National Institute for Health and Care Excellence

Draft for consultation

Metastatic spinal cord compression

[D] Evidence reviews for recognition - spinal metastases

NICE guideline number tbc

Evidence reviews underpinning recommendations 1.3.1 and 1.3.3, 1.3.5 and 1.3.6 (as well as parts of box 1 – cancer or suspected cancer and pain characteristics) in the NICE guideline

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These evidence reviews were developed by NICE

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ISBN:

Contents

Recognition - spinal metastases

Review question

What symptoms or signs, individually or in combination, or validated clinical tools, suggest the presence of spinal metastatic malignant disease or direct malignant infiltration of the spine?

Introduction

Early identification of spinal metastasis or malignant infiltration of the spine may enable treatment or surveillance to prevent spinal cord compression and its consequences. This evidence review addressed whether certain signs or symptoms indicate metastatic spinal disease or direct malignant infiltration of the spine.

Summary of the protocol

See Table 1 for a summary of the Population, Index test, Reference standard, Target Condition and Outcome (PIRTO) characteristics of this review.

Table 1: Summary of the PIRTO table

Population	Adults presenting with back pain or other signs/symptoms consistent with metastatic spinal disease or direct malignant infiltration of the spine

Index test (presence of sign or symptom)	Symptoms alone or in combination:
	• Pain location:
	  ○ in the middle (thoracic) spine
	  ○ upper (cervical) spine
	  ○ lower (lumbar) spinal
	  ○ bone pain elsewhere
	• Pain dynamics:
	  ○ New onset spinal pain
	  ○ Progressive spinal pain
	• Severe unremitting lower spinal pain
	• Spinal pain aggravated by straining (for example, at stool, or when coughing or sneezing) or weight bearing
	• Localised spinal tenderness
	• Nocturnal spinal pain preventing sleep.
	• Spinal deformity
	• Vertebral compression fractures
	• Neurological symptoms including:
	  ○ radicular pain,
	  ○ any limb weakness,
	  ○ difficulty in walking
	  ○ inability to stand
	  ○ unsteadiness (ataxia)
	  ○ sensory loss or disturbance (for example tingling)
	  ○ bladder, bowel or sexual dysfunction
	• Neurological signs of spinal cord or cauda equina compression.
	
	Any of the above in combination with potential symptoms of advanced cancer such as:

	• Weight loss • Loss of appetite • Fatigue • Change in bowel habit • New and unexplained lumps • Frequent infections • Cough or hoarseness
Reference standard	Radiological diagnosis of metastases, for example: • MRI • CT • PET-CT (particularly for haematological cancers) • Isotope bone scans • X-ray
Target conditions	• Metastatic spinal disease • Direct malignant infiltration of the spine
Outcomes	**Critical** Diagnostic accuracy: • Sensitivity, specificity • Positive and negative predictive value • Likelihood ratios For clinical prediction tools: • Calibration • Discrimination **Important** • Adverse events associated with measurement of the symptom or sign • Adverse events associated with radiology: ○ Contrast related • False positive / biopsy related adverse events

CT: computed tomography; MRI: magnetic resonance imaging; PET-CT: positron emission tomography–computed tomography

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Clinical evidence

Included studies

Eleven studies were included in this review (Bellan 2016, Cook 2012, Donner-Banzhoff 2006, He 2020, Henschke 2009, Khoo 2003, Lingawi 2004, Mijiyawa 2000, Reito 2018, Street 2020, Thiruganasambandamoorthy 2014).

Eight studies were retrospective cohort studies (Bellan 2016, Cook 2012, He 2020, Lingawi 2004, Mijiyawa 2000, Reito 2018, Street 2020 and Thiruganasambandamoorthy 2014), 2 were prospective cohort studies (Henschke 2009 and Khoo 2003) and 1 was a cluster randomised controlled trial (Donner-Banzhoff 2006).

Eight studies analysed a population of patients who had low back pain (Cook 2012, Donner-Banzhoff 2006, Henschke 2009, Lingawi 2004, Mijiyawa 2000, Reito 2018, Street 2020 and Thiruganasambandamoorthy 2014), 1 study considered cancer patients at presentation (He 2020), 1 study analysed patients with non-traumatic musculoskeletal complaints (Belllan 2016) and 1 study looked at general practice referrals for lumbar spine radiographs (Khoo 2003).

Six studies were in primary care (GP or emergency department; Bellan 2016, Donner-Banzhoff 2006, Henschke 2009, Khoo 2003, Reito 2018, Thiruganasambanda-moorthy 2014) and 5 studies were in secondary or tertiary care (Cook 2012, He 2020, Lingawi 2004, Mijiyawa 2000, Street 2020).

All studies related to signs and symptoms, and none addressed clinical prediction tools.

The included studies are summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies.

Study	Population	Sign or symptom	Outcomes
Bellan 2016 Retrospective cohort study Italy	N=1652 Patients admitted to an emergency department with non-traumatic musculoskeletal complaints Patients with cancer at presentation, n (%): not reported Age, mean (SD) years: 51 (17.8) Sex: female: n=897; male n=755.	• Back pain • Low back pain • Peripheral joint or periarticular problems	• Positive predictive value
Cook 2012 Retrospective cohort study USA	N=1109 Patients with low back pain seen at a spine surgery centre	• Pain or limitation on movement (during flexion or extension on left and right sides) • Scoliosis	• Sensitivity, specificity • Positive and negative predictive value • Likelihood ratios

Study	Population	Sign or symptom	Outcomes
	Patients with cancer at presentation, n (%): not reported Age, mean (SD) years: 54.8 (16.3) Sex: female n=655; male n=454.	• Kyphosis • Midline spinal tenderness	
Donner-Banzhoff 2006 Cluster randomised controlled trial Germany	N=1378 Patients with low back pain presenting to primary care. Patients with cancer at presentation, n (%): not reported Age, mean (SD) years: 49 (13.3) Sex: female n=692; male n=686.	• Low back pain • Unfamiliar low back pain	• Sensitivity, specificity • Positive and negative predictive value • Likelihood ratios
He 2020 Retrospective cohort study China	N=14603 Patients at initial presentation with undiagnosed cancer Patients with cancer at presentation, n (%): 14603 (100%) Age, mean (SD) years: 58.6 (11.9) Sex: female n=5241; male n=9362.	• Local pain • Radicular pain • Night-aggravating pain • Limb numbness • Limb weakness • Unstable gait • Claudication • Loss of sphincter control • Weight loss • Symptoms pooled	• Sensitivity, specificity • Positive and negative predictive value • Likelihood ratios
Henschke 2009 Prospective cohort study Australia	N=1172 Patients presenting with low back pain to primary care settings Patients with cancer at presentation, n (%): 1 (0.1%) Age, mean (SD) years: 43.97 (15.1) Sex: female n=546;	• Previous history of cancer • Age at onset of back pain • Constant, progressive, nonmechanical pain • Insidious onset of back pain • Tried bed rest, but no relief • Systematically unwell • Unexplained weight loss (>4.5kg in 6	• Specificity

Study	Population	Sign or symptom	Outcomes
	male n=626.	months) • Sensory level (altered sensation from trunk down)	
Khoo 2003 Prospective cohort study UK	N=1030 General practice referrals for lumbar spine radiographs for people with low back pain. Patients with cancer at presentation, n (%): not reported Age, mean (SD) years: 53. (not reported) Sex: not reported.	• Low back pain	• Positive predictive value
Lingawi 2004 Retrospective cohort study Saudi Arabia	N=634 Patients with low back pain sent for MRI Patients with cancer at presentation, n (%): not reported Age, mean (SD) years: 53 (not reported) Sex: female n=336; male n=298.	• Low back pain	• Positive predictive value
Mijiyawa 2000 Retrospective cohort study Togo	N=3204 Patients with low back pain visiting the rheumatology unit of the Lomé Teaching Hospital Patients with cancer at presentation, n (%): not reported Age, mean (SD) years: 44.46 (14.39) Sex: female n=1850; male n=1354.	• Low back pain	• Positive predictive value
Reito 2018 Retrospective cohort study	N=737 Patients with low back pain presenting to an	• Low back pain	• Positive predictive value

Study	Population	Sign or symptom	Outcomes
Finland	emergency department who had a possible specific spinal pathology Patients with cancer at presentation, n (%): 59 (6.6%) Age, mean (SD) years: 51.3 (17.0) Sex: male n=335; female n=402		
Street 2020 Retrospective cohort study New Zealand	N=2383 Patients with back pain referred for lumbar MRI by a specialist in a private secondary care or public tertiary care setting Patients with cancer at presentation, n (%): 36 (1.5%) Age, mean (SD) years: 52 (not reported) Sex: female n=1235; male n=1148.	• Low back pain	• Positive predictive value
Thiruganasambandamoorthy 2014 Retrospective cohort study Canada	N=329 Patients with low back pain who were assessed by an emergency physician. Patients with cancer at presentation, n (%): 20 (6.1%) Age, mean (SD) years: 49.3 (not reported) Sex: female n=167; male n=162.	• Low back pain	• Positive predictive value

1 *MRI: magnetic resonance imaging; SD: standard deviation*

2 See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

Low back pain as a symptom of spinal metastases

Low quality evidence from 6 studies in people presenting with low back pain in primary care suggested that around 0.3% would have spinal metastasis (positive predictive value; 95% CI 0.5% to 1.5%). Low quality evidence from 3 studies in people whose low back pain was being investigated in secondary or tertiary care suggested that around 1.3% would have spinal metastasis (positive predictive value; 95% CI 0.8% to 2%). This indicates that low back pain on its own is not a useful indicator of spinal metastasis in primary care (positive predictive values <3%).

Red flag symptoms of spinal metastases in people with low back pain

Other studies investigated whether there are additional red-flag signs or symptoms that could help to identify those with spinal metastases amongst people with general low back pain (see Table 3).

Moderate quality evidence from a tertiary care study suggested that absence of pain on movement, scoliosis, kyphosis and midline spinal tenderness had positive predictive values of 8.4%, 9.1%, 7.3% and 5.1% respectively for spinal metastasis. However, this was a tertiary care study where patients had a relatively high pre-test probability of spinal metastasis (6%) and the likelihood ratios indicated that these symptoms were not useful predictors of spinal metastasis in people with low back pain (positive likelihood ratio [LR+] <2, negative likelihood ratio [LR-] >0.5).

High quality evidence from a primary care study suggested that unfamiliar low back pain has a positive predictive value of 0.5% in people with low back pain and is therefore unlikely to be a useful predictor of spinal metastasis in this population.

One prospective primary care study evaluated red flag symptoms of serious spinal pathology in people presenting with low back pain. Although no cases of spinal metastatic disease were encountered, some of the proposed red flag symptoms (such as age > 50 years, insidious onset of pain, or tried bed rest but no relief) were relatively common and would likely have poor positive predictive value to identify spinal metastases in those with low back pain in primary care.

Symptoms of spinal metastases in people presenting with cancer

There was high quality evidence from a single study in people presenting with cancer that several signs and symptoms had relatively high PPV for spinal metastases. These included local pain (PPV 56%), radicular pain (53.6%), night-aggravating pain (92.4%), limb numbness (52.1%), limb weakness (29.9%), unstable gait (39%), claudication (32.3%), loss of sphincter control (24.5%), weight loss (23.7%) and all symptoms pooled (25%). The likelihood ratios indicated that several of the symptoms were useful indicators for spinal metastasis (LR+ > 5): local pain, radicular pain, night-aggravating pain and limb numbness (see Table 4). Other symptoms were potentially useful indicators (LR+ between 2 and 5): limb weakness, unstable gait, claudication, loss of sphincter control and weight loss. Absence of the individual symptoms local pain or night-aggravating pain was also potentially useful at identifying those without spinal metastases (LR- between 0.2 and 0.5). Absence of any of the symptoms was a useful way of identifying those without spinal metastases (LR- < 0.2).

See appendix F for full GRADE tables.

Table 3: Signs or symptoms of spinal metastasis in people presenting with low back pain.

Study	Sign or symptom (% prevalence)	Prevalence of spinal metastasis in study	Predictive values % [95% CI]		Sensitivity % [95% CI]	Specificity % [95% CI]	Likelihood ratios [95% CI]	
			PPV	NPV			LR+	LR-
Cook 2012	No pain on movement test[1] (42%)	0.5%[2]	1.1 [0.8 to 1.4]	99.9 [99 to 100]	91.7 [51.7 to 99.1]	58 [55 to 60.8]	2.18 [1.7 to 2.8]	0.14 [0.01 to 2.04]
Cook 2012	No pain on movement test (42%)	6.0%[3]	8.4 [6.9 to 10.2]	95.7 [94.4 to 96.8]	59 [47 to 69.9]	59 [56 to 61.9]	1.44 [1.16 to 1.78]	0.7 [0.52 to 0.93]
Cook 2012	Scoliosis (18%)		9.1 [6.2 to 13.1]	94.7 [93.9 to 95.4]	27.3 [18 to 39]	82.5 [80.1 to 84.7]	1.56 [1.03 to 2.37]	0.88 [0.76 to 1.02]
Cook 2012	Kyphosis (11%)		7.3 [4 to 12.9]	94.2 [93.6 to 94.7]	13.6 [7.3 to 23.9]	89 [86.9 to 90.7]	1.24 [0.66 to 2.33]	0.97 [0.88 to 1.07]
Cook 2012	Midline spinal tenderness (53%)		5.1 [3.9 to 6.6]	93 [91.3 to 94.3]	45.5 [34 to 57.4]	46.1 [43.1 to 49.2]	0.84 [0.64 to 1.11]	1.18 [0.94 to 1.49]
Donner-Banzhoff 2006	Unfamiliar low back pain (17%)	0.2%	0.5 [0.1 to 1.9]	99.9 [99.6 to 100]	50 [1.3 to 98.4]	82.8 [80.6 to 84.9]	2.91 [0.72 to 11.71]	0.6 [0.15 to 2.41]
Henschke 2009[4]	Previous history of cancer (4%)	0%	Not estimable	Not estimable	Not estimable	96 [94.8 to 97]	Not estimable	Not estimable
Henschke 2009	Age> 50 (34%)		Not estimable	Not estimable	Not estimable	65.9 [63.1 to 68.5]	Not estimable	Not estimable
Henschke 2009	Age> 70 (5%)		Not estimable	Not estimable	Not estimable	95.2 [93.8 to 96.3]	Not estimable	Not estimable
Henschke 2009	Constant, progressive, nonmechanical pain (3%)		Not estimable	Not estimable	Not estimable	97.1 [96 to 98]	Not estimable	Not estimable
Henschke 2009	Insidious onset (17%)		Not estimable	Not estimable	Not estimable	82.7 [80.5 to 84.8]	Not estimable	Not estimable
Henschke 2009	Systematically unwell (2%)		Not estimable	Not estimable	Not estimable	97.7 [96.6 to 98.4]	Not estimable	Not estimable
Henschke 2009	Tried bed rest, but no relief (17%)		Not estimable	Not estimable	Not estimable	83.3 [81 to 85.3]	Not estimable	Not estimable
Henschke 2009	Weight loss (<1%)		Not estimable	Not estimable	Not estimable	99.7 [99.2 to 99.9]	Not estimable	Not estimable
Henschke 2009	Sensory level (altered sensation		Not estimable	Not estimable	Not estimable	98.3 [97.4 to 98.9]	Not estimable	Not estimable

Study	Sign or symptom	Prevalence	Predictive values % [95% CI]		Sensitivity %	Specificity %	Likelihood ratios [95% CI]	
	from trunk down; 2%)							

LR+: positive likelihood ratio; LR-: negative likelihood ratio; NPV: negative predictive value; PPV: positive predictive value

1. *Absence of pain during flexion, extension and lateral flexion movements*
2. *For spinal metastasis without concomitant diagnosis – (the back pain was due to the spinal metastasis and not another [non-malignant] cause)*
3. *For any spinal metastasis*
4. *No cases of spinal metastasis were found in this study – included for specificity only.*

Table 4: Signs or symptoms of spinal metastasis in people presenting with cancer.

Study	Sign or symptom (% prevalence)	Prevalence of spinal metastasis in study	Predictive values % [95% CI]		Sensitivity % [95% CI]	Specificity % [95% CI]	Likelihood ratios [95% CI]	
			PPV	NPV			LR+	LR-
He 2020	Local pain (16%)	11.4%	56 [54.4 to 57.6]	96.8 [96.5 to 97]	76.2 [74.1 to 78.2]	92.3 [91.8 to 92.8]	9.9 [9.28 to 10.57]	0.26 [0.24 to 0.28]
He 2020	Radicular pain (6%)		53.6 [50.6 to 56.5]	91.4 [91.2 to 91.7]	29.7 [27.6 to 32]	96.7 [96.4 to 97]	8.98 [7.98 to 10.11]	0.73 [0.7 to 0.75]
He 2020	Night-aggravating pain (7%)		92.4 [90.6 to 93.8]	94.6 [94.3 to 94.8]	55.7 [53.3 to 58]	99.4 [99.3 to 99.5]	94.16 [75 to 118.22]	0.45 [0.42 to 0.47]
He 2020	Limb numbness (5%)		52.1 [48.8 to 55.4]	90.9 [90.6 to 91.1]	24 [22 to 26.1]	97.2 [96.9 to 97.4]	8.44 [7.4 to 9.64]	0.78 [0.76 to 0.8]
He 2020	Limb weakness (13%)		29.9 [28.2 to 31.7]	91.4 [91.1 to 91.7]	34.3 [32.1 to 36.6]	89.7 [89.1 to 90.2]	3.32 [3.05 to 3.61]	0.73 [0.71 to 0.76]
He 2020	Unstable gait (3%)		39 [35 to 43.2]	89.6 [89.4 to 89.7]	11.7 [10.3 to 13.4]	97.6 [97.4 to 97.9]	4.97 [4.19 to 5.91]	0.9 [0.89 to 0.92]
He 2020	Claudication (3%)		32.3 [28.2 to 36.5]	89.3 [89.1 to 89.4]	8.8 [7.5 to 10.2]	97.6 [97.3 to 97.9]	3.7 [3.06 to 4.48]	0.93 [0.92 to 0.95]
He 2020	Loss of sphincter control (15%)		24.5 [23 to 26.1]	90.9 [90.6 to 91.2]	32.1 [29.9 to 34.4]	87.2 [86.7 to 87.8]	2.52 [2.32 to 2.74]	0.78 [0.75 to 0.8]
He 2020	Weight loss (14%)		23.7 [22.1 to 25.3]	90.6 [90.4 to 90.9]	29.4 [27.3 to 31.7]	87.8 [87.2 to 88.4]	2.41 [2.21 to 2.63]	0.8 [0.78 to 0.83]
He 2020	Symptoms pooled (41%)		25 [24.5 to 25.5]	98.2 [97.9 to 98.5]	90.8 [89.4 to 92.1]	64.9 [64.1 to 65.7]	2.59 [2.52 to 2.66]	0.14 [0.12 to 0.16]

LR+: positive likelihood ratio; LR-: negative likelihood ratio; NPV: negative predictive value; PPV: positive predictive value

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

A single economic search was undertaken for all topics included in the scope of this guideline. See supplement 2 for details.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in supplement 2.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The committee prioritised diagnostic accuracy outcomes as critical for this evidence review. This was because accurately classifying malignant versus non-malignant spinal disease would allow early treatment for people with undiagnosed metastatic spinal disease and avoid sending those with benign disease for unnecessary investigations.

The committee recognised that assessment of signs or symptoms (such as pain with movement) may be uncomfortable and this was an important outcome. Signs and symptoms if positive would typically lead to definitive tests (such as imaging or biopsy) which can have adverse effects. Inappropriate treatment or investigations due to false positive results are also a potential harm. Both these outcomes were considered important for decision making.

The quality of the evidence

The quality of the evidence was assessed using GRADE and ranged from low to high quality, with most of the evidence being of a moderate or high quality. Evidence was downgraded due to risk of bias. There was also very serious heterogeneity in the estimate of the positive predictive value of low back pain for spinal metastasis when combining all studies. Subgroup analysis according to setting (primary care verses secondary or tertiary care) reduced heterogeneity but it remained serious.

No evidence was identified about clinical prediction rules, adverse effects of assessment itself or due to false positive results. As a result of these limitations in the evidence the guideline committee also drew on their own experience and expertise when drafting the recommendations.

Benefits and harms

The committee agreed that early identification of spinal metastases, direct malignant infiltration of the spine and metastatic spinal cord compression is essential in order to maximise the effectiveness of treatments and prevent disease progression.

The committee reviewed evidence which compared the presence of signs and symptoms of metastatic disease in people with cancer and those without; for example in people with low back pain resulting from other causes, as well as symptoms of spinal metastases which were reported in people with undiagnosed cancers.

On the basis of the evidence, as well as their own experience, the committee agreed to draft a recommendation listing certain symptoms that practitioners should be aware of that could be suggestive of spinal metastases or direct malignant infiltration of the spine (see box 1 in the guideline).

The committee agreed that in primary care relevant signs or symptoms in people without a history of cancer should have a positive predictive value of at least 3% - so that at least 3 in every 100 people presenting with that sign or symptom would turn out to have spinal metastasis. This could mean a lot of false positives, however the evidence did not identify any symptoms that would require urgent referral for investigation of spinal metastases in people without a history of cancer or without suspected cancer. For people with a known history of cancer or with suspected cancer the evidence suggested that the positive predictive value of symptoms of spinal metastasis (listed in box 1 of the guideline) was much higher. While there still may be some false positives the committee agreed that these are serious symptoms (such as severe pain) which require further investigation regardless of the cause.

A personal history of cancer was identified by the committee an important factor, based on their experience, because spinal metastases are a consequence of disease progression in some patients. They also identified suspected diagnosis of cancer as an important factor, based on both their experience and evidence which indicates some people already have spinal metastases at their initial presentation with cancer.

While the evidence suggested low back pain on its own was unlikely to indicate spinal metastases, the committee agreed that back pain combined with a personal history of cancer should raise suspicion of spinal metastases. In particular, the committee agreed that, based on their experience, back pain that is severe, progressive or aggravated by movement or straining is characteristic of spinal metastases. There was also evidence to support nighttime back pain, localised tenderness and claudication as potential indicators of spinal metastases.

The evidence and committee's experience supported the list of cord compression symptoms including bladder or bowel dysfunction, gait disturbance or difficulty walking, limb weakness, numbness, paraesthesia or sensory loss and radicular pain. The committee added neurological signs of spinal cord or cauda equina compression to the list based on their experience.

While the evidence suggested that weight loss was weakly associated with spinal metastases the committee agreed that it is a general symptom of cancer, and that investigations for spinal metastases would not be the most appropriate first step in patients presenting with cancer and unexplained weight loss.

If cord compression is suspected the committee agreed that the MSCC coordinator should be contacted immediately (see evidence report E) as this is an oncological emergency.

If spinal metastases or direct malignant infiltration are suspected (but without symptoms of spinal cord compression), prompt action is still needed so that the person can be assessed and where appropriate treatment is provided. All of this involves several specialties and therefore requires coordinated care. The committee agreed to recommend, based on their own experiences, that the MSCC coordinator should be contacted urgently (within 24 hours), when people with a past or current diagnosis of cancer present with back pain suggestive of spinal metastasis or direct malignant infiltration of the spine. Usually, this contact would be made to initiate oncological assessments but also to organise ongoing care to ensure that appropriate investigations are made and treatment can be given and coordinated in a timely manner.

The committee also agreed that in their experience it is common for people without known cancer to present with signs or symptoms that are suggestive of spinal metastases or direct malignant infiltration of the spine. They agreed that in these cases it was most appropriate to make an urgent oncology referral to ensure that appropriate investigations and treatments can be arranged.

The committee emphasised the importance of early identification of spinal metastases, direct malignant infiltration of the spine and/or cord compression and noted that it is especially important in people with a known history of cancer, in order to ensure that appropriate treatment can be provided. They therefore agreed to recommend that practitioners should explain to people with a current or past diagnosis of cancer presenting with back pain (but no clinical evidence of metastases, direct malignant infiltration, or cord compression in the spine) the signs that they should be aware of that suggest their risk of these conditions has increased. The committee also agreed that practitioners should emphasise to patients the importance of contacting their healthcare professional if these symptoms occur.

Cost effectiveness and resource use

No economic evidence was identified for this topic from the systematic search of previously published evidence. The committee considered cost effectiveness based on their own experience and knowledge.

Improving recognition of spinal metastases or direct malignant infiltration of the spine will be cost saving because it will mean that people can have the necessary investigations and treatments promptly improving outcomes and reducing outcomes associated with large costs and detriments to quality of life such as becoming non-ambulatory. Improved recognition will also prevent large downstream costs of more specialised and expensive treatment such as emergency surgery.

Other factors the committee took into account

The committee were aware of tools that are used for risk assessment in people presenting with low back pain in current practice so they cross referred to recommendations in the NICE guideline on low back pain and sciatica in over 16s. They were also aware that when there is a suspicion of cancer healthcare professionals should refer to the NICE guideline on suspected cancer so that they can take the appropriate action.

Recommendations supported by this evidence review

This evidence review supports recommendations Evidence reviews underpinning recommendations 1.3.1 and 1.3.3, 1.3.5 and to 1.3.6 (as well as parts of box 1 – cancer or suspected cancer and pain characteristics) in the NICE guideline.

References – included studies

Diagnostic

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Street 2020

Street K, White S, Vandal A. Clinical prevalence and population incidence of serious pathologies among patients undergoing magnetic resonance imaging for low back pain. Spine Journal, 20, 101-111, 2020

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Appendices

Appendix A Review protocols

Review protocol for review question: What symptoms or signs, individually or in combination, or validated clinical tools, suggest the presence of spinal metastatic malignant disease or direct malignant infiltration of the spine?

Table 5: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022310718
1.	Review title	Symptoms or signs suggestive of the presence of spinal metastatic malignant disease or direct malignant infiltration of the spine.
2.	Review question	What symptoms or signs, individually or in combination, or validated clinical tools, suggest the presence of spinal metastatic malignant disease or direct malignant infiltration of the spine?
3.	Objective	To establish which symptoms or signs, or validated clinical tools suggest the presence of spinal metastatic malignant disease or direct malignant infiltration of the spine.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Cumulative Index to Nursing and Allied Health Literature (CINAHL) • Embase • Epistemonikos • International Health Technology Assessment (INAHTA) database • MEDLINE & MEDLINE In-Process Searches will be restricted by: • Date: 1990 onwards (see rationale under Section 10)

ID	Field	Content
		• English language studies • Human studies Other searches: Inclusion lists of systematic reviews With the agreement of the guideline committee the searches will be re-run between 6-8 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Symptoms or signs suggestive of the presence of spinal metastatic malignant disease or direct malignant infiltration of the spine
6.	Population	Inclusion: • Adults presenting with back pain or other signs/symptoms consistent with metastatic spinal disease or direct malignant infiltration of the spine Exclusion: • Adults with spinal cord compression because of primary tumours of the spinal cord, meninges or nerve roots. • Adults with spinal cord compression because of non-malignant causes. • Adults with primary bone tumours of the spinal column. • Children and young people under the age of 18.

7.	Sign or symptom	Symptoms alone or in combination:
		• Pain location:
		  ○ in the middle (thoracic) spine
		  ○ upper (cervical) spine
		  ○ lower (lumbar) spinal
		  ○ bone pain elsewhere
		• Pain dynamics:
		  ○ New onset spinal pain

ID	Field	Content
		○ Progressive spinal pain • Severe unremitting lower spinal pain • Spinal pain aggravated by straining (for example, at stool, or when coughing or sneezing) or weight bearing • Localised spinal tenderness • Nocturnal spinal pain preventing sleep. • Spinal deformity • Vertebral compression fractures • Neurological symptoms including: ○ radicular pain, ○ any limb weakness, ○ difficulty in walking ○ inability to stand ○ unsteadiness (ataxia) ○ sensory loss or disturbance (for example tingling) ○ bladder, bowel or sexual dysfunction • Neurological signs of spinal cord or cauda equina compression. Any of the above in combination with potential symptoms of advanced cancer such as: • Weight loss • Loss of appetite • Fatigue • Change in bowel habit • New and unexplained lumps • Frequent infections • Cough or hoarseness
8.	Reference standard	Radiological diagnosis of metastatic spinal disease or direct malignant infiltration of the spine, for example by: • MRI • CT

ID	Field	Content
		• PET-CT (particularly for haematological cancers) • Isotope bone scans • X-ray
9.	Types of study to be included	Diagnostic accuracy studies evaluating clinical outcomes: • Cross-sectional studies • Cohort studies • Nested case-control
10.	Other exclusion criteria	Inclusion: • Full text papers • Exclusion: • Conference abstracts • Articles published before 1990 (the date when MRI use became regular in this population). • Papers that do not include methodological details will not be included as they do not provide sufficient information to evaluate risk of bias/study quality. • Non-English language articles
11.	Context	Metastatic spinal cord compression in adults: risk assessment, diagnosis and management (2008) NICE guideline will be updated by this review question
12.	Primary outcomes (critical outcomes)	Diagnostic accuracy: • Sensitivity, specificity • Positive and negative predictive value • Likelihood ratios For clinical prediction tools: • Calibration • Discrimination
13.	Secondary outcomes (important outcomes)	• Adverse events associated with measurement of the symptom or sign • Adverse events associated with radiology: • Contrast related

ID	Field	Content
		• False positive / biopsy related adverse events
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. The full set of records will not be dual screened because the population, interventions and relevant study designs are relatively clear and should be readily identified from titles and abstracts. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. Draft excluded studies will be circulated to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair, a standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the preferred checklist as described in Developing NICE guidelines: the manual. Quality assessment of individual studies will be performed using the following checklists: • QUADAS-2 for diagnostic accuracy studies • PROBAST tool for clinical prediction models The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Diagnostic / clinical prediction models review: Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where appropriate, meta-analysis of diagnostic test accuracy will be performed using the metandi and midas applica-

ID	Field	Content	
		tions in STATA and Cochrane Review Manager. PPV with 95% Cis will be used as the outcome for diagnostic test usefulness. Diagnostic accuracy parameters will be obtained from the studies or calculated by the technical team using data from the studies. Validity The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/	
17.	Analysis of sub-groups	Evidence will be stratified by: • History of cancer vs no history of cancer Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: • Haematological vs solid tumours Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
18.	Type and method of review	☐	Intervention
		☒	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)

ID	Field	Content		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	01 February 2022		
22.	Anticipated completion date	23 August 2023		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	5a. Named contact National Guideline Alliance 5b Named contact e-mail metastaticspinal@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
25.	Review team members	NGA Technical Team		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential		

ID	Field	Content	
		conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].	
29.	Other registration details	Not applicable	
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=310718	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Humans; Spinal Neoplasms	
33.	Details of existing review of same topic by same authors	N/A.	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	
	Relevant papers	https://doi.org/10.1016/j.amjmed.2019.06.005	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation

Appendix B Search strategy (clinical / economic)

Literature search strategies for review question: What symptoms or signs, individually or in combination, or validated clinical tools, suggest the presence of spinal metastatic malignant disease or direct malignant infiltration of the spine?

Clinical

Database: Medline – OVID interface

#	Searches
1	Spinal Cord Compression/
2	exp Spinal Cord Neoplasms/ or Spinal Neoplasms/
3	((cauda equina or cervical* or cervicothoracic or cord* or coccyx or duralsac* or dural sac* or intervertebr* or lumbar or lumbosac* or lumbo sac* or medulla* or orthothoracic or sacral or sacrum or spinal or spine* or thecal sac* or thoracic or vertebr* or epidural or extradural or extra dural) adj3 (infiltrat* or invad* or invasion or metast* or oligometast*)).ti,ab.
4	(((cauda equina or cervical* or cervicothoracic or cord* or coccyx or duralsac* or dural sac* or intervertebr* or lumbar or lumbosac* or lumbo sac* or medulla* or orthothoracic or sacral or sacrum or spinal or spine* or thecal sac* or thoracic or vertebr* or epidural or extradural or extra dural or ((axon* or neuron* or nerve*) adj2 root)) adj3 (collaps* or compress* or pinch* or press*)) and (adeno* or cancer* or carcinoma* or chordoma* or intraepithelial* or intra epithelial* or malignan* or metast* or neoplas* or oligometast* or tumo?r*)).ti,ab.
5	(mescc or mscc).tw.
6	or/1-5
7	exp Back Pain/ or Spinal Fractures/
8	(backache or dorsalgia or lumbago or ((back or cauda equina or cervical* or cervicothoracic or coccyx or dorsal or lumbar or lumbosacral or lumbo sacral or spine or spinal or vertebra* or thoracic) adj2 (ache* or aching or abnormal* or anomal* or deform* or degenerat* or disorder* or displace* or fractur* or instabilit* or numb* or pain* or prolaps* or tender* or unstab*))).ti,ab.
9	(myelopath* or myeloradiculopath* or radiculopath* or radiculitis or radicular pain* or radiating pain* or sciatica or (sciatic adj2 pain*)).ti,ab.
10	exp "Bone and Bones"/ and Pain/
11	((bone* or musculoskelet* or skelet*) adj2 (ache* or aching or abnormal* or anomal* or deform* or degenerat* or disorder* or displace* or fractur* or instabilit* or numb* or pain* or tender* or unstab*)).ti,ab.
12	Neurologic Manifestations/ or exp Gait Disorders, Neurologic/ or exp Ataxia/ or Paralysis/ or Paresthesia/ or exp Paresis/ or Reflex, Abnormal/
13	(neurolog* adj3 (deficit* or disturb* or dysfunction* or impair*)).ti,ab.
14	(Babinski* or clonus or hyperreflex* or hyper reflex* or hyperactive reflex* or Lhermitte* or electric shock*).ti,ab.
15	(ataxia* or paraly* or par?esthesia* or pares?s or ((ambulat* or balanc* or arm*1 or feet or foot or gait* or hand*1 or leg*1 or limb*1 or locomot* or motor* or move or moving or sensation* or sensory or stand or standing or walk*) adj2 (coordinat* or co ordinat* or deficit* or difficult* or disturb* or heavy or heaviness or impair* or inability or lack* or lose or losing or loss or lost or "pins and needles" or prickling or tingling or tremo?r or unable or unsteadiness or unsteady or weak*))).ti,ab.
16	Fecal Incontinence/ or exp Urinary Incontinence/ or exp Sexual Dysfunction, Physiological/
17	(((f?ecal* or f?ece* or anal or stool*1 or bowel*1 or def?ecat* or bladder* or urin*) adj2 (disorder* or disturb* or dysfunction* or incontinen* or urge* or leak* or seep* or soil*)) or (sphincter* adj2 (lose or losing or loss or lost)) or diarrh?ea*).ti,ab.
18	(((sexual* or erecti*) adj2 (declin* or difficult* or disorder* or dysfunction* or impair* or impoten* or inability or lose or losing or loss or lost or pain* or problem* or symptom* or unable)) or dyspareunia).ti,ab.
19	or/7-18
20	6 and 19
21	exp "Signs and Symptoms"/ or Symptom Assessment/ or Diagnosis/
22	(presentation or red flag* or sign? or symptom*).ti,ab.
23	((clinical* or physical* or present*) adj3 (aspect* or characteristic* or feature* or finding* or manifest* or marker* or suspect* or suspicion*)).ti,ab.
24	(assess* or clinical tool* or criteria* or diagnos* or identif* or predict* or recogni*).ti,ab.
25	or/21-24
26	20 and 25
27	letter/ or editorial/ or news/ or exp historical article/ or Anecdotes as Topic/ or comment/ or case report/ or (letter or comment*).ti.
28	randomized controlled trial/ or random*.ti,ab.
29	27 not 28
30	(animals/ not humans/) or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.
31	29 or 30
32	26 not 31
33	limit 32 to english language
34	limit 33 to yr="1990 -Current"

Health economic

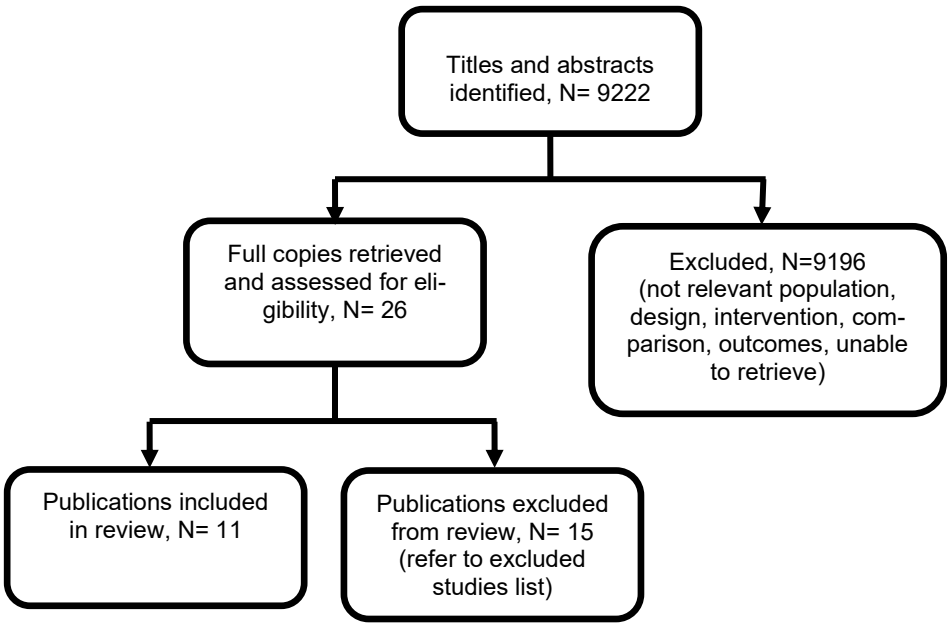
Database: Medline – OVID interface

#	Searches
1	exp Spinal Cord Neoplasms/ or Spinal Neoplasms/
2	((spine or spinal or vertebr*) adj2 (adeno* or cancer* or carcinoma* or intraepithelial* or intra epithelial* or malignan* or neoplas* or tumo?r*)).tw.
3	((spine or spinal or vertebr*) and (metast* or oligometast*)).tw.
4	or/1-3
5	Spinal Cord Compression/
6	((cauda equina or cervical* or cervicothoracic or cord* or coccyx or duralsac* or dural sac* or intervertebr* or lumbar or lumbosac* or lumbo sac* or medulla* or orthothoracic or sacral or sacrum or spinal or spine* or thecal sac* or thoracic or vertebr* or epidural or extradural or extra dural or ((axon* or neuron* or nerve*) adj2 root)) and (collaps* or compress* or pinch* or press*) and (adeno* or cancer* or carcinoma* or chordoma* or intraepithelial* or intra epithelial* or malignan* or metast* or neoplas* or oligometast* or tumo?r*)).tw.
7	(myelopath* or myeloradiculopath* or radiculopath*).tw,hw. or (radicular adj2 (disorder* or syndrome*)).tw.
8	(mescc or mscc).tw.
9	or/5-8
10	((adeno* or cancer* or carcinoma* or intraepithelial* or intra epithelial* or malignan* or metast* or neoplas* or tumo?r*) adj3 (escap* or infiltrat* or invasiv* or metast* or spread*) adj5 (cauda equina or cervical* or cervicothoracic or cord* or coccyx or duralsac* or dural sac* or intervertebr* or lumbar or lumbosac* or lumbo sac* or medulla* or orthothoracic or sacral or sacrum or spinal or spine* or thecal sac* or thoracic or vertebr* or epidural or extradural or extra dural or ((axon* or neuron* or nerve*) adj2 root))).tw.
11	or/4,9-10
12	Economics/ or Value of life/ or exp "Costs and Cost Analysis"/ or exp Economics, Hospital/ or exp Economics, Medical/ or Economics, Nursing/ or Economics, Pharmaceutical/ or exp "Fees and Charges"/ or exp Budgets/
13	(cost* or economic* or pharmacoeconomic*).ti.
14	(budget* or financ* or fee or fees or price* or pricing* or (value adj2 (money or monetary))).ti,ab.
15	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
16	or/12-15
17	11 and 16
18	limit 17 to english language
19	limit 18 to yr="2005 -Current"

Clinical evidence study selection

Study selection for: What symptoms or signs, individually or in combination, or validated clinical tools, suggest the presence of spinal metastatic malignant disease or direct malignant infiltration of the spine?

Figure 1: Study selection flow chart



Appendix C Evidence tables

Evidence tables for review question: What symptoms or signs, individually or in combination, or validated clinical tools, suggest the presence of spinal metastatic malignant disease or direct malignant infiltration of the spine?

Table 6: Evidence tables

Bellan, 2016
Bellan M, Molinari R, Castello L, et al. Profiling the patients visiting the emergency room for musculoskeletal complaints: characteristics and outcomes. Clinical Rheumatology, 35, 2835-2839x, 2016

Study details

Country/ies where study was carried out	Italy
Study type	Retrospective cohort study
Study dates	Not reported
Inclusion criteria	Patients admitted to the ER department of a hospital in one year for non-traumatic musculoskeletal complaints
Exclusion criteria	Patients admitted to paediatric (age <14 years) and obstetrics/gynaecology Ers.
Patient characteristics	N=1652 patients with non-traumatic musculoskeletal complaints Patients with known cancer at presentation, n (%): not reported Age, mean (SD) years: 51 (17.8) Sex: female: n=897; male n=755.
Index test(s)	Presenting symptoms: • Back pain • Low back pain • Peripheral joint or periarticular problems
Reference standard(s)	Radiological evidence of vertebral collapse suspected in a patient with metastatic neoplastic disease; symptoms or signs suggestive for neurologic involvement. Different reference standards were used for other (non-malignant) target conditions
Duration of follow-up	Not reported, but until diagnosis of the musculoskeletal complaint
Sources of funding	Not reported

Outcomes

Outcome		Non-traumatic musculoskeletal complaints, N=1652
Positive predictive value of low back pain for spinal metastasis. No of events / N total		2/802
Positive predictive value of any back pain for spinal metastasis. No of events / N total	2/944	
Positive predictive value of peripheral joint or periarticular problems for spinal metastasis. No of events / N total	0/708	

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear (patients did not have all the same reference standard – it depended on features of their presentation)
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear (there was no standard diagnostic pathway for all patients)

Cook 2012
Bibliographic reference Cook C, Ross M, Isaacs R, et al. Investigation of nonmechanical findings during spinal movement screening for identifying and/or ruling out metastatic cancer. Pain Practice, 12, 426-33, 2012

Study details

Country/ies where study was carried out	USA
Study type	Retrospective cohort study
Study dates	2004-2010

Inclusion criteria	Patients receiving a clinical movement screen and an imaging-supported diagnosis as part of the initial examination for suspected spinal metastases in a single specialist hospital.
Exclusion criteria	Not specified
Patient characteristics	N=1109 Patients with low back pain seen at a spine surgery centre Patients with known cancer at presentation, n (%): not reported Age, mean (SD) years: 54.8 (16.3) Sex: female n=655; male n=454.
Index test(s)	Lumbar movement restrictions and pain
Reference standard(s)	Two board-certified orthopaedic surgeons were responsible for diagnosis of each subject. The imaging method most commonly used by surgeons was T2 magnetic resonance image (MRI) (combination of axial and sagittal images)
Duration of follow-up	Not reported
Sources of funding	Not reported

Outcomes

Outcome	**Low back pain, N = 1109**
Spinal metastases diagnosis No of events	n = 66; % = 5.95

Symptom	Prevalence of symptom (%)	PPV [95% CI]	NPV [95% CI]	Sensitivity [95% CI]	Specificity [95% CI]	LR+ [95% CI]	LR- [95% CI]
Combined Results of Individual Assessments - All 4 movements are not painful[1]	42	1.1 [0.8 to 1.4]	99.9 [99 to 100]	91.7 [51.7 to 99.1]	58 [55 to 60.8]	2.18 [1.7 to 2.8]	0.14 [0.01 to 2.04]
Combined Results of Individual Assessments - All 4 movements are not painful	42	8.4 [6.9 to 10.2]	95.7 [94.4 to 96.8]	59 [47 to 69.9]	59 [56 to 61.9]	1.44 [1.16 to 1.78]	0.7 [0.52 to 0.93]
Scoliosis	18	9.1 [6.2 to 13.1]	94.7 [93.9 to 95.4]	27.3 [18 to 39]	82.5 [80.1 to 84.7]	1.56 [1.03 to 2.37]	0.88 [0.76 to 1.02]
Kyphosis	11	7.3 [4 to 12.9]	94.2 [93.6 to 94.7]	13.6 [7.3 to 23.9]	89 [86.9 to 90.7]	1.24 [0.66 to 2.33]	0.97 [0.88 to 1.07]
Midline spine tenderness	53	5.1 [3.9 to 6.6]	93 [91.3 to 94.3]	45.5 [34 to 57.4]	46.1 [43.1 to 49.2]	0.84 [0.64 to 1.11]	1.18 [0.94 to 1.49]

1.For spinal metastasis without concomitant diagnosis – (the back pain was due to the spinal metastasis and not another [non-malignant] cause)

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear (patients being assessed for spinal surgery)
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Donner-Banzhoff 2006
Donner-Banzhoff N, Roth T, Sönnichsen A, et al. Evaluating the accuracy of a simple heuristic to identify serious causes of low back pain. Family Practice, 23, 682-686, 2006

Study details

Country/ies where study was carried out	Germany
Study type	Cluster randomised controlled trial
Study dates	Not reported, before 2006
Inclusion criteria	Low back pain on the day of recruitment to GP irrespective of duration, novelty or previous history.
Exclusion criteria	Insufficient language skills, pregnancy and isolated thoracic pain.
Patient characteristics	N=1378 Patients with low back pain presenting to primary care.

	Patients with known cancer at presentation, n (%): not reported Age, mean (SD) years: 49 (13.3) Sex – female: n=692; male n=686 Duration of back pain [years—median (range)]: 16 (0–75)
Index test(s)	At baseline data on demographics, low back pain history, physical activity, general health status and functional status were collected by questionnaire and telephone interview. The written questionnaire included the question: 'Is the LBP familiar to you?' which could be answered 'yes' or 'no'.
Reference standard(s)	Patients answered a questionnaire at 1 year. Some were classified as not having a serious condition as a cause of their back pain. Among those who answered positively, 13 refused a further telephone interview or could not be reached. However, based on free text recorded at their 1 year follow-up interview, for example complaints and treatments, the reference committee was still able to classify them as having a serious condition as a cause of their back pain, or not
Duration of follow-up	12 months
Sources of funding	Funding was provided by the Federal Ministry of Education and Research

Outcomes

Outcome		**Low back pain, 12 month, N=1378**
Spinal metastases diagnosis in patients with low back pain Number of events / N Total		2 / 1378
Spinal metastases diagnosis in patients with unfamiliar low back pain Number of events / N Total	1 / 205	

Symptom	PPV [95 CI]	NPV [95 CI]	Sensitivity [95 CI]	Specificity [95 CI]	LR+ [95 CI]	LR- [95 CI]
Unfamiliar low back pain	0.5 [0.1 to 1.9]	99.9 [99.6 to 100]	50 [1.26 to 98.4]	82.8 [80.6 to 84.9]	2.91 [0.72 to 11.71]	0.6 [0.15 to 2.41]

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low

Section	Question	Answer
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High (patient reported)
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

He 2020
He S, Ye C, Gao X, et al. Distribution and predictive value of initial presenting symptoms in spinal metastases from primary cancer patients. European Spine Journal, 29, 3148-3156, 2020

Study details

Country/ies where study was carried out	China
Study type	Retrospective cohort study
Study dates	January 2008 to December 2017
Inclusion criteria	Patients who were diagnosed with lung, liver, prostate, renal, and breast cancers; who were at their first visits to the study hospital after confirming the primary malignancy; with detailed medical records in the hospital database (clear and detailed electronic documents about medical history, physical examination, and essential imagological examinations).
Exclusion criteria	Patients without definite histological diagnosis of primary cancers; patients who visited the hospital before 2008 or after 2017; patients with incomplete medical records in the database; patients with metastatic lung or liver disease from other organs (not from the included primary cancer, for example primary colorectal cancer metastasizing to liver or lung); and patients with repeated visits.
Patient characteristics	N=14603 Patients with cancer at presentation, n (%): 14603 (100%) Age, mean (SD) years: 58.6 (11.9) Sex: female n= 241; male n=9362 Spinal metastases n = 1665. Location: Cervical spine n=222,Thoracic spine n=488, Lumbar spine n=417, Sacrum n=125, ≥2 locations n= 413
Index test(s)	Signs or symptoms of spinal metastasis: • Local pain • Radicular pain • Night-aggravating pain • Limb numbness

	• Limb weakness • Unstable gait • Claudication • Loss of sphincter control • Weight loss • Symptoms pooled
Reference standard(s)	Contrast-enhanced CT of the entire spine, contrast-enhanced MRI of the entire spine, whole-body bone scintigram, or PET–CT. CT-guided biopsy was performed at the suspicious spine lesion to confirm the histological diagnosis. All the biopsy specimens were evaluated by experienced pathologists
Duration of follow-up	Not applicable (initial diagnosis of spinal metastases)
Sources of funding	Shanghai Municipal Science and Technology Commission and Second Military Medical University

Outcomes

Outcome	**Cancer patients, N=14603**
Spinal metastases diagnosis (No. of events)	n = 1665; % = 11.4

Symptom	PPV [95 CI]	NPV [95 CI]	Sensitivity [95 CI]	Specificity [95 CI]	LR+ [95 CI]	LR- [95 CI]
Local pain	56 [54.4 to 57.6]	96.8 [96.5 to 97]	76.2 [74.1 to 78.2]	92.3 [91.8 to 92.8]	9.9 [9.28 to 10.57]	0.26 [0.24 to 0.28]
Radicular pain	53.6 [50.6 to 56.5]	91.4 [91.2 to 91.7]	29.7 [27.6 to 32]	96.7 [96.4 to 97]	8.98 [7.98 to 10.11]	0.73 [0.7 to 0.75]
Night-aggravating pain	92.4 [90.6 to 93.8]	94.6 [94.3 to 94.8]	55.7 [53.3 to 58]	99.4 [99.3 to 99.5]	94.16 [75 to 118.22]	0.45 [0.42 to 0.47]
Limb numbness	52.1 [48.8 to 55.4]	90.9 [90.6 to 91.1]	24 [22 to 26.1]	97.2 [96.9 to 97.4]	8.44 [7.4 to 9.64]	0.78 [0.76 to 0.8]
Limb weakness	29.9 [28.2 to 31.7]	91.4 [91.1 to 91.7]	34.3 [32.1 to 36.6]	89.7 [89.1 to 90.2]	3.32 [3.05 to 3.61]	0.73 [0.71 to 0.76]
Unstable gait	39 [35 to 43.2]	89.6 [89.4 to 89.7]	11.7 [10.3 to 13.4]	97.6 [97.4 to 97.9]	4.97 [4.19 to 5.91]	0.9 [0.89 to 0.92]
Claudication	32.3 [28.2 to 36.5]	89.3 [89.1 to 89.4]	8.8 [7.5 to 10.2]	97.6 [97.3 to 97.9]	3.7 [3.06 to 4.48]	0.93 [0.92 to 0.95]
Loss of sphincter control	24.5 [23 to 26.1]	90.9 [90.6 to 91.2]	32.1 [29.9 to 34.4]	87.2 [86.7 to 87.8]	2.52 [2.32 to 2.74]	0.78 [0.75 to 0.8]
Weight loss	23.7 [22.1 to 25.3]	90.6 [90.4 to 90.9]	29.4 [27.3 to 31.7]	87.8 [87.2 to 88.4]	2.41 [2.21 to 2.63]	0.8 [0.78 to 0.83]
Symptoms pooled	25 [24.5 to 25.5]	98.2 [97.9 to 98.5]	90.8 [89.4 to 92.1]	64.9 [64.1 to 65.7]	2.59 [2.52 to 2.66]	0.14 [0.12 to 0.16]

Critical appraisal – QUADAS-2

Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low

Section	Question	Answer
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Henschke 2009
Henschke N, Maher C, Refshauge K, et al. Prevalence of and screening for serious spinal pathology in patients presenting to primary care settings with acute low back pain. Arthritis and Rheumatism, 60, 3072-80, 2009

Study details

Country/ies where study was carried out	Australia
Study type	Prospective cohort study
Study dates	November 2003 to July 2005
Inclusion criteria	Patients presenting to primary care with acute low back pain. Acute low back pain as 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. At least 14 years old, provided written consent to participate in the study, and were able to speak and read English
Exclusion criteria	Patients were excluded if serious pathology had been diagnosed prior to the consultation, and the serious pathology was considered to be the cause of the current episode of low back pain.
Patient characteristics	N=1172 patients with low back pain Patients with cancer at presentation, n (%): 1 (0.1%) Age, mean (SD) years: 43.97 (15.1) Sex: female n=546; male n=626. Socioeconomic status of place of residence below national mean: 207 (17.7%)
Index test(s)	25 red flag questions (such as unexplained weight loss) derived from clinical practice guidelines and discussion with experts in the field. These were designed to screen for serious pathology in patients with low back pain in primary care.
Reference stand-	Clinical follow up for 12 months

ard(s)	
Duration of follow-up	12 months
Sources of funding	National Health and Medical Research Council of Australia

Outcomes

Outcome	**Low back pain, 12 month, N = 1172**
Metastatic spinal disease diagnosis	n= 0
Previous history of cancer. Specificity (95% CI)	96 [94.8 to 97]
Age> 50. Specificity (95% CI)	65.9 [63.1 to 68.5]
Age> 70. Specificity (95% CI)	95.2 [93.8 to 96.3]
Constant, progressive, nonmechanical pain. Specificity (95% CI)	97.1 [96 to 98]
Insidious onset. Specificity (95% CI)	82.7 [80.5 to 84.8]
Systematically unwell. Specificity (95% CI)	97.7 [96.6 to 98.4]
Tried bed rest, but no relief. Specificity (95% CI)	83.3 [81 to 85.3]
Weight loss. Specificity (95% CI)	99.7 [99.2 to 99.9]
Sensory level (altered sensation from trunk down) . Specificity (95% CI)	98.3 [97.4 to 98.9]

Critical appraisal – QUADAS-2

Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear (history of cancer appears very low – may have been an exclusion criteria)
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low

Section	Question	Answer
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Khoo 2003
Khoo L, Heron C, Patel U, et al. The diagnostic contribution of the frontal lumbar spine radiograph in community referred low back pain–a prospective study of 1030 patients. Clinical Radiology 58, 606-609, 2003

Study details

Country/ies where study was carried out	UK
Study type	Prospective cohort study
Study dates	Not reported, before 2003
Inclusion criteria	General practice referrals for lumbar spine radiographs
Exclusion criteria	None
Patient characteristics	N=1030 Patients with lumbar spine radiograph referrals Patients with cancer at presentation, n (%): not reported Presenting with low back pain as the main symptom: 886 (86%) Age, mean (SD) years: 53. (not reported) Sex: not reported.
Index test(s)	Clinical indication for lumbar spine radiograph: low back pain, neurological symptoms, possible malignancy, inflammatory condition or other
Reference standard(s)	Two-view lumbar spine radiographs were taken as standard, an anteroposterior (AP) and a lateral view.
Duration of follow-up	9 months
Sources of funding	Not reported

Outcomes

Outcome	**Lumbar spine radiograph referrals, 9 month, N = 1030**

Outcome	Lumbar spine radiograph referrals, 9 month, N = 1030
Spinal metastases diagnosis No of events; %	n =1; % = 0.1
Positive predictive value of low back pain for spinal metastasis	1/1030

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High (results not reported according to main symptom)
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High (MRI usually the standard of diagnosis)
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Lingawi 2004
Lingawi S. How often is low back pain or sciatica not due to lumbar disc disease? Neurosciences 9, 94-97, 2004

Study details

Country/ies where study was carried out	Saudi Arabia
Study type	Retrospective cohort study
Study dates	January to June 2002
Inclusion criteria	Patients referred for lumbar spine MRI to investigate low back pain at a single University Hospital (identified via MRI request forms)
Exclusion criteria	Known diagnosis unrelated to disc disease
Patient characteristics	N=634 Patients with low back pain sent for MRI Patients with cancer at presentation, n (%): not reported

	Age, mean (SD) years: 53 (not reported) Sex: female n=336; male n=298.
Index test(s)	Low back pain
Reference standard(s)	MRI scan: T1 weighted sagittal conventional spin echo images, and T2 weighted fast spin echo images in the sagittal and axial planes.
Duration of follow-up	6 months
Sources of funding	Not specified

Outcomes

Outcome	**Low back pain, 6 months, N = 625**
Metastatic spinal disease diagnosis No of events; %	n =11; % = 1.7
Positive predictive value of low back pain for spinal metastasis	11/625

Critical appraisal – QUADAS-2

Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear (unclear whether index test results reported without knowledge of reference standard)
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Mijiyawa 2000
Mijiyawa M, Oniankitan O, Kolani B et al. Low back pain in hospital outpatients in Lomé (Togo). Joint Bone Spine 67, 533-8, 2000

Study details

Country/ies where study was carried out	Togo
Study type	Retrospective cohort study
Study dates	October 1989 to October 1999
Inclusion criteria	Patients with low back pain seen at a rheumatology outpatient clinic
Exclusion criteria	Patients with low back pain due to nonspinal lesions or vasoocclusive crisis complicating a haemoglobinopathy
Patient characteristics	N=3204 Patients with cancer at presentation, n (%): not reported Age, mean (SD) years: 44.46 (14.39) Sex: female n=1850; male n=1354. Age of pain onset, mean, years: 41 Duration of back pain, mean, years: 3
Index test(s)	Low back pain
Reference standard(s)	Imaging tests (radiograph, myelogram, CT not done in all cases), lab tests and clinical follow-up
Duration of follow-up	Not reported
Sources of funding	Not reported

Outcomes

Outcome		**N=3204**
Metastatic spinal disease or malignant vertebral tumour diagnosis No. of events		n=27
Positive predictive value of low back pain for spinal malignancy	27/3204	

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear (unclear whether consecutive or random sample)
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low

Section	Question	Answer
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Reito 2018
Reito A, Kyrola K, Pekkanen L, et al. Specific spinal pathologies in adult patients with an acute or subacute atraumatic low back pain in the emergency department. International Orthopaedics 42, 2843-2849, 2018

Study details

Country/ies where study was carried out	Finland
Study type	Retrospective cohort study
Study dates	January 2012 to December 2014
Inclusion criteria	Patients with a possible specific spinal pathology (ICD-10 code). Patients were identified from an institutional discharge database Aged 18+
Exclusion criteria	Not reported
Patient characteristics	N=737 Patients with cancer at presentation, n (%): 59 (6.6%) Age, mean (SD) years: 51.3 (17.0) Sex: male n=335; fe-male n=402 Median duration of pain was 7 days (IQR 3–20)
Index test(s)	Low back pain
Reference standard(s)	MRI scan
Duration of follow-up	Not reported
Sources of funding	Not reported

Outcomes

Outcome		**N=737**
Metastatic spinal disease (or myeloma in vertebra) diagnosis No of events		n = 5
Positive predictive value of acute low back pain for spinal metastasis	5/737	

Critical appraisal – QUADAS-2

Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Street 2020
Street K, White S, Vandal A. Clinical prevalence and population incidence of serious pathologies among patients undergoing magnetic resonance imaging for low back pain. Spine Journal, 20, 101-111, 2020

Study details

Country/ies where study was carried out	New Zealand
Study type	Retrospective cohort study
Study dates	October 2013 to July 2014
Inclusion criteria	Consecutive patients referred for lumbar MRI over a 10-month period. Patients were included if they had received an MRI scan for lower back pain and were 16 years of age or over
Exclusion criteria	Patients with known serious pathologies or patients undergoing lumbar MRI for reasons other than back pain (eg, for structural or congenital abnormalities not associated with back pain) were excluded.
Patient characteristics	N=2383 Patients with lumbar MRI scans Patients with cancer at presentation, n (%): 36 (1.5%)

	Age, mean, years: 52 Sex: female n=1235.
Index test(s)	Low back pain
Reference standard(s)	MRI scan. The MRI protocol included T1- and T2-weighted sagittal and coronal images, plus Short-T1 Inversion Recovery and/or fat-suppressed images if indicated
Duration of follow-up	10 months
Sources of funding	This research project did not receive any funding.

Outcomes

Outcome	**Lumbar MRI scans, N=2383**
Total malignancy in the spine diagnosis No of events	n = 36;
Positive predictive value of low back pain for spinal metastasis	36/2383

Critical appraisal – QUADAS-2

Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear (unclear whether the index test results interpreted without knowledge of the results of the reference standard)
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Thiruganasambandamoorthy 2014
Thiruganasambandamoorthy V, Turko E, Ansell D, et al. Risk factors for serious underlying pathology in adult emergency department nontraumatic low back pain patients. Journal of Emergency Medicine 47, 1-11, 2014

Study details

Country/ies where study was carried out	Canada
Study type	Retrospective cohort study
Study dates	November 2009 to January 2010
Inclusion criteria	≥ 16 years old, who had a local residential address, had a chief complaint of nontraumatic low back pain (defined as back pain below the costal margins and above the buttocks), and who were assessed by an emergency physician.
Exclusion criteria	Patients who had a history of nephrolithiasis confirmed by imaging and who presented with typical signs and symptoms consistent with renal colic.
Patient characteristics	N=329 Patients with cancer at presentation, n (%): 20 (6.1%) Age, mean (SD) years: 49.3 (not reported) Sex: female n=167; male n=162.
Index test(s)	Assessed by emergency physician
Reference standard(s)	Final diagnosis was based on review of all documents available through the computerized patient tracking system (ED records for the initial and return visits; hospital health records for inpatient, follow-up clinic or investigation, operation room documents, and death records). All diagnoses were confirmed by an independent blinded reviewer, and disagreements were resolved by consensus.
Duration of follow-up	Not reported
Sources of funding	Canadian Association of Emergency Physicians, and the Department of Emergency Medicine, University of Ottawa. The Heart and Stroke Foundation of Canada.

Outcomes

Outcome		**Low back pain, N=329**
Spinal metastases diagnosis No. of events		n=4
Positive predictive value of low back pain for spinal metastasis	4/329	

Critical appraisal – QUADAS-2

Section	**Question**	**Answer**

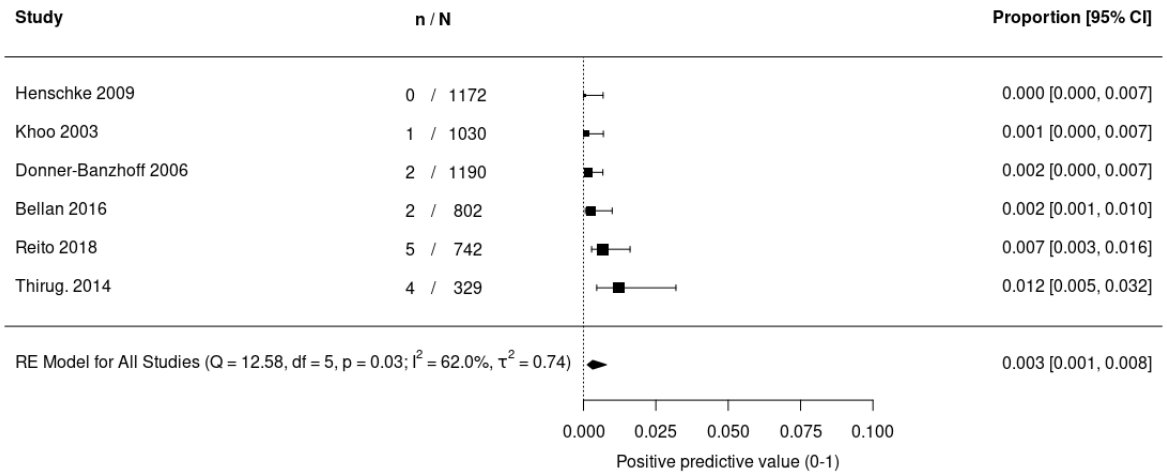
Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Appendix D Forest plots

Forest plots for review question: What symptoms or signs, individually or in combination, or validated clinical tools, suggest the presence of spinal metastatic malignant disease or direct malignant infiltration of the spine?

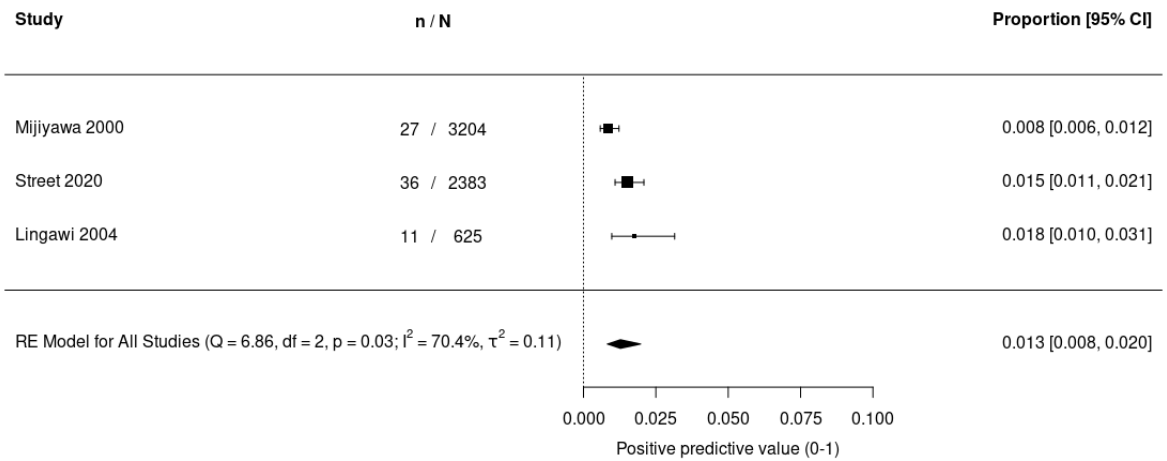
This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Figure 2: Positive predictive value of low back pain as a symptom of undiagnosed spinal metastasis (studies in primary care: GP or emergency department)



CI: confidence interval; RE: random effects

Figure 3: Positive predictive value of low back pain as a symptom of undiagnosed spinal metastasis (studies in secondary or tertiary care)



CI: confidence interval; RE: random effects

Appendix E Modified GRADE tables

GRADE tables for review question: What symptoms or signs, individually or in combination, or validated clinical tools, suggest the presence of spinal metastatic malignant disease or direct malignant infiltration of the spine?

Table 7: Evidence profile for positive predictive value of low back pain for spinal metastasis

No. of studies	Study design	No of patients with spinal metastasis / No of patients	PPV (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Positive predictive value of low back pain as a symptom of undiagnosed spinal metastasis (studies in primary care: GP or emergency department)									
6[1]	Cohort studies	14 / 5266	0.3% [0.5% to 1.5%]	Serious[2]	Serious[3]	Not serious	Not serious	Low	Critical
Positive predictive value of low back pain as a symptom of undiagnosed spinal metastasis (studies in secondary or tertiary care)									
3[4]	Cohort studies	74 / 6212	1.3% [0.8% to 2.0%]	Serious[2]	Serious[3]	Not serious	Not serious	Low	Critical

CI, confidence interval; PPV: positive predictive value
1. Bellan 2016, Donner-Banzhoff 2006, Henschke 2009, Khoo 2009, Reito 2018, Thirug. 2014
2. Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2.
3. Serious heterogeneity unexplained by further subgroup analysis.
4. Lingawi 2004, Mijiyawa 2000, Street 2020

Table 8: Evidence profile for signs and symptoms of spinal metastasis in patients with low back pain

No. of studies	Study design	Total N (n with symptom)	Prevalence of spinal metastasis	Sensitivity (95% CI)	Specificity (95% CI)	LR (95% CI)	PV (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[1]	Quality	Importance
Absence of pain during flexion, extension, and lateral flexion movements to identify spinal metastasis without a concomitant non-malignant cause of back pain in patients with low back pain													
Cook 2012	Cohort study	1109 (469)	0.5%	91.7 [51.7 to 99.1]	58 [55 to 60.8]	LR+ 2.18 [1.7 to 2.8] LR- 0.14 [0.01 to 2.04]	PPV 1.1 [0.8 to 1.4] NPV 99.9 [99 to 100]	Serious[2]	Not serious	Not serious	Not serious	Moderate	Critical

No. of studies	Study design	Total N (n with symptom)	Prevalence of spinal metastasis	Sensitivity (95% CI)	Specificity (95% CI)	LR (95% CI)	PV (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[1]	Quality	Importance
Absence of pain during flexion, extension and lateral flexion movements to identify spinal metastasis in patients with low back pain													
Cook 2012	Cohort study	1109 (469)	6.0%	59 [47 to 69.9]	59 [56 to 61.9]	LR+ 1.44 [1.16 to 1.78] LR- 0.7 [0.52 to 0.93]	PPV 8.4 [6.9 to 10.2] NPV 95.7 [94.4 to 96.8]	Serious[2]	Not serious	Not serious	Not serious	Moderate	Critical
Scoliosis to identify spinal metastasis in patients with low back pain													
Cook 2012	Cohort study	1109 (200)	6.0%	27.3 [18 to 39]	82.5 [80.1 to 84.7]	LR+ 1.56 [1.03 to 2.37] LR- 0.88 [0.76 to 1.02]	PPV 9.1 [6.2 to 13.1] NPV 94.7 [93.9 to 95.4]	Serious[2]	Not serious	Not serious	Not serious	Moderate	Critical
Kyphosis to identify spinal metastasis in patients with low back pain													
Cook 2012	Cohort study	1109 (124)	6.0%	13.6 [7.3 to 23.9]	89 [86.9 to 90.7]	LR+ 1.24 [0.66 to 2.33] LR- 0.97 [0.88 to 1.07]	PPV 7.3 [4 to 12.9] NPV 94.2 [93.6 to 94.7]	Serious[2]	Not serious	Not serious	Not serious	Moderate	Critical
Midline spinal tenderness to identify spinal metastasis in patients with low back pain													
Cook 2012	Cohort study	1109 (592)	6.0%	45.5 [34 to 57.4]	46.1 [43.1 to 49.2]	LR+ 0.84 [0.64 to 1.11] LR- 1.18 [0.94 to 1.49]	PPV 5.1 [3.9 to 6.6] NPV 93 [91.3 to 94.3]	Serious[2]	Not serious	Not serious	Not serious	Moderate	Critical
Unfamiliar low back pain to identify spinal metastasis in patients with low back pain													
Donner-Banzhoff 2006	Cluster RCT	1190 (2)	0.2%	50 [1.3 to 98.4]	82.8 [80.6 to 84.9]	LR+ 2.91 [0.72 to 11.71] LR- 0.6 [0.15 to 2.41]	PPV 0.5 [0.1 to 1.9] NPV 99.9 [99.6 to 100]	Not serious	Not serious	Not serious	Not serious	High	Critical
Previous history of cancer to identify spinal metastasis in patients with low back pain													
Hensch ke 2009	Cohort study	1172 (46)	0%	Not estimable	96 [94.8 to 97]	Not estimable	Not estimable	Not serious	Not serious	Not serious	Not serious	High	Critical

No. of studies	Study design	Total N (n with symptom)	Prevalence of spinal metastasis	Sensitivity (95% CI)	Specificity (95% CI)	LR (95% CI)	PV (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[1]	Quality	Importance
Age > 50 years to identify spinal metastasis in patients with low back pain													
Henschke 2009	Cohort study	1172 (400)	0%	Not estimable	65.9 [63.1 to 68.5]	Not estimable	Not estimable	Not serious	Not serious	Not serious	Not serious	High	Critical
Age > 70 years to identify spinal metastasis in patients with low back pain													
Henschke 2009	Cohort study	1172 (56)	0%	Not estimable	95.2 [93.8 to 96.3]	Not estimable	Not estimable	Not serious	Not serious	Not serious	Not serious	High	Critical
Constant, progressive, non-mechanical pain to identify spinal metastasis in patients with low back pain													
Henschke 2009	Cohort study	1172 (33)	0%	Not estimable	97.1 [96 to 98]	Not estimable	Not estimable	Not serious	Not serious	Not serious	Not serious	High	Critical
Insidious onset to identify spinal metastasis in patients with low back pain													
Henschke 2009	Cohort study	1172 (202)	0%	Not estimable	82.7 [80.5 to 84.8]	Not estimable	Not estimable	Not serious	Not serious	Not serious	Not serious	High	Critical
Systematically unwell to identify spinal metastasis in patients with low back pain													
Henschke 2009	Cohort study	1172 (27)	0%	Not estimable	97.7 [96.6 to 98.4]	Not estimable	Not estimable	Not serious	Not serious	Not serious	Not serious	High	Critical
Tried bed rest but no relief to identify spinal metastasis in patients with low back pain													
Henschke 2009	Cohort study	1172 (192)	0%	Not estimable	83.3 [81 to 85.3]	Not estimable	Not estimable	Not serious	Not serious	Not serious	Not serious	High	Critical
Weight loss to identify spinal metastasis in patients with low back pain													
Henschke 2009	Cohort study	1172 (3)	0%	Not estimable	99.7 [99.2 to 99.9]	Not estimable	Not estimable	Not serious	Not serious	Not serious	Not serious	High	Critical
Sensory level (altered sensation from trunk down) to identify spinal metastasis in patients with low back pain													
Henschke 2009	Cohort study	1172 (19)	0%	Not estimable	98.3 [97.4 to 98.9]	Not estimable	Not estimable	Not serious	Not serious	Not serious	Not serious	High	Critical

CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio; LR: likelihood ratios; NPV: negative predictive value; PPV: positive predictive value; PV: predictive values
1. Precision estimates based on PPV or Specificity where PPV is not reported
2. Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2.

Table 9: Evidence profile for signs and symptoms of spinal metastasis in patients presenting with undiagnosed cancer

No. of studies	Study design	Total N (n with symptom)	Prevalence of spinal metastasis	Sensitivity (95% CI)	Specificity (95% CI)	LR (95% CI)	PV (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Local pain to identify spinal metastasis in patients presenting with cancer													
He 2020	Cohort study	14603 (2264)	11.4%	76.2 [74.1 to 78.2]	92.3 [91.8 to 92.8]	LR+ 9.9 [9.28 to 10.57] LR- 0.26 [0.24 to 0.28]	PPV 56 [54.4 to 57.6] NPV 96.8 [96.5 to 97]	Not serious	Not serious	Not serious	Not serious	High	Critical
Radicular pain to identify spinal metastasis in patients presenting with cancer													
He 2020	Cohort study	14603 (923)	11.4%	29.7 [27.6 to 32]	96.7 [96.4 to 97]	LR+ 8.98 [7.98 to 10.11] LR- 0.73 [0.7 to 0.75]	PPV 53.6 [50.6 to 56.5] NPV 91.4 [91.2 to 91.7]	Not serious	Not serious	Not serious	Not serious	High	Critical
Night-aggravating pain to identify spinal metastasis in patients presenting with cancer													
He 2020	Cohort study	14603 (1003)	11.4%	55.7 [53.3 to 58]	99.4 [99.3 to 99.5]	LR+ 94.16 [75 to 118.22] LR- 0.45 [0.42 to 0.47]	PPV 92.4 [90.6 to 93.8] NPV 94.6 [94.3 to 94.8]	Not serious	Not serious	Not serious	Not serious	High	Critical
Limb numbness to identify spinal metastasis in patients presenting with cancer													
He 2020	Cohort study	14603 (766)	11.4%	24 [22 to 26.1]	97.2 [96.9 to 97.4]	LR+ 8.44 [7.4 to 9.64] LR- 0.78 [0.76 to 0.8]	PPV 52.1 [48.8 to 55.4] NPV 90.9 [90.6 to 91.1]	Not serious	Not serious	Not serious	Not serious	High	Critical
Limb weakness to identify spinal metastasis in patients presenting with cancer													
He 2020	Cohort study	14603 (1908)	11.4%	34.3 [32.1 to 36.6]	89.7 [89.1 to 90.2]	LR+ 3.32 [3.05 to 3.61] LR- 0.73 [0.71 to 0.76]	PPV 29.9 [28.2 to 31.7] NPV 91.4 [91.1 to 91.7]	Not serious	Not serious	Not serious	Not serious	High	Critical
Unstable gait to identify spinal metastasis in patients presenting with cancer													
He	Cohort	14603	11.4%	11.7 [10.3 to	97.6 [97.4	LR+ 4.97 [4.19 to	PPV 39 [35 to	Not	Not seri-	Not serious	Not serious	High	Critical

No. of studies	Study design	Total N (n with symptom)	Prevalence of spinal metastasis	Sensitivity (95% CI)	Specificity (95% CI)	LR (95% CI)	PV (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
2020	study	(502)		13.4]	to 97.9]	5.91]	43.2]	serious	ous				
						LR- 0.9 [0.89 to 0.92]	NPV 89.6 [89.4 to 89.7]						
Claudication to identify spinal metastasis in patients presenting with cancer													
He 2020	Cohort study	14603 (453)	11.4%	8.8 [7.5 to 10.2]	97.6 [97.3 to 97.9]	LR+ 3.7 [3.06 to 4.48]	PPV 32.3 [28.2 to 36.5]	Not serious	Not serious	Not serious	Not serious	High	Critical
						LR- 0.93 [0.92 to 0.95]	NPV 89.3 [89.1 to 89.4]						
Loss of sphincter control to identify spinal metastasis in patients presenting with cancer													
He 2020	Cohort study	14603 (2185)	11.4%	32.1 [29.9 to 34.4]	87.2 [86.7 to 87.8]	LR+ 2.52 [2.32 to 2.74]	PPV 24.5 [23 to 26.1]	Not serious	Not serious	Not serious	Not serious	High	Critical
						LR- 0.78 [0.75 to 0.8]	NPV 90.9 [90.6 to 91.2]						
Weight loss to identify spinal metastasis in patients presenting with cancer													
He 2020	Cohort study	14603 (2068)	11.4%	29.4 [27.3 to 31.7]	87.8 [87.2 to 88.4]	LR+ 2.41 [2.21 to 2.63]	PPV 23.7 [22.1 to 25.3]	Not serious	Not serious	Not serious	Not serious	High	Critical
						LR- 0.8 [0.78 to 0.83]	NPV 90.6 [90.4 to 90.9]						
Pooled symptoms (any of the above symptoms) to identify spinal metastasis in patients presenting with cancer													
He 2020	Cohort study	14603 (6054)	11.4%	90.8 [89.4 to 92.1]	64.9 [64.1 to 65.7]	LR+ 2.59 [2.52 to 2.66]	PPV 25 [24.5 to 25.5]	Not serious	Not serious	Not serious	Not serious	High	Critical
						LR- 0.14 [0.12 to 0.16]	NPV 98.2 [97.9 to 98.5]						

CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio; LR: likelihood ratios; NPV: negative predictive value; PPV: positive predictive value; PV: predictive values

Appendix F Economic evidence study selection

Study selection for: What symptoms or signs, individually or in combination, or validated clinical tools, suggest the presence of spinal metastatic malignant disease or direct malignant infiltration of the spine?

No economic evidence was identified which was applicable to this review question.

Appendix G

Appendix H Economic evidence tables

Economic evidence tables for review question: What symptoms or signs, individually or in combination, or validated clinical tools, suggest the presence of spinal metastatic malignant disease or direct malignant infiltration of the spine?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What symptoms or signs, individually or in combination, or validated clinical tools, suggest the presence of spinal metastatic malignant disease or direct malignant infiltration of the spine?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What symptoms or signs, individually or in combination, or validated clinical tools, suggest the presence of spinal metastatic malignant disease or direct malignant infiltration of the spine?

Excluded effectiveness/ qualitative/diagnostic/prognostic/epidemiological/service delivery studies

Table 10: Excluded studies and reasons for their exclusion

Study	Code [Reason]
De la Garza Ramos, Rafael, Benton, Joshua A, Gelfand, Yaroslav et al. (2020) Racial disparities in clinical presentation, type of intervention, and in-hospital outcomes of patients with metastatic spine disease: An analysis of 145,809 admissions in the United States. Cancer epidemiology 68: 101792	Outcomes do not match review protocol
Downie, Aron, Williams, Christopher M, Henschke, Nicholas et al. (2013) Red flags to screen for malignancy and fracture in patients with low back pain: systematic review. BMJ (Clinical research ed.) 347: f7095	Study design - systematic review without pooled results/ quantitative data, checked for relevant studies
Dubosh, N.M., Edlow, J.A., Goto, T. et al. (2019) Missed Serious Neurologic Conditions in Emergency Department Patients Discharged With Nonspecific Diagnoses of Headache or Back Pain. Annals of Emergency Medicine 74(4): 549-561	Outcomes do not match review protocol
Galliker, Gabriela, Scherer, Dominique Eva, Trippolini, Maurizio Alen et al. (2020) Low Back Pain in the Emergency Department: Prevalence of Serious Spinal Pathologies and Diagnostic Accuracy of Red Flags. The American journal of medicine 133(1): 60-72e14	Study design - systematic review without pooled results/ quantitative data, checked for relevant studies
Helweg-Larsen, S and Sorensen, P S (1994) Symptoms and signs in metastatic spinal cord compression: a study of progression from first symptom until diagnosis in 153 patients. European journal of cancer (Oxford, England : 1990) 30a(3): 396-8	Outcomes do not match protocol - does not report on the diagnostic value of validated clinical tools, or specific signs and symptoms in relation to the presence of spinal metastatic disease or direct malignant infiltration of the spine. The study focuses on the diagnosis of spinal cord compression.
Henschke, Nicholas, Maher, Christopher G, Ostelo, Raymond W J G et al. (2013) Red flags to screen for malignancy in patients with low-back pain. The Cochrane database of systematic reviews: cd008686	Study design - systematic review without pooled results/ quantitative data, checked for relevant studies
Kanna, Rishi Mugesh, Kamal, Younis, Mahesh, Anupama et al. (2017) The impact of routine whole spine MRI screening in the evaluation of spinal degenerative diseases. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Soci-	Population do not match review protocol

Study	Code [Reason]
ety, and the European Section of the Cervical Spine Research Society 26(8): 1993-1998	
Kitagawa, Yasuyuki, Ito, Toshihiko, Mizuno, Yoshihiro et al. (2019) Symptoms Related to Moderate Skeletal-Related Events as Clues for the Diagnosis of Bone Metastasis. Journal of Nippon Medical School = Nippon Ika Daigaku zasshi 86(3): 159-164	Population do not match review protocol
Leichtle, UG, Wünschel, M, Socci, M et al. (2015) Spine radiography in the evaluation of back and neck pain in an orthopaedic emergency clinic. Journal of back and musculoskeletal rehabilitation 28(1): 43-8	Outcomes do not match review protocol – does not report data relevant to diagnostic accuracy
Levack, P, Graham, J, Collie, D et al. (2002) Don't wait for a sensory level--listen to the symptoms: a prospective audit of the delays in diagnosis of malignant cord compression. Clinical oncology (Royal College of Radiologists (Great Britain)) 14(6): 472-80	Population do not match review protocol
Lu, Charles, Gonzalez, Ramon G, Jolesz, Ferenc A et al. (2005) Suspected spinal cord compression in cancer patients: a multidisciplinary risk assessment. The journal of supportive oncology 3(4): 305-12	Population do not match review protocol
Raison, NT, Alwan, W, Abbot, A et al. (2014) The reliability of red flags in spinal cord compression. Archives of trauma research 3(1): e17850	Population does not match review protocol – does not report proportion of included patients who went on to be diagnosed with spinal metastases/cord compression resulting from malignancy
ROBERTS, JAMES R. (2017) Detecting the Red Flags of Acute Spinal Cord Compression. Emergency Medicine News 39(11): 12-14	Study design - expert review/narrative
Spencer, R.J.; Amer, S.; St George, E.J. (2021) A retrospective analysis of emergency referrals and admissions to a regional neurosurgical centre 2016-2018. British Journal of Neurosurgery 35(4): 438-443	Population do not match review protocol – study does not report signs/ symptoms
Verhagen, Arianne P, Downie, Aron, Popal, Nahid et al. (2016) Red flags presented in current low back pain guidelines: a review. European spine journal, 25, 2788-802	Study design - systematic review without pooled results/ quantitative data, checked for relevant studies

Excluded economic studies

No economic evidence was identified for this review.

Appendix K Research recommendations – full details

Research recommendations for review question: What symptoms or signs, individually or in combination, or validated clinical tools, suggest the presence of spinal metastatic malignant disease or direct malignant infiltration of the spine?

No research recommendations were made for this review question.