flag' symptom in the 12 months prior to the study entry date. Clinical setting: Primary care, UK
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms: First onset rectal bleeding, first onset loss of appetite, first onset weight loss, first onset abdominal pain, first onset change in bowel habit (in the past 12 months), and anaemia (recorded haemoglobin < 11 g/dl in the past 12 months).
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	2-year follow up
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**

FLOW AND TIMING		
A. risk of bias		
Flow and timing	A total of 1342329 patients were initially identified of whom 105728 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of colorectal cancer (N = 2908), and ≥ one 'red flag' symptom recorded in the 12 months prior to study entry (N = 31973), leaving 1236601 patients. However, data is presented for 1235547/1236601 patients for all symptoms apart from change in bowel habit, which is only presented for 619651/620240 of the male patients. The missing data does not appear to include any of the cancer cases (although this cannot be ascertained for change in bowel habit), but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.	
Was there an appropriate interval between index test and reference standard?		**Yes**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**No**
Could the patient flow have introduced bias?		**Low risk**
NOTES	Please note there is some overlap between this patient sample and that of Parker (2007)	

Hippisley-Cox (2012b)

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Prospective patient series using patients in the QResearch database (version 30).	
Was a consecutive or random sample of patients enrolled?		**Yes**
Was a case-control design avoided?		**Yes**
Did the study avoid inappropriate exclusions?		**Yes**
Could the selection of patients have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Patient characteristics and setting	A total of 1243740 patients were identified from 189 practices (624352 males, 619388 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6). Current symptoms and symptoms in the preceding year: Current dysphagia (N = 8507), current abdominal pain (N = 129924), current abdominal distension (N = 4929), current appetite loss (N = 5567), current weight loss (N = 14686), constipation in the last year (N = 8476), diarrhoea in the last year (N = 12233), tiredness in the last year (N = 12688), itching in the last year (N = 1454), haemoglobin recoded in the last year (N = 214497), haemoglobin < 11 g/dl in the last year (N = 16172). Incident cases of pancreatic cancer during the 2-year follow up period: N = 781. Inclusion criteria: All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from	

	patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000) and 12 months after the patient registered with the practice, ensuring that all patients had ≥ 12 months' registration prior to study entry. For patients with incident haematuria, appetite loss, weight loss, or abdominal pain, the entry date was the date of the first consultation with the symptom within the study period. *The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.* Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of pancreatic cancer at baseline, and patients with a recorded 'red-flag' (see "Definition of symptom" below) symptom in the 12 months prior to the study entry date. Clinical setting: Primary care
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms were defined as symptoms that might alarm the patient and also indicate the presence of pancreatic cancer; that is, symptoms of dysphagia, loss of appetite, weight loss, abdominal distension or abdominal pain.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Pancreatic cancer, which was defined as incident diagnosis of pancreatic cancer during the 2 years after study entry, recorded either on the patient's GP record using the relevant UK diagnostic Read Codes, or their linked Office for National Statistics cause-of-death record, using the relevant ICD-9 code (157) or ICD-10 diagnostic codes (C25).
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	A total of 1342329 patients were initially identified of whom 98589 patients

	were excluded for the following reasons: No recorded Townsend score (N = 70847), history of pancreatic cancer (N = 96), and ≥ one 'red flag' symptom recorded in the 12 months prior to study entry (N = 27646), leaving 1243740 patients. However, data is presented for 971706 / 1243740 patients. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**No**
Could the patient flow have introduced bias?	**High risk**
NOTES	

References

Included studies

Collins, G.S., Altman, D.G. Identifying patients with undetected colorectal cancer: An independent validation of QCancer (Colorectal). British Journal of Cancer 107, 260-265. 2012.

Collins, G.S., Altman, D.G. Identifying patients with undetected gastro-oesophageal cancer in primary care: External validation of QCancer (Gastro-Oesophageal). European Journal of Cancer, http://dx.doi.org/10.1016/j.ejca.2012.10.023. 2012a.

Collins, G.S., and Altman, D.G. Identifying patients with undetected renal tract cancer in primary care: An independent and external validation of QCancer (renal) prediction model. Cancer Epidemiology, 37, 115-120. 2013.

Collins,G.S.; Altman,D.G. (2013a). Identifying patients with undetected pancreatic cancer in primary care: an independent and external validation of QCancer(®) (Pancreas). *British Journal of General Practice,* 63: 636-642.

Hamilton, W., Peters, T. J., Round, A. & Sharp, D. (2005) What are the clinical features of lung cancer before the diagnosis is made? A population based case-control study. *Thorax,* 60: 1059-1065. The data split by smoking status is available from: http://webarchive.nationalarchives.gov.uk/20130513211237/http://www.ncat.nhs.uk/sites/default/files/work-docs/ncl%20lung%20guide.pdf

Hippisley-Cox, J. and Coupland, C. Identifying patients with suspected gastro-oesophageal cancer in primary care: Derivation and validation of an algorithm. British Journal of General Practice; DOI: 10.3399/bjgp11X606609. 2011.

Hippisley-Cox, J. and Coupland, C. Identifying patients with suspected renal tract cancer in primary care: derivation and validation of an algorithm. British Journal of General Practice 62[597], e251-e260. 2012.

Hippisley-Cox, J. and Coupland, C. Identifying patients with suspected colorectal cancer in primary care: Derivation and validation of an algorithm. British Journal of General Practice 62[594], e29-e37. 2012a.

Hippisley-Cox, J. & Coupland, C. (2012b) Identifying patients with suspected pancreatic cancer in primary care: derivation and validation of an algorithm. *British Journal of General Practice,* 62: e38-e45.

WEIGHT LOSS AND APPETITE LOSS

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main validity issues to note is that patient sampling was not based on a consecutive or random series of patients in one of the studies, while the other study was conducted in a population that is not necessarily directly relevant to the current question. Studies employing non-consecutive/random sampling are at high risk of bias because, for example, case-control studies have been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection. Studies conducted in other settings than UK-based primary care are only applicable to the extent that the study populations and settings are comparable to a UK GP population as defined for the current purposes. Other bias and applicability threats to the results concern missing data and a potentially suboptimal reference standard.

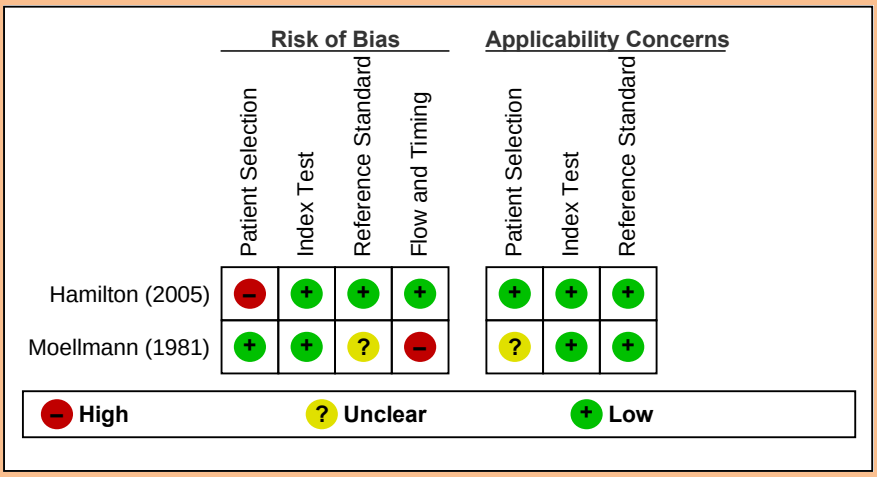

Table 1: Non-site specific symptoms of concern: Calculation of overall positive predictive value of appetite loss with weight loss for cancer

Cancer site	Study	Lower age limit	Upper age limit	PPV (95% CI), prevalence
Lung	Hamilton (2005)	40	no upper limit	2.3 (1.2-4.4)
Oesophagus	Møllmann (1981)	40	>90	0 (0-8.9) 0/50
Stomach	Møllmann (1981)	40	>90	2 (0.1-12) 1/50
Sum				4.3

Table 2: Non-site specific symptoms of concern: Positive predictive values for weight loss + appetite loss

Cancer site	Comment/relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
Lung	Rec: Offered FBC and	Hamilton (2005)	Weight loss + appetite	All included	2.3 (1.2-4.4)	both	40	no upper limit

	xray		loss	patients				
Lung	Rec: Offered FBC and xray	Hamilton (2005)	Weight loss + appetite loss	All smokers	5 (NR)	both	40	no upper limit
Oesophagus		Møllmann (1981)	Weight loss and/or anorexia	All patients	0 (0-8.9) 0/50	both	40	>90
Stomach	Rec: UGI endoscopy	Møllmann (1981)	Weight loss and/or anorexia	All patients	2 (0.1-12) 1/50	both	40	>90

Evidence statement(s):

Appetite loss with weight loss (2 studies, N = 2962) presenting in a primary care setting is associated with an overall positive predictive value of 4.3% for cancer. The studies were associated with 1-3 bias/applicability concerns (see also Table 1).

Evidence tables

Hamilton (2005)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Population-based matched case-control study involving all 21 general practices in Exeter, Devon, UK.
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: N = 247 (170 males/77 females), age at diagnosis: < 60 years: N = 35, 60-69 years: N = 60, 70-79 years: N = 118, 80+ years: N = 34. Controls: N = 1235 (850 males/385 females), age at diagnosis: < 60 years: N = 178, 60-69 years: N = 310, 70-79 years: N = 575, 80+ years: N = 174. Inclusion criteria: Cases: All patients aged ≥ 40 years with a primary lung cancer, diagnosed from 1998 to 2002, were identified from the cancer registry at the Royal

	Devon and Exeter Hospital combined with computerised searches at every practice in Devon to identify any cases missing from the cancer register. Controls: Five controls were matched to each case on sex, general practice, and age. Controls were eligible if they were alive at the time of diagnosis of their case. Exclusion criteria: Cases and controls: Unobtainable records; no consultations in the 2 years before diagnosis; previous lung cancer; or residence outside Exeter at the time of diagnosis. Clinical setting: Primary care, UK.
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	Anonymised photocopies of the full primary care records for 2 years before diagnosis were coded (blinded to case/control status) for all entries using the International Classification of Primary Care-2. Additional codes were created to incorporate all possible clinical features. Only variables occurring in ≥ 2.5% of cases or controls were analysed.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Lung cancer diagnosis in the cancer registry at the Royal Devon and Exeter Hospital or practice notes.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All the patients are accounted for.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**

Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	

Møllmann (1981)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective patient series from an open-access gastroscopy clinic in Denmark.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 1480; gender not reported; 40-44 years: N = 144; 45-49 years: N = 186; 50-69 years: N = 882; 70-74 years: N = 130; 75-79 years: N = 83; 80-89 years N = 47: 90- years: N = 8. Inclusion criteria: All patients who, for a 2-year period, presented to their GP with (any of) the following symptoms were referred to the open access gastroscopy clinic: Upper abdominal pain > 2 weeks, nausea and/or vomiting > 2 weeks, weight loss and/or anorexia, gastrointestinal bleeding, and anaemia (i.e., Hb < 80%). Exclusion criteria: Patients who had been examined for any of the above symptoms within the last 6 months. Clinical setting: GPs in Denmark
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Upper abdominal pain > 2 weeks, nausea and/or vomiting > 2 weeks, weight loss and/or anorexia, gastrointestinal bleeding, and anaemia (i.e., Hb < 80%).
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	2-stage process: Gastroscopy with photography, using a gastrocamera, performed with only local anaesthesia of the pharynx. If this investigation disclosed abnormal conditions, the next stage was gastroscopy, possibly with biopsy, using diazepam sedation.
Is the reference standard likely to correctly classify the target condition?	**Unclear**
Were the reference standard results interpreted without	**No**

knowledge of the results of the index tests?	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	177/1480 patients declined endoscopy, 2/1480 did not show up for endoscopy, and it was unsuccessful in a further 24 patients, leaving 1277 patients. However, the paper reports that only 1273 had primary endoscopy, and then reports the results for between 1181 and 1297 patients.
Was there an appropriate interval between index test and reference standard?	**Yes probably**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**No**
Could the patient flow have introduced bias?	**High risk**
NOTES	There were a total of 18 gastric cancers confirmed in the study. No oesophageal cancers were reported. This research was published in 2 papers.

References

Included studies

Hamilton, W., Peters, T. J., Round, A. & Sharp, D. (2005) What are the clinical features of lung cancer before the diagnosis is made? A population based case-control study. *Thorax,* 60: 1059-1065. The data split by smoking status is available from: http://webarchive.nationalarchives.gov.uk/20130513211237/http://www.ncat.nhs.uk/sites/default/files/work-docs/ncl%20lung%20guide.pdf

Møllmann, K.-M. Early diagnosis of gastric cancer: The possibility of delimiting high risk groups. Danish Medical Bulletin 28, 89-92. 1981.

Møllmann, K.-M. Endoscopic service for general practice. Danish Medical Bulletin 28, 96-99. 1981.

DEEP VEIN THROMBOSIS

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised in the figure below. The main validity issue to note is that the study was conducted in the Netherlands and the findings are only applicable to the extent that the study population and setting are comparable to a UK GP population as defined for the current purposes.

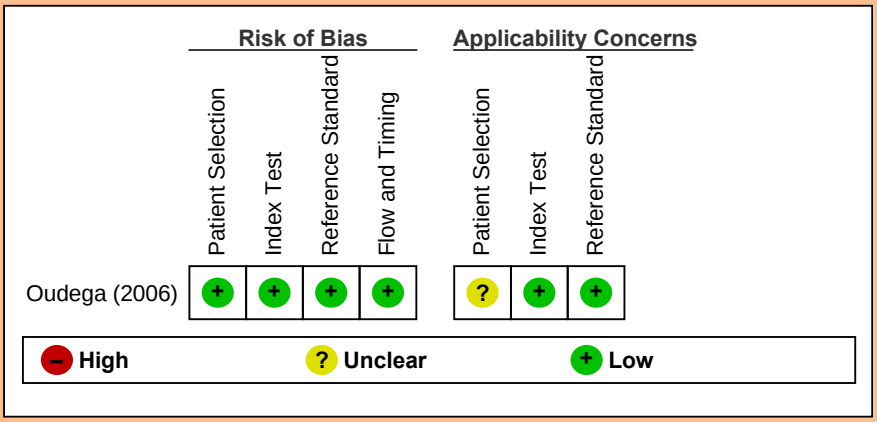

Table 1: Non-site specific symptoms of concern: Calculation of overall positive predictive value of deep vein thrombosis for cancer

Cancer site	Study	Lower age limit	Upper age limit	PPV (95% CI), prevalence
Colorectal	Oudega (2006)	No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years		0.7 (0.2-2.2) 3/430
Urogenital	Oudega (2006)	No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years		1.16 (0.4-2.9) 5/430
Breast	Oudega (2006)	No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years		0.93 (0.3-2.53) 4/430
Lung	Oudega (2006)	No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years		0.7 (0.2-2.2) 3/430
Sum				3.49

Table 2: Non-site specific symptoms of concern: Positive predictive values for deep vein thrombosis

Cancer site	Comment/relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit

Colorectal		Oudega (2006)	Deep vein thrombosis	All included patients	0.7 (0.2-2.2) 3/430	both	No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years
Urogenital		Oudega (2006)	Deep vein thrombosis	All included patients	1.16 (0.4-2.9) 5/430	both	No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years
Breast		Oudega (2006)	Deep vein thrombosis	All included patients	0.93 (0.3-2.53) 4/430	women	No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years
Lung		Oudega (2006)	Deep vein thrombosis	All included patients	0.7 (0.2-2.2) 3/430	both	No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years
Other		Oudega (2006)	Deep vein thrombosis	All included patients	0.93 (0.3-2.53) 4/430	both	No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years

Evidence statement(s):

Deep vein thrombosis (1 study, N = 430) presenting in a primary care setting is associated with an overall positive predictive value of 3.49% for cancer. The study was associated with 1 applicability concern (see also Table 1).

Evidence tables

Oudega (2006)

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Prospective study of all primary care physicians (N = 50) within a catchment area (ca 130000 inhabitants) of a non-teaching hospital in The Netherlands.	
Was a consecutive or random sample of patients enrolled?		**Yes**
Was a case-control design avoided?		**Yes**
Did the study avoid inappropriate exclusions?		**Yes**
Could the selection of patients have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Patient characteristics and setting	N = 430; 162 males, 268 females; mean age (SD) = 60.7 (18.2) years. Inclusion criteria: Consecutive patients who consulted their GP between January 1996 and July 2002 and who, after investigation (not referral) was	

	confirmed to have deep vein thrombosis. Exclusion criteria: Patients with a known malignancy or a malignancy detected within 2 weeks of deep vein thrombosis diagnosis. Clinical setting: Primary care, The Netherlands.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Deep vein thrombosis (suspicion based on painful swollen leg ≤ 30 days). Patients were classified as having secondary deep vein thrombosis if ≥ 1 of the following risk factors for deep vein thrombosis were present: Recent surgery, prolonged immobilisation, use of oral contraceptives or hormonal replacement therapy. If no risk factors were present patients were classified as having idiopathic deep vein thrombosis.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	2 years follow up.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	In total N = 19 had cancer: 3 colorectal, 5 urogenital (not further subgrouped), 4 breast, 3 lung and 4 other. The urogenital data is added to the renal cancer evidence review.

References

Included studies

Oudega, R. (2006) Deep vein thrombosis in primary care: Possible malignancy? *British Journal of General Practice,* 56: 693-696.

DYSPEPSIA

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main validity issues to note is that patient sampling was not clearly consecutive or random in a number of the studies, and the vast majority of the studies were conducted in populations that are not clearly directly relevant to the current question. Studies employing non-consecutive/random sampling are at risk of bias because, for example, case-control studies have been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection. Studies conducted in other settings than UK-based primary care are only applicable to the extent that the study populations and settings are comparable to a UK GP population as defined for the current purposes. Other bias and applicability threats to the results concern missing data and a potentially suboptimal reference standard.

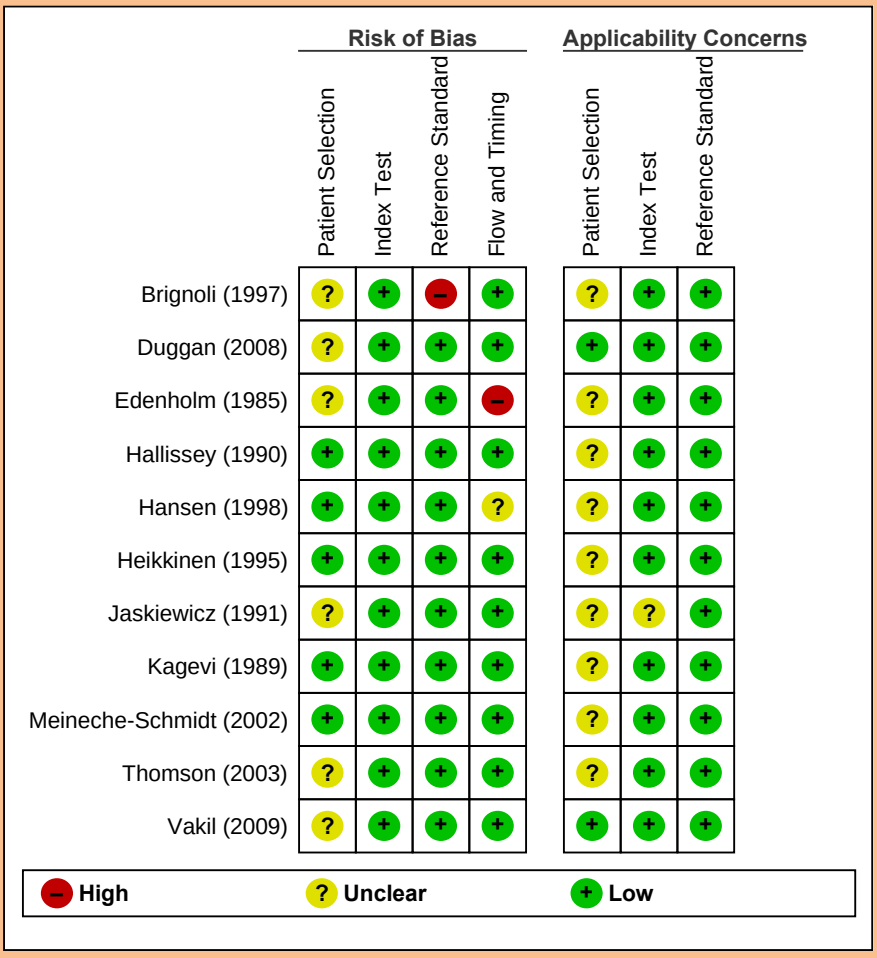

Table 1: Non-site specific symptoms of concern: Calculation of overall positive predictive value of dyspepsia for cancer

Cancer site	Study	Lower age limit	Upper age limit	PPV (95% CI), prevalence
Liver	Hallissey (1990)	40	no upper limit	0.04 (0.002-0.25) 1/2585
Pancreatic	Hallissey (1990)	40	no upper limit	0.23 (0.09-0.53)

				6/2585
Uterine	Hallissey (1990)	40	no upper limit	0.04 (0.002-0.25) 1/2585
Leukaemia	Hallissey (1990)	40	no upper limit	0.04 (0.002-0.3) 1/2585
Gall bladder	Hallissey (1990)	40	no upper limit	0.04 (0.002-0.3) 1/2585
Prostate	Hallissey (1990)	40	no upper limit	0.08 (0.01-0.3) 2/2585
Bronchial	Hallissey (1990)	40	no upper limit	0.3 (0.1-0.6) 8/2585
Oesophagus/stomach	Meta-analysis	varied	varied	0.65 (0.33-1.3)
Colorectal	Meta-analysis	varied	varied	0.6 (0.27-1.35)
Sum				2.02

Table 2: Non-site specific symptoms of concern: Positive predictive values for dyspepsia

Cancer site	Comment/relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
Liver		Hallissey (1990)	Dyspepsia	All patients	0.04 (0.002-0.25) 1/2585	both	40	no upper limit
Pancreatic		Hallissey (1990)	Dyspepsia	All patients	0.23 (0.09-0.53) 6/2585	both	40	no upper limit
Uterine		Hallissey (1990)	Dyspepsia	All patients	0.04 (0.002-0.25) 1/2585	both	40	no upper limit
Leukaemia		Hallissey (1990)	Dyspepsia	All patients	0.04 (0.002-0.3) 1/2585	both	40	no upper limit
Gall bladder		Hallissey (1990)	Dyspepsia	All patients	0.04 (0.002-0.3) 1/2585	both	40	no upper limit
Prostate		Hallissey (1990)	Dyspepsia	All patients	0.08 (0.01-0.3) 2/2585	both	40	no upper limit
Bronchial		Hallissey (1990)	Dyspepsia	All patients	0.3 (0.1-0.6) 8/2585	both	40	no upper limit

Other		Hallissey (1990)	Dyspepsia	All patients	0.3 (0.1-0.6) 8/2585	both	40	no upper limit
Other		Meineche-Schmidt (2002)	Dyspepsia	All patients	0.4 (0.16-0.92) 6/1491	both	18	65+
META-ANALYSES (1) Oesophageal								
Oesophagus/stomach	2 combining gastro-oesophageal and 9 reporting on oesophageal cancer separately	Meta-analysis	Dyspepsia	N = 11403/11 studies	0.25 (0.13-0.5)	both	2 studies > 15, 2 studies > 18, 1 study > 40, 1 study 17-80, 2 studies 18-70, 1 study 19-87, 1 study 18- >65, 1 study NR but mean (SD) = 41-42 (15-16) Individual study details provided below	
The 11 studies below are those included in the meta-analysis reported in the cell above (Please note the same data from Hansen (1998) and Meineche-Schmidt (2002) appear both here and under stomach, avoid double counting it):								
Oesophageal		Brignoli (1997)	Dyspepsia	All patients	0 (0-0.58) 0/828	both	Mean (SD) age = 41-42 (15-16) years	
Oesophageal		Duggan (2008)	Dyspepsia	All patients	0.27 (0.05-1.1) 2/753	both	18	70
Oesophageal		Edenholm (1985)	Persisten epigastric pain/ulcer-like dyspepsia	All patients who received an UGI endoscopy	0.61 (0.03-3.8) 1/165	both	17	80
Oesophageal		Hallissey (1990)	Dyspepsia	All patients	0.58 (0.33-0.98) 15/2585	both	40	No upper limit
Oesophageal/stomach		Hansen (1998)	Dyspepsia	All patients	1 (0.4-2.2) 6/612	both	Mean age (SD) = 47 (16.8)	
Oesophageal		Heikkinen (1995)	Dyspepsia	All patients	0.5 (0.09-2) 2/400	both	77% were > 44 years.	

Oesophageal		Jaskiewicz (1991)	Dyspepsia	All included patients	0 (0-0.8) 0/585	both	19	87
Oesophageal		Kagevi (1989)	Dyspepsia	All included patients	0 (0-2.7) 0/172	both	16	No upper limit
Oesophageal/stomach		Meineche-Schmidt (2002)	Dyspepsia	All patients	0.54 (0.25-1.1) 8/1491	both	18	65+
Oesophageal		Thomson (2003)	Dyspepsia	All patients	0.1 (0.01-0.6) 1/1040	both	18	84
Oesophageal		Vakil (2009)	Dyspepsia without alarm symptoms	All included patients	0.1 (0.03-0.35) 3/2741	both	18	70
The following results are any extra analyses reported by the studies included in the above meta-analysis:								
Oesophageal		Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 45 years old	0.18 (0.03-0.71) 2/1127	both	45	70
Oesophageal		Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 50 years old	0.24 (0.04-1) 2/829	both	50	70
Oesophageal		Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 55 years old	0.18 (0.01-1.16) 1/554	both	55	70
Oesophageal		Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 60 years old	0.3 (0.02-2) 1/323	both	60	70
Oesop		Hanse	Ulcer-	All	0.6 (0.03-	both	Mean age (SD) = 47 (16.8)	

hageal /stom ach		n (1998)	like dyspeps ia	patien ts	3.9) 1/161		
Oesop hageal /stom ach		Hanse n (1998)	Dysmoti lity-like dyspeps ia	All patien ts	0 (0-2.9) 0/163	both	Mean age (SD) = 47 (16.8)
Oesop hageal /stom ach		Hanse n (1998)	Reflux-like dyspeps ia	All patien ts	1.16 (0.2-4.6) 2/173	both	Mean age (SD) = 47 (16.8)
Oesop hageal /stom ach		Hanse n (1998)	Unclassi fiable dyspeps ia	All patien ts	0.9 (0.05-5.8) 1/107	both	Mean age (SD) = 47 (16.8)
META-ANALYSES (2) Stomach							
Oesop hagus /stom ach	2 combini ng gastro-oesopha geal and 9 reportin g on stomach cancer separat ely	Meta-analysi s	Dyspeps ia	N = 11403 /11 studie s	0.65 (0.33-1.3)	both	2 studies > 15, 2 studies > 18, 1 study > 40, 1 study 17-80, 2 studies 18-70, 1 study 19-87, 1 study 18- >65, 1 study NR but mean (SD) = 41-42 (15-16) Individual study details provided below.
The 11 studies below are those included in the meta-analysis reported in the cell above (Please note the same data from Hansen (1998) and Meineche-Schmidt (2002) appear both here and under oesophageal, avoid double counting it):							
Stoma ch		Brignol i (1997)	Dyspeps ia	All patien ts	0.4 (0.09-1.14) 3/828	both	Mean (SD) age = 41-42 (15-16) years
Stoma ch		Dugga n (2008)	Dyspeps ia	All patien ts	0.27 (0.05-1.1) 2/753	both	18 70
Stoma ch		Edenh olm (1985)	Persiste n epigastri c pain/ulc er-like dyspeps ia	All patien ts who receiv ed an UGI endos copy	1.2 (0.21-4.77) 2/165	both	17 80
Stoma ch		Halliss ey (1990)	Dyspeps ia	All patien ts	2.28 (1.76-3) 59/2585	both	40 No upper limit
Oesop hageal		Hanse n	Dyspeps ia	All patien	1 (0.4-2.2)	both	Mean age (SD) = 47 (16.8)

/stomach		(1998)		ts	6/612			
Stomach		Heikkinen (1995)	Dyspepsia	All patients	1.75 (0.8-3.7) 7/400	both	77% were > 44 years.	
Stomach		Jaskiewicz (1991)	Dyspepsia	All included patients	2.7 (1.6-4.5) 16/585	both	19	87
Stomach		Kagevi (1989)	Dyspepsia	All included patients	1.16 (0.2-4.6) 2/172	both	16	No upper limit
Oesophageal/stomach		Meineche-Schmidt (2002)	Dyspepsia	All patients	0.54 (0.25-1.1) 8/1491	both	18	65+
Stomach		Thomson (2003)	Dyspepsia	All patients	0.1 (0.01-0.6) 1/1040	both	18	84
Stomach		Vakil (2009)	Dyspepsia without alarm symptoms	All included patients	0.1 (0.03-0.35) 3/2741	both	18	70
The following results are any extra analyses reported by the studies included in the above meta-analysis:								
Stomach		Jaskiewicz (1991)	Dyspepsia	Males	3.4 (1.8-6) 12/355	Males	19	87
Stomach		Jaskiewicz (1991)	Dyspepsia	Females	1.7 (0.6-4.7) 4/230	Females	19	87
Oesophageal/stomach		Hansen (1998)	Ulcer-like dyspepsia	All patients	0.6 (0.03-3.9) 1/161	Both	Mean age (SD) = 47 (16.8)	
Oesophageal/stomach		Hansen (1998)	Dysmotility-like dyspepsia	All patients	0 (0-2.9) 0/163	Both	Mean age (SD) = 47 (16.8)	
Oesophageal/stomach		Hansen (1998)	Reflux-like dyspepsia	All patients	1.16 (0.2-4.6) 2/173	Both	Mean age (SD) = 47 (16.8)	
Oesophageal		Hansen	Unclassifiable	All patien	0.9 (0.05-5.8)	Both	Mean age (SD) = 47 (16.8)	

/stomach		(1998)	dyspepsia	ts	1/107			
Stomach		Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 45 years old	0.27 (0.07-0.84) 3/1127	both	45	70
Stomach		Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 50 years old	0.36 (0.09-1.15) 3/829	both	50	70
Stomach		Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 55 years old	0 (0-0.86) 0/554	both	55	70
Stomach		Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 60 years old	0 (0-1.47) 0/323	both	60	70
META-ANALYSES (3) Colorectal								
Colorectal	1 study from 15, 1 study from 18-65+ and 1 study from 40.	Meta-analysis	Dyspepsia	3 studies, N = 4476	0.6 (0.27-1.35)	both	15-18	65+
The 3 studies below are those included in the meta-analysis reported in the cell above:								
Colorectal		Hallissey (1990)	Dyspepsia	All patients	0.5 (0.3-0.9) 14/2585	both	40	No upper limit
Colorectal		Heikkinen (1995)	Dyspepsia	All patients	0/400	both	77% were > 44 years.	
Colorectal		Meineche-Schmidt (2002)	Dyspepsia	All patients	1.14 (0.7-1.9)	both	18	65+

Evidence statement(s):

Dyspepsia (11 studies, N = 18464) presenting in a primary care setting is associated with an overall positive predictive value of 2.02% for cancer. The study was associated with 1-3 bias/applicability concerns (see also Table 1).

Evidence tables

Brignoli (1997)

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Prospective patient series from Switzerland.	
Was a consecutive or random sample of patients enrolled?		**Unclear**
Was a case-control design avoided?		**Yes**
Did the study avoid inappropriate exclusions?		**Unclear**
Could the selection of patients have introduced bias?		**Unclear risk**
B. Concerns regarding applicability		
Patient characteristics and setting	N = 828; 329 men, 499 women; mean (SD) age = 41-42 (15-16) years. Inclusion criteria: "Adult patients with epigastric complaints were admitted to the multicentre [omega]-project if their symptoms persisted for over 1 month and their clinical history and appearance did not suggest an organic disorder (i.e. absence of alarm features, such as gastrointestinal blood loss, palpable tumour mass, massive weight loss, etc.). The studies were conducted by general practitioners acting as primary care physicians." Exclusion criteria: None listed Clinical setting: Primary care, Switzerland	
Are there concerns that the included patients and setting do not match the review question?		**Unclear concern**
INDEX TEST		
A. Risk of bias		
Index test	Epigastric complaints (dyspepsia)	
Were the index test results interpreted without knowledge of the results of the reference standard?		**Yes**
Could the conduct or interpretation of the index test have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		**Low concern**
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	Endoscopy and 84-day follow up.	
Is the reference standard likely to correctly classify the target condition?		**No**
Were the reference standard results interpreted without knowledge of the results of the index tests?		**No**

Could the reference standard, its conduct, or its interpretation have introduced bias?	**High risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients are accounted for
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	3 patients had gastric cancer, 0 patients had oesophageal cancer, and 2 patients had cancer outside the digestive tract.

Duggan (2008)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective patient series from 43 GP practices in the UK.
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 762; 411 men, 351 women; mean (range) age = 42 (18-73) years. Inclusion criteria: Patients aged 18-70 with dyspepsia thought by the GP to arise from the upper GI tract and of sufficient severity to justify empirical treatment with an H_2 antagonist or PPI. Exclusion criteria: Patients thought to be unfit for investigation, with alarm symptoms suggestive of malignancy (dysphagia, weight loss > 5 g, anaemia, haematemesis, melaena or jaundice), previous radiological or endoscopic diagnosis of peptic ulcer disease or reflux oesophagitis, investigation for dyspepsia in the previous 5 years with either procedure or symptom onset within 6 months of commencement of NSAID therapy, previous H. pylori eradication therapy or more than 3 prescriptions for acid suppression therapy in the previous 6 months. Clinical setting: Primary care, UK
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	Dyspepsia
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**

Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Endoscopy and 1-2-year follow up.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	At 12-month follow up GP data were available for 753/762.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	2 patients had gastric cancer, 2 patients had oesophageal cancer (the authors report that these patients should not have been included as they had a history of dysphagia).

Edenholm (1985)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective patient series from the Distric General Clinic in Huskvarna, Sweden.
Was a consecutive or random sample of patients enrolled?	**Unclear**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Unclear**
Could the selection of patients have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 187; 96 men, 91 women; mean/median (range) age = 44 (17-80) years. Inclusion criteria: Patients who between November 1982 and June 1984 called on the clinic because of abdominal pain and who were diagnosed by the general practitioner as having ulcer-like dyspepsia. The criterion used was persistent epigastric pain. Most patients also had additional symptoms such as acid regurgitation, nausea, belching or vomiting.

	Exclusion criteria: None listed Clinical setting: GPs in Sweden	
Are there concerns that the included patients and setting do not match the review question?		**Unclear concern**
INDEX TEST		
A. Risk of bias		
Index test	Ulcer-like dyspepsia. The criterion used was persistent epigastric pain.	
Were the index test results interpreted without knowledge of the results of the reference standard?		**Yes**
Could the conduct or interpretation of the index test have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		**Low concern**
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	UGI endoscopy	
Is the reference standard likely to correctly classify the target condition?		**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?		**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		**Low concern**
FLOW AND TIMING		
A. risk of bias		
Flow and timing	20/187 patients declined endoscopy and it was unsuccessful in a further 2 patients. Thus the PPV is likely to be an over-estimate, calculated as 2/165.	
Was there an appropriate interval between index test and reference standard?		**Yes probably**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**No**
Could the patient flow have introduced bias?		**High risk**
NOTES	There were a total of 3 cancers confirmed in the 165 patients who received UGI endoscopy: 1 oesophageal cancer, 1 stomach cancer, and 1 cancer of the duodenum, the latter of which was included with the stomach cancer	

Hallissey (1990)

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Propective consecutive patient series from a group of 10 general practices in England.	
Was a consecutive or random sample of patients enrolled?		**Yes**

Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 2585 aged > 40 years. No other information reported. The patient group was equally divided between new patients with dyspepsia, old patients with uninvestigated dyspepsia, and old patients with investigated dyspepsia. Inclusion criteria: All patients over 40 years making their first attendance during the study period (4 years and 9 months) with any degree of dyspepsia Exclusion criteria: None listed. Clinical setting: Primary care, England.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Dyspepsia of any degree
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Upper gastrointestinal endoscopy within 4 weeks and follow up.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	2659 patients were seen and 2585 attended for investigation
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	Malignancy was detected in 115 patients: Gastric adenocarcinoma (57), gastric lymphoma (1; added to the gastric adenocarcinoma data in the PPV),

	oesophageal cancer (15), colorectal (14), pancreatic (6), bronchial (8), prostatic (2), duodenal (1, also added to the gastric carcinoma data in the PPV), liver (1), gall bladder (1), carcinoid (1), uterine (1), leukaemia (1), carcinomatosis of unknown primary (7).

1

2 **Hansen (1998)**

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Prospective patient series from general an open-access endoscopy clinic in Denmark.	
Was a consecutive or random sample of patients enrolled?		**Yes**
Was a case-control design avoided?		**Yes**
Did the study avoid inappropriate exclusions?		**Yes**
Could the selection of patients have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Patient characteristics and setting	N = 612 from 66 GPs; 288 males / 324 females; mean age (SD) = 47 (16.8) years. Inclusion criteria: "All general practitioners (n = 108) in the city of Odense (population, 170,000) were invited to participate in the study. GPs were asked to refer all patients who consulted them with dyspepsia, regardless of the severity of the symptoms. To obtain compliance with this request the participating GPs were sent numerous reminders. Because of a limited endoscopy capacity not all GPs took part in the study at the same time."Study period was 11 March 1991-27 March 1992. Exclusion criteria: Aged < 18 years, signs of UGI bleeding, abdominal emergency, jaundice, previous surgery in the UGI tract except for closure of an ulcer, supposed acute bacterial or viral infection, pregnancy, or endoscopy contyraindicated. Clinical setting: GPs in Denmark	
Are there concerns that the included patients and setting do not match the review question?		**Unclear concern**
INDEX TEST		
A. Risk of bias		
Index test	Epigastric or retrosternal pain or discomfort, with or without heartburn, nausea, vomiting, and any other symptom considered to be referable to the proximal alimentary tract.	
Were the index test results interpreted without knowledge of the results of the reference standard?		**Yes**
Could the conduct or interpretation of the index test have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		**Low concern**
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	Endoscopy within 1 week of referral and follow up	

Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	56 eligible patients declined participation. These patients were older than the study group (mean age = 52 years versus 47 years) and they were characterised by a shorter dyspepsia history (median duration = 1 month, range = 4 days to 35 years versus 2 months, range = 4 days to 14 years). Fewer of the non-participating patients had had a previous endoscopy or UGI radiography (22% versus 43%, but identical proportions of the patients had an ulcer history (11% versus 14%).
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**No**
Could the patient flow have introduced bias?	**Unclear risk**
NOTES	There were a total of 4 cancers histologically confirmed in the study. No subclassification of the cancers reported. Follow up of the 364 patients with normal endoscopy revealed missing date in 5% of the cases and 1 lymphoma and 1 rectal carcinoma. These 6 cancers (NOS) are included in the overall PPV for dyspepsia.

Heikkinen (1995)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Consecutive patient series from 11 GPs (from 3 rural health centres) and from the catchment area of 6 physicians in the health centre of an urban area (population [individuals > 14 years old] of study area = 24600) in Finland.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 400; 152 males, 248 females; 77% were > 44 years. Inclusion criteria: Consecutive patients who consulted their GP from January 11th 1993 to January 12th 1994 for dyspepsia (defined as upper abdominal or retrosternal pain, discomfort, heartburn, nausea, vomiting, or other symptoms considered to be referable to the proximal alimentary tract).

	Exclusion criteria: Patients with symptoms of an acute condition within the abdomen or who had had an upper intestinal endoscopy performed within the last 3 months or aged < 15 years Clinical setting: Primary care, Finland.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Dyspepsia (defined as upper abdominal or retrosternal pain, discomfort, heartburn, nausea, vomiting, or other symptoms considered to be referable to the proximal alimentary tract).
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Upper gastrointestinal endoscopy, upper abdominal ultrasound, more detailed interview, blood count, serum screening (creatinine, alkaline phosphatise, alanine aminotransferase, amylase, and C-reactive protein), lactose intolerance test, and follow up of ≥ 1 month.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	In total N = 9 had cancer: 0 colorectal, 2 oesophageal and 7 stomach (of which 3 were lymphomas of the MALT type (Mucosa-associated lymphoid tissue).

Jaskiewicz (1991)

PATIENT SELECTION

A. risk of bias	
Patient sampling	Patient series from a program aimed at screening patients with chronic gastric complaints for gastric carcinoma in the South and North-Western Cape Province of South Africa.
Was a consecutive or random sample of patients enrolled?	**Unclear**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Unclear**
Could the selection of patients have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 585, 355 males, 230 females; mean (range) age males = 45.1 (19-87) years, mean (range) age females = 47.2 (19-87) years. Inclusion criteria: "participants who were treated for dyspeptic complaints such as epigastric pain, heartburn, post-prandial pain and bloating, vomiting or nausea with a duration of at least 3 months. Patients represented various areas in the south-and north-western Cape province including Namaqualand, and formed part of a programme aimed at screening patients with chronic gastric complaints for gastric carcinoma." Exclusion criteria: None listed Clinical setting: Unclear, South Africa.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Unspecified dyspepsia (dyspeptic complaints such as epigastric pain, heartburn, post-prandial pain and bloating, vomiting or nausea wiuth a duration of at least 3 months).
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Unclear concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Endoscopy
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**

FLOW AND TIMING		
A. risk of bias		
Flow and timing	All patients appear to be accounted for	
Was there an appropriate interval between index test and reference standard?		**Yes**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**Yes**
Could the patient flow have introduced bias?		**Low risk**
NOTES	In total N = 16 had gastric cancer. No oesophageal cancers reported	

Kagevi (1989)

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Propective consecutive patient series from a primary care centre in Sweden.	
Was a consecutive or random sample of patients enrolled?		**Yes**
Was a case-control design avoided?		**Yes**
Did the study avoid inappropriate exclusions?		**Yes**
Could the selection of patients have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Patient characteristics and setting	N = 172; 88 men, 84 women; mean (SD) age = 43 (16) years. Inclusion criteria: "All patients visiting the medical center with complaints referable to the digestive tract were considered for inclusion. Even when the patient consulted the primary care center because of another complaint and coincidentally mentioned gastrointestinal problem, the patient was considered for inclusion. The patient's gastrointestinal problem could have been reported in connection with an earlier visit at the primary care center." Exclusion criteria: Patients with jaundice, gastrointestinal bleeding or acute abdominal pain were excluded and so were patients judged to have a non-gastro-enterologic cause of their symptoms (gynaecologic problems, spondylosis deformans, etc), patients aged < 16 years and patients unwilling to participate. Clinical setting: Primary care Center, Sweden.	
Are there concerns that the included patients and setting do not match the review question?		**Unclear concern**
INDEX TEST		
A. Risk of bias		
Index test	Dyspepsia defined as any pain, discomfort, or other symptoms referable to the digestive tract ≥ 2 weeks. Symptoms could be intermittent or continuous.	
Were the index test results interpreted without knowledge of the results of the reference standard?		**Yes**
Could the conduct or interpretation of the index test have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		**Low concern**

REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Esophagogastroduodenoscopy withion 1 week and 6 month follow up.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	13/185 patients were excluded as they did not want to have an endoscopy
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	2 patients had gastric cancer, 0 patients had oesophageal cancer.

Meineche-Schmidt (2002)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Consecutive patient series from 82 GPs in Denmark.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 1491; 688 males, 803 females; age groups: 18-37 years: N = 377; 38-50 years: N = 369; 51-64 years: N = 338; 65- years: N = 402. Inclusion criteria: Consecutive patients who consulted their GP between June 1991 and May 1993 for dyspepsia (defined as pain or discomfort in the abdomen judged by the GP to be related to the gastrointestinal tract). Exclusion criteria: None listed. Clinical setting: Primary care, Denmark.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Dyspepsia (defined as pain or discomfort in the abdomen judged by the GP to be related to the gastrointestinal tract).

Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	18 months-3 years and 10 months follow up.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appear to be accounted for
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	In total N = 31 had cancer: 17 colorectal, 8 gastro-oesophageal (no subgroup analyses presented for these patients) and 6 other.

Thomson (2003)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Propective patient series from a group of 49 family physician practices in Canada.
Was a consecutive or random sample of patients enrolled?	**Unclear**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Unclear**
Could the selection of patients have introduced bias?	**Unclear risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 1040, 520 males / 520 females; mean (range) age =45.6 (18-84) years. Inclusion criteria: Patients ≥ 18 years with a primary complaint of ≥ 3 months intermittent or continuous dyspepsia. Patients could not have used proton pump inhibitiors within 30 days or prokinetics or prescription H_2-receptor

	antagonists (H_2RAS) within 14 days of enrolment. Exclusion criteria: Heartburn or acid regurgitation as their sole symptom; documented history of upper GI pathology/surgery; clinical investigation of dyspepsia by endoscopy or radiology in the previous 6 months or more than twice in the past 10 years; H. pylori eradication treatment in the previous 6 months; irritable bowel syndrome as assessed by the presence of ≥ manning criteria; or severe concurrent disease. Clinical setting: Family physician practice, Canada.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Dyspepsia defined as symptom complex of epigastric pain/discomfort in association with other upper GI symptoms, including heartburn and acid regurgitation.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Upper gastrointestinal endoscopy within 10 days and 6-months follow up.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients are accounted for. 1100/1171 enrolled patients consented to endoscopy, but 60/1100 did not received endoscoy (eligibility criteria not fulfilled [27], lost to follow up [3], withdrew consent [9], non-compliant with the protocol [1], endoscopy-intolerable [2], other [18]).
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	Malignancy was detected in 2 patients: Gastric (MALToma; 1), oesophageal cancer (1).

Vakil (2009)

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Prospective patient series	
Was a consecutive or random sample of patients enrolled?		**Unclear**
Was a case-control design avoided?		**Yes**
Did the study avoid inappropriate exclusions?		**Yes (probably)**
Could the selection of patients have introduced bias?		**Unclear risk**
B. Concerns regarding applicability		
Patient characteristics and setting	N = 2741, mean (range) age = not reported (not reported) years, numbers of females/males: Not reported. Inclusion criteria: Patients aged 18-70 years who met Rome II criteria for dyspepsia (intermittent or continuous pain or burning centered in the upper abdomen for ≥ 3 months). Exclusion criteria: Past diagnosis of gastro-oesophageal reflux disease, predominant symptom of heartburn or regurgitation, history of heartburn or regurgitation > 2 days/week, treatment > 2 days/week with non-steroidal anti-inflammatory drugs or cyclooxygenase-2 selective inhibitors or aspirin (except for cardiovascular prophylaxis at doses ≤ 325 mg/day), concurrent alarm features (e.g., dysphagia, recurrent vomiting, unexplained anaemia, gastro-intestinal bleeding), H pylori eradication treatment within 12 months, maintenance therapy with either a proton pump or an H2-receptor antagonist within 6 months. Clinical setting: The study was conducted in 190 primary care health centers in 17 countries (Argentina, Belgium, Brazil, Canada, Denmark, France, Germany, Greece, Iceland, Italy, Norway, Romania, Singapore, South Africa, Spain, Sweden, Switzerland). Patients were recruited from primary care clinics where flyers publicising the study were placed and the primary care physicians recruited patients presenting to their offices with dyspepsia *[random or consecutive sampling unlikely].*	
Are there concerns that the included patients and setting do not match the review question?		**Low concern**
INDEX TEST		
A. Risk of bias		
Index test	Dyspepsia/ intermittent or continuous pain or burning centered in the upper abdomen for ≥ 3 months. Symptoms were evaluated using a scale validated in a number of languages	
Were the index test results interpreted without knowledge of the results of the reference standard?		**Yes**
Could the conduct or interpretation of the index test have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		**Low concern**
REFERENCE STANDARD		
A. risk of bias		

Reference standard(s)	All patients received outpatient endoscopy
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No (but all patients had a positive index test)**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All the patients are accounted for in the results.
Was there an appropriate interval between index test and reference standard?	**Yes (probably)**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	Supported by AstraZeneca R&D Sweden. The authors state that "The sponsor did not play any role in the calculations or in the writing of the manuscript". Six patients had cancer: 3 oesophagus and 3 stomach.

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WEIGHT LOSS

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The body of evidence was generally of high quality. The main validity issues to note is that patient sampling was not clearly consecutive or random in a number of the studies, and that some of studies suffered from missing data. Studies employing non-consecutive/random sampling are at risk of bias because, for example, case-control studies have been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection. The statistical analyses employed by these studies are however likely to have gone some way in addressing this issue. One study was conducted in a setting that is unlikely to be directly applicable to UK-based primary care and, as a consequence, also seems to present inflated PPVs that may be more reflective of secondary care. Finally, some of the studies were compromised by missing data, the influence of which on the results is difficult to determine.

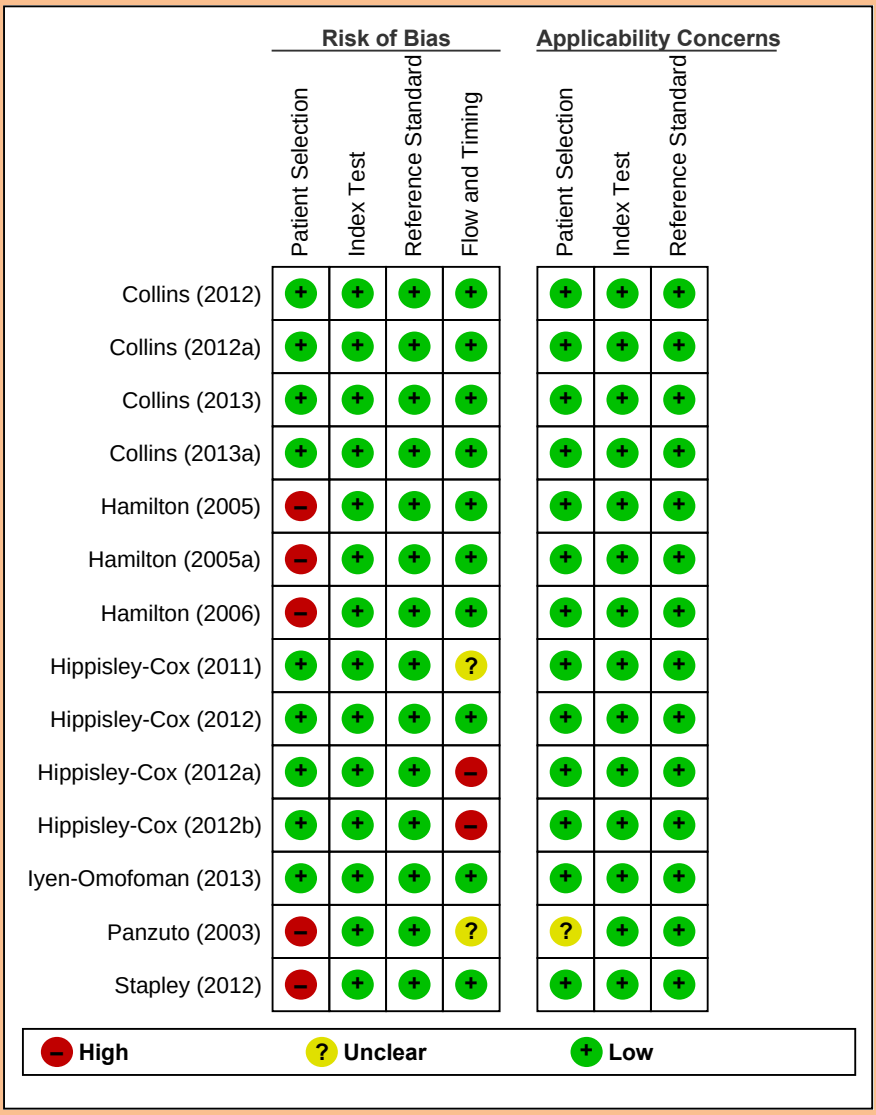

Table 1: Non-site specific symptoms of concern: Calculation of overall positive predictive value of weight loss for cancer

Cancer site	Study	Lower age limit	Upper age limit	PPV (95% CI), prevalence
Bladder/renal	Hippisley-Cox (2012)	30	84	0.41 (0.3-0.6)
Colorectal	Meta-analysis	18	87	3 (0.32-22.89)
Lung	Hamilton (2005)	40	No upper limit	1.1 (0.8-1.6)
Oesophagus/stomach	Hippisley-Cox (2011)	30	84	1.2 (1-1.4) 107/9170
Pancreatic	Hippisley-Cox (2012)	30	84	0.6 (0.5-0.8)
Prostate	Hamilton (2006)	40	No upper limit	0.75 (0.38-1.4)
Sum				7.06

Table 2: Non-site specific symptoms of concern: Positive predictive values for weight loss

Cancer site	Comment/relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
Bladder/renal		Collins (2013a)	Weight loss	Women	0.1 (0.1-0.2)	Women	30	84
Bladder/renal		Hippisley-Cox (2012b)	Weight loss	All patients	0.41 (0.3-0.6)	both	30	84
Lung		Hamilton (2005a)	Weight loss	All included patients	1.1 (0.8-1.6)	both	40	no upper limit
Lung		Hamilton (2005a)	Weight loss (reported twice)	All included patients	1.2 (0.7-2.3)	both	40	no upper limit
Lung		Hamilton (2005a)	Weight loss	All smokers	2.1 (NR)	both	40	no upper limit
Lung		Hamilton (2005a)	Weight loss (reported twice)	All smokers	1.7 (NR)	both	40	no upper limit
Lung		Iyen-Omofoman (2013)	Weight loss	Validation cohort	0.34 (0.23-0.5)	both	40	no upper limit

Oesophagus/stomach		Collins (2012a)	Weight loss	All patients	0.8 (0.7-0.9) 218/28403	both	30	84
Oesophagus/stomach		Collins (2012a)	Weight loss	Women	0.6 (0.4-0.7) 86/15465	Women	30	84
Oesophagus/stomach		Collins (2012a)	Weight loss	Men	1 (0.9-1.2) 132/12938	Men	30	84
Oesophagus/stomach		Hippisley-Cox (2011)	Weight loss	All patients	1.2 (1-1.4) 107/9170	both	30	84
Pancreatic		Collins (2013)	Weight loss	All patients	0.28 (0.22-0.35)	both	30	84
Pancreatic		Collins (2013)	Weight loss	Women	0.16 (0.11-0.24)	women	30	84
Pancreatic		Collins (2013)	Weight loss	Men	0.42 (0.32-0.54)	men	30	84
Pancreatic		Hippisley-Cox (2012a)	Weight loss	All patients	0.6 (0.5-0.8)	both	30	84
Pancreatic		Stapley (2012)	Weight loss	All patients	0.44 (0.36-0.55)	both	40	no upper limit
Pancreatic		Stapley (2012)	Weight loss	Patients ≥ 60 years	0.8 (0.7-1)	both	60	no upper limit
Prostate		Hamilton (2006)	Loss of weight	All included patients	0.75 (0.38-1.4)	men	40	no upper limit
Prostate		Hamilton (2006)	Loss of weight (reported twice)	All included patients	2.1 (NR)	men	40	no upper limit
Colorectal		Hamilton (2005)	Loss of weight (reported once)	All patients	1.2 (0.9-1.6) Cases: 94/349 Controls: 92/1744	both	40	no upper limit

Colorectal		Hamilton (2005)	Loss of weight (reported twice)	All patients	1.4 (0.8-2.6)	both	40	no upper limit
Colorectal		Hamilton (2005)	Loss of weight	Patients 40-69 years	0.74 (NR)	both	40	69
Colorectal		Hamilton (2005)	Loss of weight	Patients ≥ 70 years	2.5 (NR)	both	70	no upper limit
Colorectal		Hamilton (2005)	Weight loss 5-10% (read off graph)	Men aged < 60 years	0.1 (0.05-0.2)	Males	40	59
Colorectal		Hamilton (2005)	Weight loss 5-10% (read off graph)	Men aged 60-69 years	0.3 (0.2-0.4)	Males	60	69
Colorectal		Hamilton (2005)	Weight loss 5-10% (read off graph)	Men aged 70-79 years	0.7 (0.5-0.8)	Males	70	79
Colorectal		Hamilton (2005)	Weight loss 5-10% (read off graph)	Men aged ≥ 80 years	0.5 (0.3-0.8)	Males	80	no upper limit
Colorectal		Hamilton (2005)	Weight loss ≥ 10% (read off graph)	Men < 60 years	0.2 (0.1-0.3)	Males	40	59
Colorectal		Hamilton (2005)	Weight loss ≥ 10% (read off graph)	Men 60-69 years	0.7 (0.4-0.9)	Males	60	69
Colorectal		Hamilton (2005)	Weight loss ≥ 10% (read off graph)	Men 70-79 years	1.5 (1.2-1.8)	Males	70	79
Colorectal		Hamilton (2005)	Weight loss ≥ 10% (read off graph)	Men ≥ 80 years	0.8 (0.6-1.4)	Males	80	no upper limit

Colorectal		Hamilton (2005)	Weight loss 5-10% (read off graph)	Women < 60 years	0.05 (0.05-0.05)	Females	40	59
Colorectal		Hamilton (2005)	Weight loss 5-10% (read off graph)	Women 60-69 years	0.2 (0.1-0.3)	Females	60	69
Colorectal		Hamilton (2005)	Weight loss 5-10% (read off graph)	Women 70-79 years	0.4 (0.3-0.6)	Females	70	79
Colorectal		Hamilton (2005)	Weight loss 5-10% (read off graph)	Women ≥ 80 years	0.4 (0.3-0.6)	Females	80	no upper limit
Colorectal		Hamilton (2005)	Weight loss ≥ 10% (read off graph)	Women < 60 years	0.06 (0.06-0.08)	Females	40	59
Colorectal		Hamilton (2005)	Weight loss ≥ 10% (read off graph)	Women 60-69 years	0.5 (0.3-0.7)	Females	60	69
Colorectal		Hamilton (2005)	Weight loss ≥ 10% (read off graph)	Women 70-79 years	0.8 (0.6-1.1)	Females	70	79
Colorectal		Hamilton (2005)	Weight loss ≥ 10% (read off graph)	Women ≥ 80 years	0.8 (0.6-1.1)	Females	80	no upper limit
META-ANALYSES (1) Colorectal								
Colorectal		Meta-analysis	Weight loss	N = 42338 patients/3 studies	3 (0.32-22.89)	both	2 studies 30-84, 1 study 18-87 Individual study details below	
The 3 studies below are those included in the meta-analysis reported in the cell above:								
Colorectal		Collins (2012)	Weight loss	All patients (N =	0.8 (0.7-0.9)	both	30	84

				28289)				
Colorectal		Hippisley-Cox (2012)	Weight loss	All patients (N = 14007)	0.8 (0.7-0.9)	both	30	84
Colorectal		Panzuto (2003)	Weight loss	All patients (N = 42)	35.7 (22-52)	both	18	87
The following results are any extra analyses reported by the studies included in the above meta-analysis:								
Colorectal		Collins (2012)	Weight loss	Males	1 (0.8-1.1)	Males	30	84
Colorectal		Collins (2012)	Weight loss	Females	0.6 (0.5-0.7)	Females	30	84

Evidence statement(s):

Weight loss (8 studies, N = 3768550) presenting in a primary care setting is associated with an overall positive predictive value of 7.06% for cancer. The studies were associated with 0-3 bias/applicability concerns (see also Table 1).

Evidence tables

Collins (2012)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Retrospective patient series using the THIN database.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 2135540 patients were identified from 364 practices. Symptoms: Rectal bleeding (N = 56234; 28423 men, 27811 women), abdominal pain (N = 245989; 102192 men, 143797 women), appetite loss (N = 5776; 2481 men, 3295 women), weight loss (N = 28289; 12891 men, 15398 women), anaemia (N = 18125; 4466 men, 13659 women), change in bowel habit (men only, N = 1670). Incident cases of colorectal cancer during the 2-year follow up period: N = 3712 (2036 men, 1676 women). Inclusion criteria: Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. Exclusion criteria: Patients without a postcode-related Townsend score,

	patients with a history of colorectal cancer at baseline, and patients with a recorded 'red-flag' symptom in the 12 months prior to the study entry date. Clinical setting: Primary care, UK
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms: Rectal bleeding, loss of appetite, weight loss, abdominal pain, change in bowel habit (men only), and anaemia.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	2-year follow up
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients seem to be accounted for
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	The is ***very large, if not complete, overlap*** of the data used in this study with those used in Hamilton (2008 [for anaemia], 2009)

Collins (2012a)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Retrospective patient series using the THIN database.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**

Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 2135540 patients were identified from 364 practices. Symptoms: Dysphagia (N = 19237; 8846 men, 10391 women), abdominal pain (N = 246998; 102732 men, 144266 women), appetite loss (N = 5838; 2521 men, 3317 women), weight loss (N = 28403; 12938 men, 15465 women), haematemesis (N = 10792; 6162 men, 4630 women), anaemia (N = 18355; 4563 men, 13792 women). Incident cases of gastro-oesophageal cancer during the 2-year follow up period: N = 1766 (1184 men, 582 women; 32% gastric cancer, 68% oesophageal cancer). Inclusion criteria: Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. Exclusion criteria: Patients with a prior diagnosis of gastro-oesophageal cancer, registration with the general practice < 12 months, or with invalid dates. Clinical setting: Primary care, UK
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms: Haematemesis, dysphagia, loss of appetite, weight loss, anaemia, and abdominal pain.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	2-year follow up
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	

Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients seem to be accounted for
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	The study did not distinguish between gastric and oesophageal cancer

Collins (2013)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Retrospective patient series using the THIN database.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 2150322 patients were identified from 364 practices. Symptoms: Dysphagia (men only: N = 9326), abdominal pain (N = 255058; 106768 men, 148290 women), appetite loss (N = 6102; 2658 men, 3444 women), weight loss (N = 29464; 13484 men, 15980 women), abdominal distension (women only: N = 4457), constipation (men only, N = 5326). Incident cases of pancreatic cancer during the 2-year follow up period: N = 287 (331 men, 287 women). Inclusion criteria: Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. Exclusion criteria: Patients with a prior diagnosis of pancreatic cancer, registration < 12 months with the general practice, or invalid dates. Clinical setting: Primary care, UK
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms: Dysphagia (men only), loss of appetite, weight loss, abdominal pain, abdominal distension (women only), and constipation (men only).
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test	**Low risk**

have introduced bias?	
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	2-year follow up
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients seem to be accounted for
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	

Collins (2013a)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Retrospective patient series using the THIN database.
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 2145133 patients (1063355 men, 1081778 women) were identified from 364 practices. Symptoms: Haemoglobin < 11 g/dl recorded in the last year (N = 16961; 3969 men, 12992 women), abdominal pain (N = 253344; 105247 men, 148097 women), appetite loss (N = 6097; 2616 men, 3481 women), weight loss (N = 29369; 13332 men, 16037 women), haematuria (N = 37810; 22810 men, 15000 women), previous diagnosis of cancer apart from renal tract cancer at study entry (N = 49303; 18130 men, 31173 women). Incident cases of renal tract cancer during the 2-year follow up period:

	N = 2283 (1685 men, 598 women). Inclusion criteria: Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (e.g., haematuria, abdominal pain, weight loss, appetite loss, and anaemia), the date of the first recorded onset within the study period. Exclusion criteria: Patients with a prior diagnosis of renal tract cancer, registered less than 12 months with the general practice, had invalid dates, < 30 years old or ≥ 85 years old. Clinical setting: Primary care, UK
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms were defined as symptoms that might alarm the patient and also indicate the presence of renal tract cancer; that is, symptoms of haematuria, loss of appetite, weight loss, or abdominal pain.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Renal tract cancer, which was defined as incident diagnosis of cancer of the bladder, kidney, ureter, or urethra during the 2 years after study entry, recorded either on the patient's GP record using the relevant UK diagnostic Read Codes. Patients without the outcome were censored at the earliest of the date of death, date of leaving the practice study of 2 years of follow up.
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients seem to be accounted for
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**

Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	It is unclear why no data has been presented for men for the symptoms of appetite loss and weight loss.

Hamilton (2005)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Population-based matched case-control study involving all 21 general practices in Exeter, Devon, UK.
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: N = 349 (177 males/172 females), age at diagnosis: < 60 years: N = 45, 60-69 years: N = 97, 70-79 years: N = 113, 80+ years: N = 94. 210/349 had tumours at or distal to the splenic flexure, and 126/349 had tumours proximal to the splenic flexure, the remaining 13/349 has tumours in multiple or unknown sites. Duke's staging was known for 305/349: 170/305 were Duke's A or B, and 135/305 were Duke's C or D. Controls: N = 1744 (885 males/859 females), age at diagnosis: < 60 years: N = 225, 60-69 years: N = 487, 70-79 years: N = 555, 80+ years: N = 477. Inclusion criteria: Cases: All patients aged ≥ 40 years with a primary colorectal cancer, diagnosed from 1998 to 2002, were identified from the cancer registry at the Royal Devon and Exeter Hospital combined with computerised searches at every practice in Devon to identify any cases missing from the cancer register. Controls: Five controls were matched to each case on sex, general practice, and age (to 1-year bands if possible, increased in 1-year multiples to a maximum of 5 years). Controls were eligible if they were alive at the time of diagnosis of their case. Exclusion criteria: Cases and controls: Unobtainable records; no consultations in the 2 years before diagnosis; previous colorectal cancer; or residence outside Exeter at the time of diagnosis. Clinical setting: Primary care, UK.
Are there concerns that the included patients and setting do not match the review question?	**Low concern**

INDEX TEST		
A. Risk of bias		
Index test	Anonymised photocopies of the full primary care records for 2 years before diagnosis were coded (blinded to case/control status) for all entries using the International Classification of Primary Care-2. Additional codes were created to incorporate all possible clinical features. Only variables occurring in ≥ 2.5% of cases or controls were analysed.	
Were the index test results interpreted without knowledge of the results of the reference standard?		**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?		**Yes**
Could the conduct or interpretation of the index test have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		**Low concern**
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	Colorectal cancer diagnosis in the cancer registry at the Royal Devon and Exeter Hospital or practice notes.	
Is the reference standard likely to correctly classify the target condition?		**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?		**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		**Low concern**
FLOW AND TIMING		
A. risk of bias		
Flow and timing	All the patients are accounted for.	
Was there an appropriate interval between index test and reference standard?		**Yes**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**Yes**
Could the patient flow have introduced bias?		**Low risk**
NOTES		

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2 **Hamilton (2005a)**

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Population-based matched case-control study involving all 21 general practices in Exeter, Devon, UK.	
Was a consecutive or random sample of patients enrolled?		**No**

Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: N = 247 (170 males/77 females), age at diagnosis: < 60 years: N = 35, 60-69 years: N = 60, 70-79 years: N = 118, 80+ years: N = 34. Controls: N = 1235 (850 males/385 females), age at diagnosis: < 60 years: N = 178, 60-69 years: N = 310, 70-79 years: N = 575, 80+ years: N = 174. Inclusion criteria: Cases: All patients aged ≥ 40 years with a primary lung cancer, diagnosed from 1998 to 2002, were identified from the cancer registry at the Royal Devon and Exeter Hospital combined with computerised searches at every practice in Devon to identify any cases missing from the cancer register. Controls: Five controls were matched to each case on sex, general practice, and age. Controls were eligible if they were alive at the time of diagnosis of their case. Exclusion criteria: Cases and controls: Unobtainable records; no consultations in the 2 years before diagnosis; previous lung cancer; or residence outside Exeter at the time of diagnosis. Clinical setting: Primary care, UK.
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	Anonymised photocopies of the full primary care records for 2 years before diagnosis were coded (blinded to case/control status) for all entries using the International Classification of Primary Care-2. Additional codes were created to incorporate all possible clinical features. Only variables occurring in ≥ 2.5% of cases or controls were analysed.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**

REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	Lung cancer diagnosis in the cancer registry at the Royal Devon and Exeter Hospital or practice notes.	
Is the reference standard likely to correctly classify the target condition?		**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?		**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		**Low concern**
FLOW AND TIMING		
A. risk of bias		
Flow and timing	All the patients are accounted for.	
Was there an appropriate interval between index test and reference standard?		**Yes**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**Yes**
Could the patient flow have introduced bias?		**Low risk**
NOTES		

Hamilton (2006)

PATIENT SELECTION		
A. risk of bias		
Patient sampling	Population-based case-control study, involving all 21 general practices in Exeter, Devon, UK.	
Was a consecutive or random sample of patients enrolled?		**No**
Was a case-control design avoided?		**No**
Did the study avoid inappropriate exclusions?		**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?		**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?		**Yes**
Could the selection of patients have introduced bias?		**High risk**
B. Concerns regarding applicability		
Patient characteristics and setting	Cases: 217 male patients; age at diagnosis: < 60 years: N = 15 (7%); 60-69 years: N = 51 (24%); 70-79 years: N = 100 (46%): ≥ 80 years: N = 51 (24%); median number of consultations in the 2 years preceding diagnosis = 14 (IQR = 10-21). Controls: 1080 male patients; age at diagnosis: < 60 years: N = 79 (7%); 60-69 years: N = 253 (23%); 70-79 years: N = 494 (46%): ≥ 80 years: N = 254 (24%); median	

	number of consultations in the 2 years preceding diagnosis = 14 (IQR = 10-21). Inclusion criteria: Cases: All patients aged 40 years or over with prostate cancer, diagnosed from 1998 to 2002 inclusive, were identified from the cancer registry at the Royal Devon and Exeter Hospital (the only hospital offering urological services to Exeter patients). Computerised searches at every practice identified any cases missing from the register. Cases without positive histology were included if the records contained a consultant urologist diagnosis of cancer based on strong clinical evidence. Controls: Five male controls were matched to each case on general practice and on age (to 1-year bands if possible, increased in 1-year multiples to a maximum of 5 years). Controls were eligible if they were alive at the time of diagnosis of their case. Exclusion criteria: Unobtainable records; no consultations in the 2 years before diagnosis; previous prostate cancer; or residence outside Exeter at the time of diagnosis. Clinical setting: Primary care, UK
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	All entries into the primary care records for 2 years before diagnosis were coded, blinded to case/control status, using the International Classification of Primary Care-2. Only variables occurring in >2.5% of cases or controls were analysed.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Prostate cancer code, from 1998 to 2002 inclusive, in the cancer registry at the Royal Devon and Exeter Hospital or the general practice records
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	

Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All patients appears to be accounted for
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	

Hippisley-Cox (2011)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective patient series using patients in the QResearch database (version 30).
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 1238971 patients were identified from 189 practices (621478 males, 617493 females), mean (SD) age = 50.1 (15) years, mean (SD) Townsend score = -0.2 (3.6). Symptoms: Current dysphagia (N = 8165), current haematemesis (N = 7119), current abdominal pain (N = 126161), current appetite loss (N = 6133), current weight loss (N = 5377), tiredness in the last year (N = 14119), haemoglobin recorded in the last year (N = 12638, haemoglobin < 11 g/dl in the lasy year (N = 218862. Incident cases of gastro-oesophageal cancer during the 2-year follow up period: N = 1343 (776 oesophageal and 567 gastric). Inclusion criteria: All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000); 12 months after the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. *The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.* Exclusion criteria: Patients without a postcode-related Townsend score,

	patients with a history of gastro-oesophageal cancer at baseline, and patients with a recorded 'red-flag' symptom in the 12 months prior to the study entry date. Clinical setting: Primary care, UK	
Are there concerns that the included patients and setting do not match the review question?		**Low concern**
INDEX TEST		
A. Risk of bias		
Index test	'Red-flag' symptoms: Incident dysphagia, haematemesis, loss of appetite, weight loss, anaemia, and abdominal pain.	
Were the index test results interpreted without knowledge of the results of the reference standard?		**Yes**
Could the conduct or interpretation of the index test have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		**Low concern**
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	2-year follow up	
Is the reference standard likely to correctly classify the target condition?		**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?		**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		**Low concern**
FLOW AND TIMING		
A. risk of bias		
Flow and timing	A total of 1342329 patients were initially identified of whom 103358 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of gastro-oesophageal cancer (N = 538), and ≥ one 'red flag' symptom recorded in the 12 months prior to study entry (N = 31973), leaving 1238971 patients. However, data is presented for 963040/1238971 patients for all symptoms. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.	
Was there an appropriate interval between index test and reference standard?		**Yes**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**No**
Could the patient flow have introduced bias?		**Unclear risk**
NOTES	Results not presented separately for gastric and oesophageal cancer	

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1 **Hippisley-Cox (2012)**

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective patient series using patients in the QResearch database (version 30).
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 1236601 patients were identified from 189 practices (620240 males, 616361 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6). Symptoms: Current rectal bleeding (N = 29118), current abdominal pain (N = 125816), current appetite loss (N = 5358), current weight loss (N = 14065), recent change in bowel habit (N = 1821). Incident cases of colorectal cancer during the 2-year follow up period: N = 2603 (1562 colon and 1041 rectum). Inclusion criteria: All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000); 12 months after the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. *The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.* Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of colorectal cancer at baseline, and patients with a recorded 'red-flag' symptom in the 12 months prior to the study entry date. Clinical setting: Primary care, UK
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms: First onset rectal bleeding, first onset loss of appetite, first onset weight loss, first onset abdominal pain, first onset change in bowel habit (in the past 12 months), and anaemia (recorded haemoglobin < 11 g/dl in the past 12 months).
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	

Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	2-year follow up
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	A total of 1342329 patients were initially identified of whom 105728 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of colorectal cancer (N = 2908), and ≥ one 'red flag' symptom recorded in the 12 months prior to study entry (N = 31973), leaving 1236601 patients. However, data is presented for 1235547/1236601 patients for all symptoms apart from change in bowel habit, which is only presented for 619651/620240 of the male patients. The missing data does not appear to include any of the cancer cases (although this cannot be ascertained for change in bowel habit), but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**No**
Could the patient flow have introduced bias?	**Low risk**
NOTES	Please note there is some overlap between this patient sample and that of Parker (2007)

Hippisley-Cox (2012a)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective patient series using patients in the QResearch database (version 30).
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and	A total of 1243740 patients were identified from 189 practices (624352 males, 619388 females), mean (SD) age = 50.1 (14.9) years, mean (SD)

setting	Townsend score = -0.2 (3.6). Current symptoms and symptoms in the preceding year: Current dysphagia (N = 8507), current abdominal pain (N = 129924), current abdominal distension (N = 4929), current appetite loss (N = 5567), current weight loss (N = 14686), constipation in the last year (N = 8476), diarrhoea in the last year (N = 12233), tiredness in the last year (N = 12688), itching in the last year (N = 1454), haemoglobin recoded in the last year (N = 214497), haemoglobin < 11 g/dl in the last year (N = 16172). Incident cases of pancreatic cancer during the 2-year follow up period: N = 781. Inclusion criteria: All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000) and 12 months after the patient registered with the practice, ensuring that all patients had ≥ 12 months' registration prior to study entry. For patients with incident haematuria, appetite loss, weight loss, or abdominal pain, the entry date was the date of the first consultation with the symptom within the study period. *The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.* Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of pancreatic cancer at baseline, and patients with a recorded 'red-flag' (see "Definition of symptom" below) symptom in the 12 months prior to the study entry date. Clinical setting: Primary care
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms were defined as symptoms that might alarm the patient and also indicate the presence of pancreatic cancer; that is, symptoms of dysphagia, loss of appetite, weight loss, abdominal distension or abdominal pain.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Pancreatic cancer, which was defined as incident diagnosis of pancreatic cancer during the 2 years after study entry, recorded either on the patient's

	GP record using the relevant UK diagnostic Read Codes, or their linked Office for National Statistics cause-of-death record, using the relevant ICD-9 code (157) or ICD-10 diagnostic codes (C25).
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	A total of 1342329 patients were initially identified of whom 98589 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of pancreatic cancer (N = 96), and ≥ one 'red flag' symptom recorded in the 12 months prior to study entry (N = 27646), leaving 1243740 patients. However, data is presented for 971706 / 1243740 patients. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**No**
Could the patient flow have introduced bias?	**High risk**
NOTES	

Hippisley-Cox (2012b)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective patient series using patients in the QResearch database (version 30).
Was a consecutive or random sample of patients enrolled?	**Yes**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Yes**
Could the selection of patients have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Patient characteristics and setting	A total of 1240722 patients were identified from 189 practices (622166 males, 618556 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6). Current symptoms and symptoms in the preceding year: Current haematuria (N = 25553), current abdominal pain (N = 128721), current appetite loss (N = 5531), current weight loss (N = 14464), constipation in the last year (N = 8472), diarrhoea in the last year (N = 12171), tiredness in the last year (N = 12669), haemoglobin recoded in the

	last year (N = 216201), haemoglobin < 11 g/dl in the last year (N = 16169). Incident cases of renal tract cancer during the 2-year follow up period: N = 1622; mean age at diagnosis = 70 years, 1187 males/ 435 females; **Type of cancer: Bladder: N = 1292; Kidney: N = 307; Ureter: N = 21; Urethra: N = 2.** Inclusion criteria: All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000) and 12 months after the patient registered with the practice, ensuring that all patients had ≥ 12 months' registration prior to study entry. For patients with incident haematuria, appetite loss, weight loss, or abdominal pain, the entry date was the date of the first consultation with the symptom within the study period. *The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.* Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of renal tract cancer at baseline, and patients with a recorded 'red-flag' (see "Definition of symptom" below) symptom in the 12 months prior to the study entry date. Clinical setting: Primary care
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	'Red-flag' symptoms were defined as symptoms that might alarm the patient and also indicate the presence of renal tract cancer; that is, symptoms of haematuria, loss of appetite, weight loss, or abdominal pain.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Renal tract cancer, which was defined as incident diagnosis of cancer of the bladder, kidney, ureter, or urethra during the 2 years after study entry, recorded either on the patient's GP record using the relevant UK diagnostic Read Codes, or their linked Office for National Statistics cause-of-death record, using the relevant ICD-9 codes (188 or 189) or ICD-10 diagnostic codes (C64–67).
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without	**Unclear**

knowledge of the results of the index tests?	
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	A total of 1342329 patients were initially identified of whom 101607 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of renal tract cancer (N = 1506), and ≥ one 'red flag' symptom recorded in the 12 months prior to study entry (N = 29254), leaving 1240722 patients. However, data is presented for 967681 / 1240722 patients. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**No**
Could the patient flow have introduced bias?	**High risk**
NOTES	

Iyen-Omofoman (2013)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Case-control study using The Health Improvement Network (THIN) database, which had data from 446 UK general practices with a total of 8.2 million patients.
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No (for derivation cohort)** **Yes (for validation cohort)**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk (for derivation cohort)** **Low risk (for validation cohort)**
B. Concerns regarding applicability	
Patient characteristics and setting	Cases: N = 12074 (7154 males/4920 females), age at diagnosis: 40-45 years: N = 95, 45-50 years: N = 220, 50-55 years: N = 469, 55-60 years: N = 896, 60-65 years: N = 1488, 65-70 years: N = 1750, 70-75 years: N = 2212, 75-80 years: N = 2305, > 80 years: N = 2639.

	Controls: N = 120731 (58034 males/62697 females), age at diagnosis (of cases): 40-45 years: N = 18969, 45-50 years: N = 16756, 50-55 years: N = 15963, 55-60 years: N = 15439, 60-65 years: N = 13475, 65-70 years: N = 11201, 70-75 years: N = 9940, 75-80 years: N = 8191, > 80 years: N = 10797. Validation cohort: N = 1826293 (886994 males/939299 females). Age: Not reported. Incident cases of lung cancer during the 1-year follow up: N = 1728. Inclusion criteria: Cases: All incident cases of lung cancer diagnosed between 1 January 2000 and 28 July 2009 in patients aged ≥ 40 years. Controls: Ten randomly selected controls aged ≥ 40 years with ≥ 1 year of active records were matched to each case on general practice. Validation cohort: All THIN patients aged > 39 years, free from lung cancer on 29 July 2009, and ≥ 1 year general practice follow up. Exclusion criteria: Cases: Patients with < 1 year of active records prior to their first diagnosis of lung cancer. Clinical setting: Primary care, UK.
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	Cough, chest/shoulder pain, dyspnoea, weight loss, hoarseness, upper and lower respiratory tract infections, non-specific chest infections, constipation, depressive disorders, and chronic obstructive pulmonary disease (COPD), recorded over the 2-year period before lung cancer diagnosis.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Lung cancer diagnosis in THIN database
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	

Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	All the patients are accounted for.
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**Yes**
Could the patient flow have introduced bias?	**Low risk**
NOTES	

Panzuto (2003)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective 8-week study of patients presenting to 159 primary care physicians (approximately 63600 patient visits during the study period in total) in Italy.
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**Yes**
Did the study avoid inappropriate exclusions?	**Unclear**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient characteristics and setting	N = 280; 120 males, 160 females; median age (range) = 61 (18-87) years. Inclusion criteria: Consecutive patients who consulted their GP "with symptoms considered suspicious for the presence of a colon disease to rule out the presence of colorectal cancer" and who were investigated with a colonoscopy or double-contrast barium enema [The decision of how (colonoscopy or double-contrast barium enema) and when to investigate the colon was made only by the physicians on the basis of the clinical evaluation during the visit]. Exclusion criteria: Patients with previous diagnoses of colorectal disorders or a recent large bowel examination. Clinical setting: Primary care, Italy.
Are there concerns that the included patients and setting do not match the review question?	**Unclear concern**
INDEX TEST	
A. Risk of bias	
Index test	Abdominal pain, bloating, constipation, rectal bleeding, diarrhoea, iron-deficiency anaemia (haemoglobin levels < 14 g/dl for males and < 12 g/dl for females, in the presence of ferritin < 30 µg/l and a median corpuscular value < 80 fl), change in bowel habits (onset of diarrhoea or constipation or altered stool in the previous 3 months) and weight loss (decrease of ≥ 3 kg in the 3 months prior to the visit).
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
Could the conduct or interpretation of the index test	**Low risk**

have introduced bias?	
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	**Low concern**
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	Histology
Is the reference standard likely to correctly classify the target condition?	**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?	**No**
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	**Low concern**
FLOW AND TIMING	
A. risk of bias	
Flow and timing	56/332 patients were excluded due to lack of mandatory fields (age, sex, clinical history, presenting symptoms and procedure results) in the database (N = 35) or violation of exclusion criteria (N = 18)
Was there an appropriate interval between index test and reference standard?	**Yes**
Did all patients receive the same reference standard?	**Yes**
Were all patients included in the analysis?	**No**
Could the patient flow have introduced bias?	**Unclear risk**
NOTES	

Stapley (2012)

PATIENT SELECTION	
A. risk of bias	
Patient sampling	Matched case-control study using patients in the UK's General Practice Research Database (GPRD).
Was a consecutive or random sample of patients enrolled?	**No**
Was a case-control design avoided?	**No**
Did the study avoid inappropriate exclusions?	**Yes**
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?	**Yes**
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?	**Yes**
Could the selection of patients have introduced bias?	**High risk**
B. Concerns regarding applicability	
Patient	Cases:

characteristics and setting	N = 3635, 1743 males / 1892 females; median number of consultations = 18 (IQR = 11-27); aged 40-49 years: N = 107; 50-59 years: N = 529; 60-69 years: N = 829; 70-79 years: N = 1212; ≥ 80 years: N = 958; UK. Controls: N = 16459, gender not reported; median number of consultations = 9 (IQR = 4-15); aged 40-49 years: N = 422; 50-59 years: N = 2239; 60-69 years: N = 3755; 70-79 years: N = 5702; ≥ 80 years: N = 4341; UK. Inclusion criteria: Cases: Patients with a record of one of 25 GPRD pancreatic cancer codes between January 2000 and December 2009 inclusive, aged ≥ 40 years, with min. 1 year of data before diagnosis. The first instance of a pancreatic cancer code was assigned the data of diagnosis/index date. Controls: Up to 5 controls were matched to cases on sex, general practice, and to 1 year of age of the case. The index date was the index date of the matched case. Exclusion criteria: Pancreatic cancer (controls), no consultations in the year before diagnosis. Clinical setting: Primary care
Are there concerns that the included patients and setting do not match the review question?	**Low concern**
INDEX TEST	
A. Risk of bias	
Index test	All symptoms, physical signs or abnormal investigations compiled from the pancreatic cancer literature were studied, and supplemented by discussion with two pancreatic cancer charities. Libraries of codes relating to these were collated. All codes for fractures were also identified, as a test for any recording bias between cases and controls (making the assumption that the fracture rate would be approximately equal). Occurrences of these features in the year before the index date were identified. Features were only retained for further study if they occurred in ≥5% of cases or controls. Repeat attendances with the same symptom were also retained if the subsequent consultation also occurred in ≥5% of cases or controls. New-onset diabetes was defined as a code for diabetes, or a random blood glucose above the local laboratory's normal range, without similar codes more than 1 year before the index date. For laboratory tests, patients without a test were considered to be the same status as those with a normal result, making our binary variable abnormal result/ no abnormal result. Abnormal liver function was defined as any liver enzyme above the normal range, and raised inflammatory markers as either abnormal erythrocyte sedimentation rate or C-reactive protein, as there were too few plasma viscosity results.
Were the index test results interpreted without knowledge of the results of the reference standard?	**Yes**
For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?	**Yes**
Could the conduct or interpretation of the index test have introduced bias?	**Low risk**
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or	**Low concern**

interpretation differ from the review question?		
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	Pancreatic cancer code in the UK's General Practice Research Database.	
Is the reference standard likely to correctly classify the target condition?		**Yes**
Were the reference standard results interpreted without knowledge of the results of the index tests?		**Unclear**
Could the reference standard, its conduct, or its interpretation have introduced bias?		**Low risk**
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		**Low concern**
FLOW AND TIMING		
A. risk of bias		
Flow and timing	A total of 21624 patients were identified, 17977 controls and 3647 cases. Of the controls the following exclusions were applied: pancreatic cancer (N = 64), case excluded (N = 40), and no data in year pre-index date (N = 1414). Of the cases the following exclusions were applied: No controls (N = 2), and cancer not of pancreatic origin (N = 10).	
Was there an appropriate interval between index test and reference standard?		**Yes**
Did all patients receive the same reference standard?		**Yes**
Were all patients included in the analysis?		**Yes**
Could the patient flow have introduced bias?		**Low risk**
NOTES		

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