National Institute for Health and Care Excellence

Suspected cancer: recognition and referral

[D] Technical appendices for unexplained weight loss as a non-site specific symptom in adults in primary care

NICE guideline NG12

Technical data underpinning diagnostic review D

April 2026

Final

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Contents

Appendix A Review protocols

Review protocol for effectiveness review of Unexplained weight loss as a non-site specific symptom in adults in primary care

Field	Content
Review title	Unexplained weight loss as a non-site specific symptom in adults in primary care
Review question	At what age thresholds should unexplained weight-loss be used to refer adults via a suspected cancer pathway?
Objective	Recommendation on unexplained weight loss as a non-specific symptom currently does not stratify by age. This review aims to compare the accuracy of different age thresholds used to refer adults via a suspected cancer pathway when presenting with unexplained weight loss as a non-specific symptom in primary care.
Searches	The following databases will be searched: • Clinical searches – Medline ALL, Embase, Epistemonikos, Cochrane CDSR • Economic searches - Medline ALL, Embase and INAHTA The principal search strategy will be developed in MEDLINE and then adapted, as appropriate, for use in the other sources listed, taking into account their size, search functionality and subject coverage. To ensure comprehensive coverage, the following will be done to supplement the database searches: • Forward citation searching using a key paper that prompted the surveillance review for this question • Backward citation searching using a key paper that prompted the surveillance review for this question Database functionality will be used, where available, to exclude:

	• Animal studies • Editorials, letters, news items and commentaries • Conference abstracts and posters • Registry entries for ongoing clinical trials or those that contain no results • Theses and dissertations • Papers not published in the English language. • Non-OECD countries Date limits: 2015 - present Search filters and classifiers: The following standard NICE filters will be used to limit results by study type: cost effectiveness studies. The information services team at NICE will quality assure the principal search strategy. Any revisions or additional steps will be agreed by the review team before being implemented. The full search strategies for all databases will be published in the final review.
Condition or domain being studied	Age thresholds for referring adults with unexplained weight-loss for non-specific cancer sites.
Population	Inclusion: Adults (≥18 years old) presenting to primary care* with unexplained weight loss as a non-specific symptom. *When a paper includes populations from primary and secondary care and the data cannot be disaggregated if at least 80% of the population are from primary care the paper will be considered. Exclusion: • Adults with a history of any type of cancer

Index Test	Age thresholds in adults with unexpected weight loss (a >5% mean weight loss within a 6-month period) that might trigger a referral via a suspected cancer pathway.
Reference standard	Cancer diagnosis within six months following a referral via a suspected cancer pathway.
Types of study to be included	Include published full-text papers: • Prospective cohort studies • Retrospective cohort studies • Diagnostic accuracy studies • Systematic reviews of these studies The number of papers identified for consideration for full paper review and data extraction will be reviewed and a process of prioritisation may be implemented where studies with prospective data are prioritised in order to manage resources to complete the review and to focus the review on the most pertinent data.
Other exclusion criteria	Inclusion: • All other study types • Full text papers • OECD countries - UK based studies will be prioritised, but publications from other OECD countries will be considered Exclusion: • Conference abstracts • 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 • Studies using qualitative methods only • Studies where multivariate regression analysis was not conducted, or where important

	confounders were not adjusted for in the analysis, will be excluded. • Non-English language articles
Context	In March 2025, an exceptional surveillance review of the suspected cancer: recognition and referral guideline (NG12) guideline highlighted the need for the recommendation on unexplained weight loss as a non-specific symptom (1.13.2) to refer patients via the suspected cancer pathway according to age categories. This guidance will update recommendation 1.13.2 and seek to provide age thresholds to inform primary care decision making when making a referral to the suspected cancer pathway based on unexplained weight loss as a non-specific symptom.
Primary outcomes	Accuracy of age thresholds for non-site specific cancer diagnosis within 6 months based on unexpected weight loss: • Sensitivity • Specificity • Positive predictive value • False negative rate The suggested thresholds for sensitivity and specificity are: • Sensitivity – upper 90, lower 10 • Specificity – upper 80, lower 50
Secondary outcomes	Not applicable
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI R5 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. 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. 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 (age, sex, ethnicity) inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data (see Primary outcomes) and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • QUADAS-2 for diagnostic accuracy studies The quality assessment will be performed by one reviewer, and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. For each reported age threshold, the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted. If more than one study reports a given age threshold, the results will be meta-analysed, if feasible, to provide a summary estimate indicating the likelihood of cancer diagnosis based on unexpected weight loss (a >5% mean weight loss within a 6-month period) associated with each age threshold. The positive predictive value will form the basis of the risk

	estimate. A positive predictive value threshold of 3% or more for urgent cancer investigation will be used. Where appropriate, meta-analysis of diagnostic test accuracy will be performed using the metaDTA app (https://crsu.shinyapps.io/MetaDTA/) . Cochrane Review Manager software may be used to help with visually displaying information. Sensitivity, specificity, positive and negative likelihood ratios with 95% CIs will be used as outcomes for diagnostic test accuracy. These diagnostic accuracy parameters will be obtained from the studies or calculated by the technical team using data from the studies. 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/"
Analysis of sub-groups	Evidence will be stratified by: • Cancer site Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes: • Groups identified in the equality and health inequalities assessment (EHIA) as outlined in the scope including: o socioeconomic and geographical factors o age o ethnicity o disabilities o people for whom English is not their first language or who have other communication needs. o trans people o non-binary people

	Where evidence is stratified or sub-grouped 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.		
Type and method of review	☐ Intervention ☒ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
Language	English		
Country	England		
Anticipated or actual start date	20/08/2025		
Anticipated completion date	01/10/2025		
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	☐	☒
Named contact	**5a. Named contact** NICE **5b Named contact e-mail** SuspectedCancer@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		
Review team members	• Robby Richey – Topic lead • Steven Barnes – Technical advisor • James Jagroo – Senior technical analyst • Yolanda Martinez - Technical analyst • Lindsay Claxton - Health economist • Amy Finnegan - Information specialist • Jon Littler – Project manager		
Funding sources/sponsor	This systematic review is being completed by NICE which receives funding from the Department of Health and Social Care.		
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 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.		
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: https://www.nice.org.uk/guidance/indevelopment/gid-ng10443
Other registration details	N/A
Reference/URL for published protocol	N/A
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.
Keywords	Age thresholds, non-site-specific symptoms, unexplained weight-loss, suspected cancer referral.
Details of existing review of same topic by same authors	This is a new review question that will update recommendation 1.13.2 in Suspected cancer: recognition and referral guideline introducing age thresholds for unexplained weight loss as a non-specific symptom be used to refer adults via suspected cancer pathway.
Current review status	☐ Ongoing ☒ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
Additional information	N/A
Details of final publication	www.nice.org.uk

Economic review protocol

ID	Field	Content
1.	Review title	Unexplained weight loss as a non-site specific symptom in adults in primary care
2.	Objective	To identify economic studies that compare different age thresholds used to refer adults via a suspected cancer pathway when presenting with unexplained weight loss as a non-specific symptom in primary care
3.	Inclusion criteria	• Populations, interventions and comparators must be as specified in the effectiveness review protocol. • Relevant comparative economic study design: cost–utility analysis, cost–effectiveness analysis, cost–consequences analysis, comparative cost analysis • Decision analytic model-based or within-trial economic analyses • OECD countries (except USA) • Healthcare and personal social services cost perspective • Studies published from 2015 – this cut off has been applied to restrict the review to more recent studies which will have more applicable resource use and costs. High-quality studies in line with the NICE reference case (recent UK NHS/PSS cost-utility analyses using the QALY as the measure of outcome) are the most applicable to NICE decision making. Not all studies meeting the inclusion criteria will therefore necessarily be used in decision-making - see Review strategy below for details.
4.	Exclusion criteria	• Conference posters or abstract only studies – these do not provide sufficient information for quality assessment. • Studies published before 2015 – this cut off has been applied to restrict the review to more recent studies which will have more applicable resource use and costs. • Studies from non-OECD countries or the USA – these are considered unlikely to be applicable to the UK NHS setting due to substantial differences in healthcare delivery and unit costs. • Non-comparative economic analyses including cost-of-illness studies. • Letters, editorials or commentaries, study protocols or reviews of economic evaluations (recent reviews will be ordered and the bibliographies will be checked for relevant individual economic studies, which will then be ordered and checked for eligibility). • Non-English language papers.

		• Studies considering exclusively intervention costs, e.g. medicine acquisition costs, without considering wider healthcare costs associated with unexplained weight loss for suspected cancer. • Studies comparing costs of branded vs generic forms of the same medicine. • Studies only focussing on productivity losses or gains.
5.	Search strategy	An economic study search will be undertaken using question-specific terms. For search details see appendix B below.

6.	Review strategy	• Studies meeting the inclusion and exclusion criteria will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist in appendix H of Developing NICE guidelines: the manual.
		• The NICE economic evaluation checklist assesses:
		  ○ Applicability to the NICE guideline decision making context with consideration of the NICE reference case relevant to the guideline. Recent UK studies that use the NICE reference case methods are the most applicable when considering cost effectiveness.
		  ○ Methodological limitations.
		• The aim is to present the best available economic evidence to inform committee decision-making in the context of the guideline, the current UK NHS setting and NICE methods. Therefore, the health economist may not present all studies that meet inclusion criteria. If recent high quality, UK cost-utility analyses are available for a question, it is often not deemed informative to present studies that are less applicable or lower quality such as older UK analyses or analyses from other countries. A similar principle is deemed to apply more generally when considering applicability and methodological limitations. Some specific examples are given below:
		  ○ If multiple versions of a model are available for the UK and other countries it is usually reasonable to only present the UK version.
		  ○ If multiple versions of the same UK model are available, it is usually reasonable to present only the most recent.
		  ○ If there has been a NICE MTA or guideline model that informs current NHS practice it is usually reasonable not to present older studies, unless they address a different subpopulation or other specific issue.
		  ○ If a UK model that includes all interventions in the decision space is available it may be reasonable not to present

		studies that only include individual or fewer interventions, if the analysis is sufficiently applicable and of good methodological quality.
		• Quality and relevance of effectiveness data used in the economic analysis: the more closely the clinical effectiveness data used in the economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.
		• Hierarchy of economic evaluation evidence based on quality assessment
		  ○ 'Directly applicable' and 'Minor limitations' (only recent UK CUAs can get this rating). Usually presented and used in decision-making.
		  ○ Directly or partially applicable combined with minor or potentially serious limitations (other than 1). Discretion over whether these are presented and used in decision-making, depending on the availability of more relevant evidence.
		  ○ 'Not applicable' or 'Very serious limitations'. Typically not presented and not used in decision-making.
		
		The health economist will make a decision based on the relative applicability and quality of the available evidence for each question, in discussion with the guideline committee if required. All decisions will be transparently reported in the evidence report. Studies that are presented to the committee and used in decision-making when formulating recommendations will be included in the summary tables and will have an evidence extraction. Other studies may not be presented to the committee in detail but will be listed, with the reason for not being presented to the committee and thus not used in decision-making being provided. Committee members can review and query the decision not to present studies with the health economist and will be provided with full details of these studies where requested.

Appendix B Literature search strategies

Background and development

Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches. The MEDLINE strategies below were quality assured (QA) by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

This search report is based on the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess "low-probability" matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The suspected cancer and weight loss lines have been adapted from the following source:

Suspected cancer: recognition and referral (2015) NICE guideline NG12

but changed structurally due to changes to the review question.

Search limits and other restrictions

Formats

Limits were applied in adherence to standard NICE practice (as set out in the Identifying the evidence chapter of the manual) and the eligibility criteria listed in the review protocol to exclude:

- Animal studies
- Editorials, letters, news items and commentaries
- Conference abstracts and posters

- Registry entries for ongoing clinical trials or those that contain no results
- Theses and dissertations
- Papers not published in the English language.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from:

> Dickersin K, Scherer R & Lefebvre C. (1994) Systematic reviews: identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Date limits

A date limit of 01/01/2015 to 15/09/2025 was applied, as stated in the review protocol, because the question was an update of a recommendation from the 2015 guideline based on multiple review questions on different cancer sites.

Search filters and classifiers

Effectiveness searches

OECD countries filter:

The MEDLINE and Embase searches were limited to evidence from Organisation for Economic Co-operation and Development (OECD) member states using the validated NICE filter.

The OECD countries filters were used without modification:

Ayiku, L., Hudson, T., Williams, C., Levay, P., & Jacob, C. (2021). The NICE OECD countries' geographic search filters: Part 2 - Validation of the MEDLINE and Embase (Ovid) filters. *Journal of the Medical Library Association*, 109(4), 583–589.

Cost effectiveness searches

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Note: Several modifications have been made to these filters over the years that are standard NICE practice.

Key decisions

Translations of the databases for the effectiveness and cost-effectiveness searches were done as appropriate to the size and interface of the individual databases.

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Database of Systematic Reviews (CDSR)	15/09/2025	Wiley	Cochrane Database of Systematic Reviews Issue 9 of 12, September 2025	2
Embase	15/09/2025	Ovid	Embase <1974 to 2025 September 11>	856
Epistimonikos	15/09/2025	https://www.epistemonikos.org/	n/a	183
MEDINE ALL	15/09/2025	Ovid	Ovid MEDLINE(R) ALL <1946 to September 12, 2025>	289

Additional search methods

Additional methods	Date searched	No. of results downloaded
Backwards citation searching	15/09/2025	28
Forward citation searching	15/09/2025	7

Search strategy history

Database name: Cochrane CDSR

Searches
#1 [mh ^“Early Detection of Cancer”] 2711
#2 [mh “Neoplasms”]di 165758
#3 (suspect* NEAR/5 (neoplas* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta NEXT sta* or adenom* or leukemia* or leukaemia* or myeloma* or lymphoma*)):ti,ab 1475

Searches
#4 (early NEAR/5 (neoplas* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta NEXT sta* or adenom* or leukemia* or leukaemia* or myeloma* or lymphoma*)):ti,ab 13507
#5 (predict* NEAR/5 (neoplas* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta NEXT sta* or adenom* or leukemia* or leukaemia* or myeloma* or lymphoma*)):ti,ab 4972
#6 ((assess* or investigat*) NEAR/3 (neoplas* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta NEXT sta* or adenom* or leukemia* or leukaemia* or myeloma* or lymphoma*)):ti,ab 11798
#7 (diagnos* NEAR/3 (neoplas* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta NEXT sta* or adenom* or leukemia* or leukaemia* or myeloma* or lymphoma*)):ti,ab 19447
#8 ((symptom* or sign* or present*) NEAR/5 (neoplas* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta NEXT sta* or adenom* or leukemia* or leukaemia* or myeloma* or lymphoma*)):ti,ab 24665
#9 (risk* NEAR/3 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)):ti,ab 15896
#10 {OR #1-#9} 207128
#11 [mh ^“Primary Health Care”] 6684
#12 [mh ^“Practice Patterns, Physicians’”] 2043
#13 [mh “General Practice”] 3104
#14 [mh ^“Primary Care Nursing”] 43
#15 [mh ^“Family Nursing”] 49
#16 [mh ^“Physicians, Primary Care”] 241
#17 [mh ^“Physicians, Family”] 542
#18 [mh ^“General Practitioners”] 604
#19 [mh ^“Nurse Practitioners”] 376
#20 [mh ^“Community Health Workers”] 868
#21 [mh “Referral and Consultation”] 3422
#22 [mh ^“community health services”] 1381
#23 [mh “Community Health Nursing”] 396
#24 [mh ^“Community Pharmacy Services”] 385
#25 [mh ^“ambulatory care”] 3854
#26 [mh ^“ambulatory care facilities”] 799
#27 [mh ^“home care services”] 2446
#28 [mh ^“Home Nursing”] 314
#29 [mh ^“Clinical Decision-Making”] 704
#30 [mh ^“Symptom Assessment”] 431
#31 (primary NEAR/4 (care or healthcare)):ti,ab 35155
#32 ((community or communities* or family or primary or ambulatory* or outpatient* or neighbourhood* or neighborhood*) NEAR/2 (care or clinician* or doctor* or health* or medicine or physician* or practi* or service* or nurs* or pharmac* or facility* or facilities* or clinic or clinics or department* or service* or setting*)):ti,ab 85979
#33 ((clinician* or doctor* or general* or physician* or nurs*) NEAR/2 (practi* or clinic or clinics)):ti,ab 19150
#34 (GP or GPs or generalist*):ti,ab 9817

Searches
#35 ((patient* or cancer* or neoplas* or tumor* or tumour*) NEAR/3 (referral* or referred* or consultation*)):ti,ab 10061
#36 {OR #11-#35} 123410
#37 [mh “Weight Loss”] 9263
#38 [mh ^“Body Weight”] 10598
#39 [mh ^“body weight changes”] 132
#40 (cachexia or emaciat*):ti,ab 988
#41 (wast* NEAR/2 syndrome*):ti,ab 54
#42 (weight NEAR/3 (los* or reduc* or decreas* or declin*)):ti,ab 33423
#43 {OR #37-#42} 42667
#44 #10 AND #36 AND #43 with Cochrane Library publication date Between Jan 2015 and Sep 2025, in Cochrane Reviews, Cochrane Protocols 2

Database name: Embase

Searches
1 exp *malignant neoplasm/di 568478
2 *cancer diagnosis/ 42811
3 early cancer diagnosis/ 17946
4 (suspect* adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 43762
5 (early adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 236274
6 (predict* adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 178614
7 ((assess* or investigat*) adj3 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 199867
8 (diagnos* adj3 (earl* or miss* or delay* or first or preliminary) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 48427
9 ((symptom* or sign* or present*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 931443
10 (risk* adj3 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 313895
11 or/1-10 2042143
12 exp *primary health care/ 85214
13 general practice/ 90895
14 family nursing/ 1609
15 primary nursing/ 112
16 community health nursing/ 24816
17 *general practitioner/ 31275

Searches	
18	nurse practitioner/ 31944
19	family nurse practitioner/ 218
20	exp patient referral/ 189455
21	exp ambulatory care/ 58223
22	health center/ 48899
23	community care/ 65441
24	health auxiliary/ 12721
25	home care/ 77112
26	clinical decision making/ 88245
27	symptom assessment/ 14787
28	(primary adj4 (care or healthcare)).ti,ab. 292477
29	((community or communities* or family or primary or ambulatory* or outpatient* or neighbourhood* or neighborhood*) adj2 (care or clinician* or doctor* or health* or medicine or physician* or practi* or service* or nurs* or pharmac* or facility* or facilities* or clinic or clinics or department* or service* or setting*)).ti,ab. 759324
30	((clinician* or doctor* or general* or physician* or nurs*) adj2 (practi* or clinic or clinics)).ti,ab. 246298
31	(GP or GPs or generalist*).ti,ab. 129327
32	((patient* or cancer* or neoplas* or tumo?r*) adj3 (referral* or referred* or consultation*)).ti,ab. 172740
33	or/12-32 1617733
34	exp body weight loss/ 279726
35	*body weight/ 39189
36	cachexia/ 20876
37	(cachexia or emaciat*).ti,ab. 19222
38	(wast* adj2 syndrome*).ti,ab. 2741
39	(weight adj3 (los* or reduc* or decreas* or declin*)).ti,ab. 311492
40	or/34-39 457623
41	and/11,33,40 2813
42	limit 41 to english language 2754
43	limit 42 to dc=20150101-20250917 2107
44	limit 42 to dd=20150101-20250917 2120
45	43 or 44 2121
46	letter.pt. or letter/ 1397121
47	note.pt. 1019300
48	editorial.pt. 847196
49	(letter or comment*).ti. 263366
50	or/46-49 3327452
51	randomized controlled trial/ or random*.ti,ab. 2629772
52	50 not 51 3289590
53	45 not 52 2087
54	53 not conference*.db,pt,su. 992
55	animal/ 1728944
56	nonhuman/ 8299713
57	exp Animal Experiment/ 3421958
58	exp Experimental Animal/ 910526
59	animal model/ 1964330

Searches
60 exp Rodent/ 4381862
61 (rat or rats or mouse or mice or rodent*).ti. 1734040
62 or/55-61 10921426
63 62 not human/ 7707283
64 54 not 63 984
65 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ 1942321
66 exp "organisation for economic co-operation and development"/ 3663
67 exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/ 4080757
68 european union/ 34079
69 developed country/ 37270
70 or/66-69 4117569
71 65 not 70 1770547
72 64 not 71 926
73 limit 72 to "remove clinical trial (clinicaltrials.gov) records" 856

Database name: Epistemonikos

Searches
(title:((title:((title:(((suspect* OR early OR predict* OR assess* OR investigat* OR diagnos* OR symptom* OR sign* OR present*) AND (neoplas* OR cancer* OR tumor* OR tumour* OR carcinoma* OR malignan* OR oncolo* OR metasta*))) OR abstract:(((suspect* OR early OR predict* OR assess* OR investigat* OR diagnos* OR symptom* OR sign* OR present*) AND (neoplas* OR cancer* OR tumor* OR tumour* OR carcinoma* OR malignan* OR oncolo* OR metasta*))))) OR abstract:((title:(((suspect* OR early OR predict* OR assess* OR investigat* OR diagnos* OR symptom* OR sign* OR present*) AND (neoplas* OR cancer* OR tumor* OR tumour* OR carcinoma* OR malignan* OR oncolo* OR metasta*))) OR abstract:(((suspect* OR early OR predict* OR assess* OR investigat* OR diagnos* OR symptom* OR sign* OR present*) AND (neoplas* OR cancer* OR tumor* OR tumour* OR carcinoma* OR malignan* OR oncolo* OR metasta*)))))) AND (title:((title:((primary AND (care OR healthcare))) OR abstract:((primary AND (care OR healthcare)))) OR (title:(((community OR family OR primary OR ambulatory*) AND (care OR clinician* OR doctor* OR health* OR medicine OR physician* OR practi* OR service* OR pharmac* OR setting*))) OR abstract:(((community OR family OR primary OR ambulatory*) AND (care OR clinician* OR doctor* OR health* OR medicine OR physician* OR practi* OR service* OR pharmac* OR setting*)))) OR (title:(((clinician* OR doctor* OR general* OR physician* OR nurs*) AND (practi* OR clinic OR clinics))) OR abstract:(((clinician* OR doctor* OR general* OR physician* OR nurs*) AND (practi* OR clinic OR clinics)))) OR (title:((gp OR gps)) OR abstract:((gp OR gps))) OR (title:(((patient* OR cancer*) AND (referral* OR referred*))) OR abstract:(((patient* OR cancer*) AND (referral* OR referred*))))) OR abstract:((title:((primary AND (care OR healthcare))) OR abstract:((primary AND (care OR healthcare)))) OR (title:(((community OR family OR primary OR ambulatory*) AND (care OR clinician* OR doctor* OR health* OR medicine OR physician* OR practi* OR service* OR pharmac* OR setting*))) OR abstract:(((community OR family OR primary OR ambulatory*) AND (care OR clinician* OR doctor* OR health* OR medicine OR physician* OR practi* OR service* OR pharmac* OR setting*)))) OR (title:(((clinician* OR doctor* OR general* OR physician* OR nurs*) AND (practi* OR clinic OR clinics))) OR abstract:(((clinician* OR doctor* OR general* OR physician* OR nurs*) AND (practi* OR clinic OR clinics)))) OR (title:((gp OR gps)) OR abstract:((gp OR gps))) OR (title:(((patient* OR cancer*) AND (referral* OR referred*))) OR abstract:(((patient* OR cancer*) AND (referral* OR referred*)))))) AND (title:((title:((cachexia OR emaciat*)) OR abstract:((cachexia OR emaciat*))) OR (title:((wast* AND syndrome*)) OR abstract:((wast* AND syndrome*))) OR (title:((weight AND (los* OR reduc* OR decreas* OR declin*))) OR abstract:((weight AND (los* OR reduc* OR decreas* OR declin*))))) OR abstract:((title:((cachexia OR emaciat*)) OR abstract:((cachexia OR emaciat*))) OR (title:((wast* AND syndrome*)) OR abstract:((wast* AND syndrome*))) OR (title:((weight AND (los* OR reduc* OR decreas* OR declin*))) OR abstract:((weight AND (los* OR reduc* OR decreas* OR declin*)))))) OR abstract:((title:((title:(((suspect* OR early OR predict* OR assess* OR investigat* OR diagnos* OR symptom* OR sign* OR present*) AND (neoplas* OR cancer* OR tumor* OR tumour* OR carcinoma* OR malignan* OR oncolo* OR metasta*))) OR abstract:(((suspect* OR early OR predict* OR assess* OR investigat* OR diagnos* OR symptom* OR sign* OR present*) AND (neoplas* OR cancer* OR tumor* OR tumour* OR carcinoma* OR malignan* OR oncolo* OR metasta*))))) OR abstract:((title:(((suspect* OR early OR predict* OR assess* OR investigat* OR diagnos* OR symptom* OR sign* OR present*) AND (neoplas* OR cancer* OR tumor* OR tumour* OR carcinoma* OR malignan* OR oncolo* OR metasta*))) OR abstract:(((suspect* OR early OR predict* OR assess* OR investigat* OR diagnos* OR symptom* OR sign* OR present*) AND (neoplas* OR cancer* OR tumor* OR tumour* OR carcinoma* OR malignan* OR oncolo* OR metasta*)))))) AND (title:((title:((primary AND (care OR healthcare))) OR abstract:((primary AND (care OR healthcare)))) OR (title:(((community OR family OR primary OR ambulatory*) AND (care OR clinician* OR doctor* OR health* OR medicine OR physician* OR practi* OR service* OR pharmac* OR setting*))) OR abstract:(((community OR family OR primary OR ambulatory*) AND (care OR clinician* OR doctor* OR health* OR medicine OR physician* OR practi* OR service* OR pharmac* OR setting*)))) OR (title:(((clinician* OR doctor* OR general* OR physician* OR nurs*) AND (practi* OR clinic

Searches
OR clinics))) OR abstract:(((clinician* OR doctor* OR general* OR physician* OR nurs*) AND (practi* OR clinic OR clinics)))) OR (title:((gp OR gps)) OR abstract:((gp OR gps))) OR (title:(((patient* OR cancer*) AND (referral* OR referred*))) OR abstract:(((patient* OR cancer*) AND (referral* OR referred*))))) OR abstract:((title:((primary AND (care OR healthcare))) OR abstract:((primary AND (care OR healthcare)))) OR (title:(((community OR family OR primary OR ambulatory*) AND (care OR clinician* OR doctor* OR health* OR medicine OR physician* OR practi* OR service* OR pharmac* OR setting*))) OR abstract:(((community OR family OR primary OR ambulatory*) AND (care OR clinician* OR doctor* OR health* OR medicine OR physician* OR practi* OR service* OR pharmac* OR setting*)))) OR (title:(((clinician* OR doctor* OR general* OR physician* OR nurs*) AND (practi* OR clinic OR clinics))) OR abstract:(((clinician* OR doctor* OR general* OR physician* OR nurs*) AND (practi* OR clinic OR clinics)))) OR (title:((gp OR gps)) OR abstract:((gp OR gps))) OR (title:(((patient* OR cancer*) AND (referral* OR referred*))) OR abstract:(((patient* OR cancer*) AND (referral* OR referred*)))))) AND (title:((title:((cachexia OR emaciat*)) OR abstract:((cachexia OR emaciat*))) OR (title:((wast* AND syndrome*)) OR abstract:((wast* AND syndrome*))) OR (title:((weight AND (los* OR reduc* OR decreas* OR declin*))) OR abstract:((weight AND (los* OR reduc* OR decreas* OR declin*))))) OR abstract:((title:((cachexia OR emaciat*)) OR abstract:((cachexia OR emaciat*))) OR (title:((wast* AND syndrome*)) OR abstract:((wast* AND syndrome*))) OR (title:((weight AND (los* OR reduc* OR decreas* OR declin*))) OR abstract:((weight AND (los* OR reduc* OR decreas* OR declin*))))))))

Database name: MEDLINE ALL

Searches
1 "Early Detection of Cancer"/ 45349
2 exp Neoplasms/di 609992
3 (suspect* adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 27375
4 (early adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 153693
5 (predict* adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 118681
6 ((assess* or investigat*) adj3 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 127292
7 (diagnos* adj3 (earl* or miss* or delay* or first or preliminary) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 33895
8 ((symptom* or sign* or present*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 621478
9 (risk* adj3 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 210595
10 or/1-9 1563280
11 Primary Health Care/ 99942
12 Practice Patterns, Physicians'/ 71021

Searches	
13	exp General Practice/ 80588
14	Primary Care Nursing/ 632
15	Family Nursing/ 1617
16	Physicians, Primary Care/ 4848
17	Physicians, Family/ 17647
18	General Practitioners/ 12095
19	Nurse Practitioners/ 19614
20	Community Health Workers/ 7328
21	exp "Referral and Consultation"/ 91570
22	community health services/ 33947
23	exp Community Health Nursing/ 20494
24	Community Pharmacy Services/ 6444
25	ambulatory care/ 48018
26	ambulatory care facilities/ 23502
27	home care services/ 38458
28	Home Nursing/ 8677
29	Clinical Decision-Making/ 16789
30	Symptom Assessment/ 7317
31	(primary adj4 (care or healthcare)).ti,ab. 208850
32	((community or communities* or family or primary or ambulatory* or outpatient* or neighbourhood* or neighborhood*) adj2 (care or clinician* or doctor* or health* or medicine or physician* or practi* or service* or nurs* or pharmac* or facility* or facilities* or clinic or clinics or department* or service* or setting*)).ti,ab. 529462
33	((clinician* or doctor* or general* or physician* or nurs*) adj2 (practi* or clinic or clinics)).ti,ab. 193259
34	(GP or GPs or generalist*).ti,ab. 91804
35	((patient* or cancer* or neoplas* or tumo?r*) adj3 (referral* or referred* or consultation*)).ti,ab. 85293
36	or/11-35 1100962
37	exp Weight Loss/ 54310
38	Body Weight/ 203398
39	body weight changes/ 11
40	(cachexia or emaciat*).ti,ab. 13065
41	(wast* adj2 syndrome*).ti,ab. 2249
42	(weight adj3 (los* or reduc* or decreas* or declin*)).ti,ab. 196880
43	or/37-42 397299
44	and/10,36,43 726
45	limit 44 to english language 682
46	limit 45 to ed=20150101-20250917 342
47	limit 45 to dt=20150101-20250917 396
48	46 or 47 414
49	letter/ 1309289
50	editorial/ 736177
51	news/ 231977
52	exp historical article/ 417095
53	Anecdotes as Topic/ 4748
54	comment/ 1055775

Searches
55 (letter or comment*).ti. 218780
56 case reports.pt. 2502662
57 or/49-56 5303356
58 randomized controlled trial/ or random*.ti,ab. 1800977
59 57 not 58 5266912
60 48 not 59 307
61 60 not overall.pt. 307
62 animals/ or exp Animals, Laboratory/ or exp Animal Experimentation/ or exp Models, Animal/ or exp Rodentia/ 7761949
63 (rat or rats or mouse or mice or rodent*).ti. 1540225
64 (62 or 63) not humans/ 5467201
65 61 not 64 307
66 afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/ 1452196
67 "organisation for economic co-operation and development"/ 702
68 australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/ 3702426
69 european union/ 18630
70 developed countries/ 21888
71 or/67-70 3719450
72 66 not 71 1358218
73 65 not 72 289

Additional search methods

Backward citation searching

Date of search	15/09/2025
How the seed reference was identified	Surveillance report
Sources and tools used	Citation Chaser
Date of last update	n/a
How results were managed and selected	A doi search was done in Citation Chaser for the seed reference and the selected results exported as a RIS file. Pre 2015 records were excluded in line with the date limits in the protocol
No. of results	28 (after pre 2015 results removed)
List of seed references used	Nicholson B D, Virdee P, Aveyard P, Price S J, Hobbs F D R, Koshiaris C et al. Prioritising primary care patients with unexpected weight loss for cancer investigation: diagnostic accuracy study (update) BMJ 2024; 387 :e080199

Forward citation searching

Date of search	15/09/2025
How the seed reference was identified	Surveillance report
Sources and tools used	Citation Chaser
Date of last update	n/a
How results were managed and selected	A doi search was done in Citation Chaser for the seed reference and the selected results exported as a RIS file. Pre 2015 records were excluded in line with the date limits in the protocol
No. of results	7
List of seed references used	Nicholson B D, Virdee P, Aveyard P, Price S J, Hobbs F D R, Koshiaris C et al. Prioritising primary care patients with unexpected weight loss for cancer investigation: diagnostic accuracy study (update) BMJ 2024; 387 :e080199

Cost-effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	15/09/2025	Ovid	Embase <1974 to 2025 September 11>	155
INAHTA	15/09/2025	https://database.inahta.org/	n/a	15
MEDLINE ALL	15/09/2025	Ovid	Ovid MEDLINE(R) ALL <1946 to September 12, 2025>	79

Search strategy history

Database name: Embase

Searches
1 exp *malignant neoplasm/di 568478
2 *cancer diagnosis/ 42811
3 early cancer diagnosis/ 17946
4 (suspect* adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 43762
5 (early adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 236274
6 (predict* adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 178614
7 ((assess* or investigat*) adj3 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 199867
8 (diagnos* adj3 (earl* or miss* or delay* or first or preliminary) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 48427

Searches
9 ((symptom* or sign* or present*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 931443
10 (risk* adj3 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 313895
11 or/1-10 2042143
12 exp body weight loss/ 279726
13 *body weight/ 39189
14 cachexia/ 20876
15 (cachexia or emaciat*).ti,ab. 19222
16 (wast* adj2 syndrome*).ti,ab. 2741
17 (weight adj3 (los* or reduc* or decreas* or declin*)).ti,ab. 311492
18 or/12-17 457623
19 11 and 18 38512
20 Health economics/ 37644
21 exp health care cost/ 377495
22 exp Fee/ 47173
23 exp Budget/ 37270
24 Funding/ 83389
25 budget*.ti,ab. 53913
26 cost*.ti. 215802
27 (economic* or pharmaco?economic*).ti. 86408
28 (price* or pricing*).ti,ab. 83998
29 (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. 350841
30 (financ* or fee or fees).ti,ab. 278677
31 (value adj2 (money or monetary)).ti,ab. 4676
32 or/20-31 1226240
33 19 and 32 617
34 limit 33 to english language 608
35 limit 34 to dc=20150101-20250917 476
36 limit 34 to dd=20150101-20250917 477
37 35 or 36 477
38 letter.pt. or letter/ 1397121
39 note.pt. 1019300
40 editorial.pt. 847196
41 (letter or comment*).ti. 263366
42 or/38-41 3327452
43 randomized controlled trial/ or random*.ti,ab. 2629772
44 42 not 43 3289590
45 37 not 44 472
46 45 not conference*.db,pt,su. 219
47 animal/ or nonhuman/ or exp Animal Experiment/ or exp Experimental Animal/ or animal model/ or exp Rodent/ 10891452
48 (rat or rats or mouse or mice or rodent*).ti. 1734040
49 47 or 48 10921426

Searches
50 49 not human/ 7707283
51 46 not 50 213
52 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ 1942321
53 exp "organisation for economic co-operation and development"/ 3663
54 exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/ 4080757
55 european union/ 34079
56 developed country/ 37270
57 or/53-56 4117569
58 52 not 57 1770547
59 51 not 58 198
60 limit 59 to "remove clinical trial (clinicaltrials.gov) records" 155

Database name: International HTA

Searches
((((suspect* OR early OR predict* OR assess* OR investigat* OR diagnos* OR symptom* OR sign* OR present* or risk*)) AND ((neoplas* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or adenom* or leukemia* or leukaemia* or myeloma* or lymphoma*))) OR

Searches
(("Early detection of cancer")[mh]) OR ("Neoplasms"[mhe])) AND (((weight) AND ((los* or reduc* or decreas* or declin*))) OR ((wast*) AND (syndrome*)) OR (((cachexia or emaciat*))) OR (("Body weight")[mh] OR ("Body weight changes")[mh]) OR ("Weight Loss"[mhe]))

Database name: MEDLINE ALL

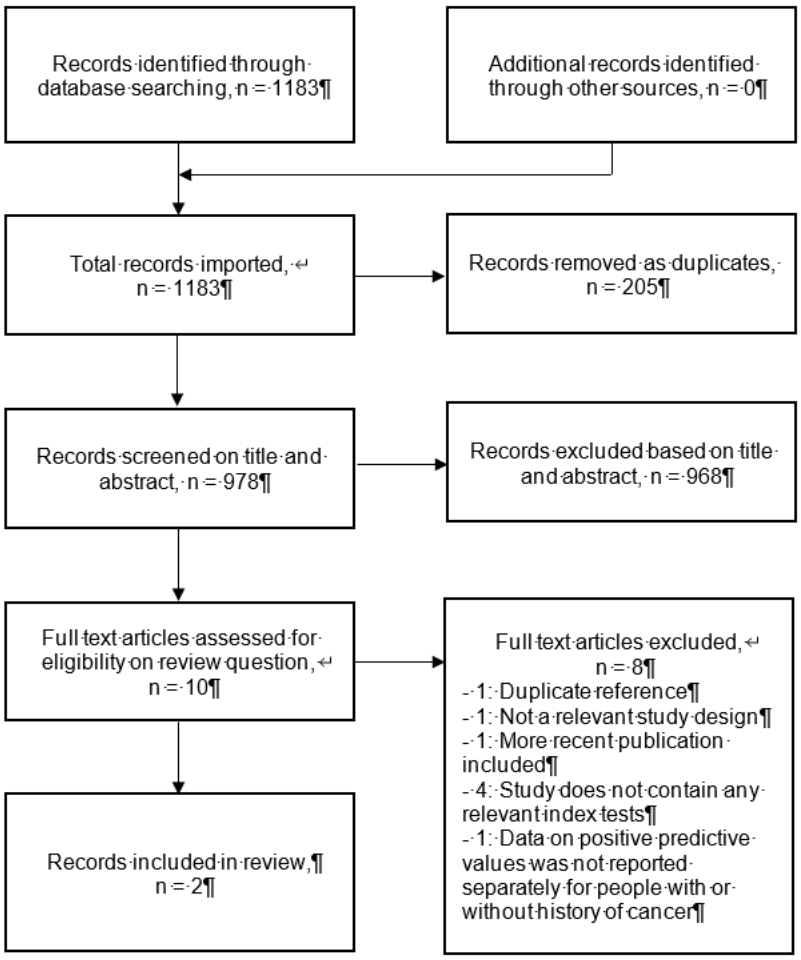
Searches
1 "Early Detection of Cancer"/ 45349
2 exp Neoplasms/di 609992
3 (suspect* adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 27375
4 (early adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 153693
5 (predict* adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 118681
6 ((assess* or investigat*) adj3 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 127292
7 (diagnos* adj3 (earl* or miss* or delay* or first or preliminary) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 33895
8 ((symptom* or sign* or present*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 621478
9 (risk* adj3 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncolo* or metasta* or meta-sta* or adenom* or leuk?emia* or myeloma* or lymphoma*)).ti,ab. 210595
10 or/1-9 1563280
11 exp Weight Loss/ 54310
12 Body Weight/ 203398
13 body weight changes/ 11
14 (cachexia or emaciat*).ti,ab. 13065
15 (wast* adj2 syndrome*).ti,ab. 2249
16 (weight adj3 (los* or reduc* or decreas* or declin*)).ti,ab. 196880
17 or/11-16 397299
18 10 and 17 16467
19 Economics/ 27557
20 Value of life/ 5850
21 exp "Costs and Cost Analysis"/ 281827
22 exp Economics, Hospital/ 26294
23 exp Economics, Medical/ 14467
24 Economics, Nursing/ 4014
25 Economics, Pharmaceutical/ 3168
26 exp "Fees and Charges"/ 31737

Searches
27 exp Budgets/ 14407
28 budget*.ti,ab. 40486
29 cost*.ti. 160154
30 (economic* or pharmaco?economic*).ti. 69043
31 (price* or pricing*).ti,ab. 61486
32 (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. 253286
33 (financ* or fee or fees).ti,ab. 190177
34 (value adj2 (money or monetary)).ti,ab. 3489
35 or/19-34 835294
36 18 and 35 140
37 limit 36 to english language 132
38 limit 37 to ed=20150101-20250917 74
39 limit 37 to dt=20150101-20250917 87
40 38 or 39 87
41 letter/ 1309289
42 editorial/ 736177
43 news/ 231977
44 exp historical article/ 417095
45 Anecdotes as Topic/ 4748
46 comment/ 1055775
47 (letter or comment*).ti. 218780
48 case reports.pt. 2502662
49 or/41-48 5303356
50 randomized controlled trial/ or random*.ti,ab. 1800977
51 49 not 50 5266912
52 40 not 51 82
53 52 not overall.pt. 82
54 animals/ or exp Animals, Laboratory/ or exp Animal Experimentation/ or exp Models, Animal/ or exp Rodentia/ 7761949
55 (rat or rats or mouse or mice or rodent*).ti. 1540225
56 (54 or 55) not humans/ 5467201
57 53 not 56 81
58 afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or

Searches
palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/ 1452196
59 "organisation for economic co-operation and development"/ 702
60 australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/ 3702426
61 european union/ 18630
62 developed countries/ 21888
63 or/59-62 3719450
64 58 not 63 1358218
65 57 not 64 79

Appendix C Study selection

Figure 1 Diagnostic evidence study selection



Appendix D Diagnostic evidence

Lee, 2025

Bibliographic Reference	Lee, Alex; de Mendonca, Lucas; McCarthy, Damien; Nelson, Craig; Rafiq, Meena; Venning, Brent; Chima, Sophie; Daly, Deborah; Fishman, George; Kearney, Chris; Hunter, Barbara; Lim, Fong Seng; Manski-Nankervis, Jo-Anne; Nicholson, Brian D; Emery, Jon; Martinez-Gutierrez, Javiera; Primary care patients presenting with unexpected weight loss in Australian general practices: replication of a diagnostic accuracy study.; BMJ open; 2025; vol. 15 (no. 7); e104690

Table 1 Lee 2025 study details

Study Characteristics

Study type	Retrospective cohort study Retrospective diagnostic accuracy study using routinely collected data from Australian primary care electronic health records
Study details	Study location Australia Setting Primary care Study dates 1 July 2007 and 1 February 2022 Sources of funding This study has been partly supported by funding from the Bupa Health Foundation; State Government of Victoria, Department of Health and the Victorian Comprehensive Cancer Centre Alliance.
Inclusion criteria	Patients who are over 18 years of age Patients who have at least one presentation for UWL between 1 July 2007 and 1 February 202
Exclusion criteria	Patients who have a previous diagnosis of cancer prior to the index date Patients who have an observed increase in weight in the 6months prior to the index date Patients who have had a prescription for a weight loss medication (for the purposes of losing weight) Patients who have had bariatric surgery in the 6 months prior to the index date
Number of participants	Victorian UWL cohort: N=13 306

Length of follow-up	6 months
Loss to follow-up	Not applicable (retrospective cohort study)
Index test(s)	Unexpected weight loss visit to primary care
Reference standard (s)	Cancer diagnosis within 6 months of index test The Victorian Cancer Registry was used to determine which patients had been diagnosed with cancer along with their dates of diagnosis. Primary care data was considered between 1/7/2007 and 1/2/2022, since this was the largest time period for which a patient appearing at primary care could have a cancer diagnosis 6 months later that is recorded in the available data.
Additional comments	Data was reported for age thresholds (years): 40 - 49 50 - 59 60 - 69 70 - 79 ≥80 Due to the ambiguous way that weight loss was recorded, two cohorts were considered: one consisting of patients who had a definite unintended weight loss symptom (the more restrictive cohort) and another that also included patients with a symptom 'weight loss – intent unknown' (the more inclusive cohort) All PPV extracted from the 'Australia inclusive' group (unintended and intent unknown weight loss); n=13 306 (women n=8 698, men n=4 600). Study did not report sensitivity, specificity, true positive, false positive, false negative or true negative data for age subgroups. Signs and symptoms were not reported (this made unclear whether participants had or did not have signs and symptoms as well as weight loss.

Abbreviations: UWL: unexpected weight loss

Population characteristics

Study-level characteristics

Characteristic	Study (N = 13306)
% Women No of events	n = 8698 ; % = 65.4

Characteristic	Study (N = 13306)
Age groups (years) - 18 to 39 No of events	n = 4143 ; % = 31.1
Age groups (years) - 40 to 49 No of events	n = 1916 ; % = 14.4
Age groups (years) - 50 to 59 No of events	n = 1823 ; % = 13.7
Age groups (years) - 60 to 69 No of events	n = 1563 ; % = 11.7
Age groups (years) - 70 to 79 No of events	n = 1510 ; % = 11.3
Age groups (years) - 80 or older No of events	n = 2351 ; % = 17.7
Cancer diagnosis - Yes No of events	n = 244 ; % = 1.8
Cancer diagnosis - No No of events	n = 13389 ; % = 98.6

Risk of bias

Directness

Critical appraisal - QUADAS-2

Question	Answer
Risk of Bias	Low *(Index test and reference standard were interpreted with full knowledge of each other; however, index test and reference standard are objective so decreases the likelihood of bias.)*
Directness	Partially applicable *(No threshold was specified for unexpected weight loss. Therefore, not all participants had >5% mean weight loss within a 6-month period.)*

Nicholson, 2024

Bibliographic Reference	Nicholson BD; Virdee P; Aveyard P; Price SJ; Hobbs FDR; Koshiaris C; Hamilton W; Prioritising primary care patients with unexpected weight loss for cancer investigation: diagnostic

	accuracy study (update).; BMJ (Clinical research ed.); 2024; vol. 387

Table 2 Nicholson 2024 study details

Study Characteristics

Study type	Retrospective cohort study Retrospective single-gate cross-sectional DTA study
Study details	Study location UK (England) Setting Primary care Study dates 1 January 2000 - 31 December 2019 Sources of funding Non-industry funded
Inclusion criteria	People who were ≥18 years old People who were registered with a general practice contributing data to CPRD and eligible for linkage to NCRAS, HES, and ONS People who had at least one code for unexpected weight loss and at least 12 months of data before the first recorded unexpected weight loss code (the index date)
Exclusion criteria	People who had a prescription of weight reducing treatment (orlistat) People who had a code for bariatric surgery in the previous six months People who had a cancer diagnosis before the index date
Number of participants	N=117 769 (participants with no signs or symptoms)
Length of follow-up	6 months
Loss to follow-up	Not applicable (retrospective cohort study)
Index test(s)	Unexpected weight loss visit to primary care Weight loss defined as a mean weight loss of ≥5% within a six month period.
Reference standard (s)	Cancer diagnosis within 6 months of index test All cancers diagnosed in the six months after the index date were identified in CPRD and linked NCRAS data.

Additional comments	Data was reported for age thresholds (years): 18 - 39 40 - 49 50 - 59 60 - 69 70 - 79 ≥80 Study did not report sensitivity, specificity, true positive, false positive, false negative or true negative data for age subgroups.

Abbreviations: CPRD: Clinical Practice Research Datalink; DTA: diagnostic test accuracy; HES: Hospital Episode Statistics; NCRAS: National Cancer Registrations and Analysis Service; ONS: Office for National Statistics data

Population characteristics

Study-level characteristics

Characteristic	Study (N = 326240)
% Women No of events	n = 184270 ; % = 56.5
Age groups (years) - 18 to 39 No of events	n = 67983 ; % = 20.8
Age groups (years) - 40 to 49 No of events	n = 38356 ; % = 11.8
Age groups (years) - 50 to 59 No of events	n = 43393 ; % = 13.3
Age groups (years) - 60 to 69 No of events	n = 47856 ; % = 14.7
Age groups (years) - 70 to 79 No of events	n = 61939 ; % = 19
Age groups (years) - 80 and older No of events	n = 66713 ; % = 20.4
Age group (years) for women - 18 to 39 No of events	n = 42600 ; % = 23.1
Age group (years) for women - 40 to 49 No of events	n = 20699 ; % = 11.2
Age group (years) for women - 50 to 59	n = 21483 ; % = 11.7

Characteristic	Study (N = 326240)
No of events	
Age group (years) for women - 60 to 69 No of events	n = 23687 ; % = 12.9
Age group (years) for women - 70 to 79 No of events	n = 33426 ; % = 18.1
Age group (years) for women - 80 and older No of events	n = 42375 ; % = 23
Age group (years) for men - 18 to 39 No of events	n = 25383 ; % = 17.9
Age group (years) for men - 40 to 49 No of events	n = 17657 ; % = 12.4
Age group (years) for men - 50 to 59 No of events	n = 21910 ; % = 15.4
Age group (years) for men - 60 to 69 No of events	n = 24169 ; % = 17
Age group (years) for men - 70 to 79 No of events	n = 28513 ; % = 20.1
Age group (years) for men - 80 and older No of events	n = 24338 ; % = 17.1
Body mass index - Underweight No of events	n = 19829 ; % = 6.1
Body mass index - Normal No of events	n = 142654 ; % = 43.7
Body mass index - Overweight No of events	n = 73909 ; % = 22.7
Body mass index - Obese No of events	n = 41948 ; % = 12.9
Body mass index - Missing No of events	n = 47900 ; % = 14.7
Cancer diagnosis - Yes No of events	n = 15624 ; % = 4.8
Cancer diagnosis - No	n = 310616 ; % = 95.2

Characteristic	Study (N = 326240)
No of events	

Risk of bias

Directness

Critical appraisal - QUADAS-2

Question	Answer
Risk of Bias	Low *(Index test and reference standard were interpreted with full knowledge of each other; however, index test and reference standard are objective so decreases the likelihood of bias.)*
Directness	Directly applicable

Appendix E Forest plots

No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F GRADE summary

Table 3 Diagnostic evidence summary: age thresholds in adults with unexpected weight loss (a >5% mean weight loss within a 6-month period) as a non-site specific symptom in primary care compared to cancer diagnosis within six months following a referral via a suspected cancer pathway (study directly applicable)

No of studies	Study design	Sample size[1]	Effect size (95% CI)[2]	PPV % (95% CI)	FNR[2] (%)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
1 (Nicholson 2024) **Age group**: 18 to 39	Retrospective cohort	37 574	Sensitivity: NR Specificity: NR	0.14 (0.10 to 0.18)	NR	Not serious	Serious[3]	Not serious	Serious[4]	LOW
1 (Nicholson 2024) **Age group**: 40 to 49	Retrospective cohort	17 489	Sensitivity: NR Specificity: NR	0.65 (0.53 to 0.78)	NR	Not serious	Serious[3]	Not serious	Serious[4]	LOW
1 (Nicholson 2024) **Age group**: 50 to 59	Retrospective cohort	17 194	Sensitivity: NR Specificity: NR	2.15 (1.93 to 2.37)	NR	Not serious	Serious[3]	Not serious	Serious[4]	LOW
1 (Nicholson 2024) **Age group**: 60 to 69	Retrospective cohort	15 482	Sensitivity: NR Specificity: NR	4.82 (4.49 to 5.17)	NR	Not serious	Serious[3]	Not serious	Serious[4]	LOW
1 (Nicholson 2024) **Age group**: 70 to 79	Retrospective cohort	15 823	Sensitivity: NR Specificity: NR	7.17 (6.78 to 7.59)	NR	Not serious	Serious[3]	Not serious	Serious[4]	LOW
1 (Nicholson 2024) **Age group**: 80 or older	Retrospective cohort	14 207	Sensitivity: NR Specificity: NR	6.29 (5.90 to 6.70)	NR	Not serious	Serious[3]	Not serious	Serious[4]	LOW

Abbreviations: CI: confidence interval; FNR: false negative rate; NR: not reported; PPV: positive predictive value.
Meta-analysis was not possible as a minimum of 3 studies are needed for bivariate meta-analysis.
1. Sample size was obtained from contacting the authors (Nicholson et al. 2024).
2. Included studies did not report sensitivity, specificity, false negative rate or data to calculate those outcomes.
3. Single study - downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default.

4. Serious imprecision - downgraded once, study did not report sensitivity and specificity. Positive predictive value can not be used to grade the evidence.

Table 4 Diagnostic evidence summary: age thresholds in adults with unexpected weight loss (a >5% mean weight loss within a 6-month period) as a non-site specific symptom in primary care compared to cancer diagnosis within six months following a referral via a suspected cancer pathway (study partially applicable)

Lee et al. (2025) study had limitations: no threshold for unexpected weight loss (this means that not all participants had >5% mean weight loss within a 6-month period); signs and symptoms were not reported (this made unclear whether participants had or did not have signs and symptoms as well as weight loss). Cancer prevalence in Lee et al. (2025) was half of the prevalence compared to the UK study (1.8% compared to 4.8%).

No of studies	Study design	Sample size	Effect size (95% CI)[1]	PPV % (95% CI)	FNR[1] (%)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
1 (Lee 2025) **Age group**: 40 to 49	Retrospective cohort	1 916	Sensitivity: NR Specificity: NR	0.26 (0.09 to 0.61)	NR	Not serious	Serious[2]	Serious[3]	Serious[4]	VERY LOW
1 (Lee 2025) **Age group**: 50 to 59	Retrospective cohort	1 823	Sensitivity: NR Specificity: NR	1.77 (1.21 to 2.49)	NR	Not serious	Serious[2]	Serious[3]	Serious[4]	VERY LOW
1 (Lee 2025) **Age group**: 60 to 69	Retrospective cohort	1 563	Sensitivity: NR Specificity: NR	2.19 (1.52 to 3.05)	NR	Not serious	Serious[2]	Serious[3]	Serious[4]	VERY LOW
1 (Lee 2025) **Age group**: 70 to 79	Retrospective cohort	1 510	Sensitivity: NR Specificity: NR	4.41 (3.43 to 5.58)	NR	Not serious	Serious[2]	Serious[3]	Serious[4]	VERY LOW
1 (Lee 2025) **Age group**: 80 or older	Retrospective cohort	2 351	Sensitivity: NR Specificity: NR	3.94 (3.18 to 4.82)	NR	Not serious	Serious[2]	Serious[3]	Serious[4]	VERY LOW

Abbreviations: CI: confidence interval; FNR: false negative rate; NR: not reported; PPV: positive predictive value.
Meta-analysis was not possible as a minimum of 3 studies are needed for bivariate meta-analysis.

1. Included studies did not report sensitivity, specificity, false negative rate or data to calculate those outcomes.
2. Single study - downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default.
3. Serious indirectness - downgraded once, no threshold was specified for unexpected weight loss. Therefore, not all participants had >5% mean weight loss within a 6-month period.
4. Serious imprecision - downgraded once, study did not report sensitivity and specificity. Positive predictive value can not be used to grade the evidence.

Table 5 Diagnostic evidence summary: age thresholds in adults with unexpected weight loss (a >5% mean weight loss within a 6-month period) as a non-site specific symptom in primary care compared to cancer diagnosis within six months following a referral via a suspected cancer pathway (study directly applicable; subgroup: women)

No of studies	Study design	Sample size[1]	Effect size (95% CI)[2]	PPV % (95% CI)	FNR[2] (%)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
1 (Nicholson 2024) **Age group**: 18 to 39	Retrospective cohort	22 508	Sensitivity: NR Specificity: NR	0.11 (0.07 to 0.16)	NR	Not serious	Serious[3]	Not serious	Serious[4]	LOW
1 (Nicholson 2024) **Age group**: 40 to 49	Retrospective cohort	8 704	Sensitivity: NR Specificity: NR	0.48 (0.35 to 0.65)	NR	Not serious	Serious[3]	Not serious	Serious[4]	LOW
1 (Nicholson 2024) **Age group**: 50 to 59	Retrospective cohort	7 969	Sensitivity: NR Specificity: NR	1.47 (1.22 to 1.76)	NR	Not serious	Serious[3]	Not serious	Serious[4]	LOW
1 (Nicholson 2024) **Age group**: 60 to 69	Retrospective cohort	7 249	Sensitivity: NR Specificity: NR	3.57 (3.16 to 4.03)	NR	Not serious	Serious[3]	Not serious	Serious[4]	LOW
1 (Nicholson 2024) **Age group**: 70 to 79	Retrospective cohort	8 103	Sensitivity: NR Specificity: NR	4.89 (4.43 to 5.38)	NR	Not serious	Serious[3]	Not serious	Serious[4]	LOW
1 (Nicholson 2024) **Age group**: 80 or older	Retrospective cohort	8 876	Sensitivity: NR Specificity: NR	4.48 (4.06 to 4.94)	NR	Not serious	Serious[3]	Not serious	Serious[4]	LOW

Abbreviations: CI: confidence interval; FNR: false negative rate; NR: not reported; PPV: positive predictive value.
Meta-analysis was not possible as a minimum of 3 studies are needed for bivariate meta-analysis.
1. Sample size was obtained from contacting the authors (Nicholson et al. 2024).

2. Included studies did not report sensitivity, specificity, false negative rate or data to calculate those outcomes.
3. Single study - downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default.
4. Serious imprecision - downgraded once, study did not report sensitivity and specificity. Positive predictive value can not be used to grade the evidence.

Table 6 Diagnostic evidence summary: age thresholds in adults with unexpected weight loss (a >5% mean weight loss within a 6-month period) as a non-site specific symptom in primary care compared to cancer diagnosis within six months following a referral via a suspected cancer pathway (study partially applicable; subgroup: women)

Lee et al. (2025) study had limitations: no threshold for unexpected weight loss (this means that not all participants had >5% mean weight loss within a 6-month period); signs and symptoms were not reported (this made unclear whether participants had or did not have signs and symptoms as well as weight loss). Cancer prevalence in Lee et al. (2025) was half of the prevalence compared to the UK study (1.8% compared to 4.8%).

No of studies	Study design	Sample size	Effect size (95% CI)[1]	PPV % (95% CI)	FNR[1] (%)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
1 (Lee 2025) **Age group**: 40 to 49	Retrospective cohort	NR[2]	Sensitivity: NR Specificity: NR	0.08 (0.00 to 0.44)	NR	Not serious	Serious[3]	Serious[4]	Serious[5]	VERY LOW
1 (Lee 2025) **Age group**: 50 to 59	Retrospective cohort	NR[2]	Sensitivity: NR Specificity: NR	1.59 (0.95 to 2.51)	NR	Not serious	Serious[3]	Serious[4]	Serious[5]	VERY LOW
1 (Lee 2025) **Age group**: 60 to 69	Retrospective cohort	NR[2]	Sensitivity: NR Specificity: NR	1.61 (0.88 to 2.69)	NR	Not serious	Serious[3]	Serious[4]	Serious[5]	VERY LOW
1 (Lee 2025) **Age group**: 70 to 79	Retrospective cohort	NR[2]	Sensitivity: NR Specificity: NR	2.74 (1.76 to 4.05)	NR	Not serious	Serious[3]	Serious[4]	Serious[5]	VERY LOW
1 (Lee 2025) **Age group**: 80 or older	Retrospective cohort	NR[2]	Sensitivity: NR Specificity: NR	3.00 (2.20 to 3.99)	NR	Not serious	Serious[3]	Serious[4]	Serious[5]	VERY LOW

Abbreviations: CI: confidence interval; FNR: false negative rate; NR: not reported; PPV: positive predictive value.
Meta-analysis was not possible as a minimum of 3 studies are needed for bivariate meta-analysis.
1. Included studies did not report sensitivity, specificity, false negative rate or data to calculate those outcomes.
2. The total population of women was reported (n=8 698) but the population of women per age group was not reported.
3. Single study - downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default.
4. Serious indirectness - downgraded once, no threshold was specified for unexpected weight loss. Therefore, not all participants had >5% mean weight loss within a 6-month period.
5. Serious imprecision - downgraded once, study did not report sensitivity and specificity. Positive predictive value can not be used to grade the evidence.

Table 7 Diagnostic evidence summary: age thresholds in adults with unexpected weight loss (a >5% mean weight loss within a 6-month period) as a non-site specific symptom in primary care compared to cancer diagnosis within six months following a referral via a suspected cancer pathway (study directly applicable; subgroup: men)

No of studies	Study design	Sample size[1]	Effect size (95% CI)[2]	PPV % (95% CI)	FNR[2] (%)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
1 (Nicholson 2024) **Age group**: 18 to 39	Retrospective cohort	15 066	Sensitivity: NR Specificity: NR	0.18 (0.12 to 0.26)	NR	Not serious	Serious[3]	Not serious	Serious[4]	LOW
1 (Nicholson 2024) **Age group**: 40 to 49	Retrospective cohort	8 785	Sensitivity: NR Specificity: NR	0.81 (0.63 to 1.02)	NR	Not serious	Serious[3]	Not serious	Serious[4]	LOW
1 (Nicholson 2024) **Age group**: 50 to 59	Retrospective cohort	9 225	Sensitivity: NR Specificity: NR	2.73 (2.41 to 3.09)	NR	Not serious	Serious[3]	Not serious	Serious[4]	LOW
1 (Nicholson 2024) **Age group**: 60 to 69	Retrospective cohort	8 233	Sensitivity: NR Specificity: NR	5.93 (5.43 to 6.46)	NR	Not serious	Serious[3]	Not serious	Serious[4]	LOW
1 (Nicholson 2024) **Age group**: 70 to 79	Retrospective cohort	7 720	Sensitivity: NR Specificity: NR	9.57 (8.93 to 10.25)	NR	Not serious	Serious[3]	Not serious	Serious[4]	LOW
1 (Nicholson 2024) **Age group**: 80 or older	Retrospective cohort	5 331	Sensitivity: NR Specificity: NR	9.30 (8.54 to 10.12)	NR	Not serious	Serious[3]	Not serious	Serious[4]	LOW

Abbreviations: CI: confidence interval; FNR: false negative rate; NR: not reported; PPV: positive predictive value.
Meta-analysis was not possible as a minimum of 3 studies are needed for bivariate meta-analysis.
1. Sample size was obtained from contacting the authors (Nicholson et al. 2024).
2. Included studies did not report sensitivity, specificity, false negative rate or data to calculate those outcomes.
3. Single study - downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default.
4. Serious imprecision - downgraded once, study did not report sensitivity and specificity. Positive predictive value can not be used to grade the evidence.

Table 8 Diagnostic evidence summary: age thresholds in adults with unexpected weight loss (a >5% mean weight loss within a 6-month period) as a non-site specific symptom in primary care compared to cancer diagnosis within six months following a referral via a suspected cancer pathway (study partially applicable; subgroup: men)

Lee et al. (2025) study had limitations: no threshold for unexpected weight loss (this means that not all participants had >5% mean weight loss within a 6-month period); signs and symptoms were not reported (this made unclear whether participants had or did not have signs and symptoms as well as weight loss). Cancer prevalence in Lee et al. (2025) was half of the prevalence compared to the UK study (1.8% compared to 4.8%).

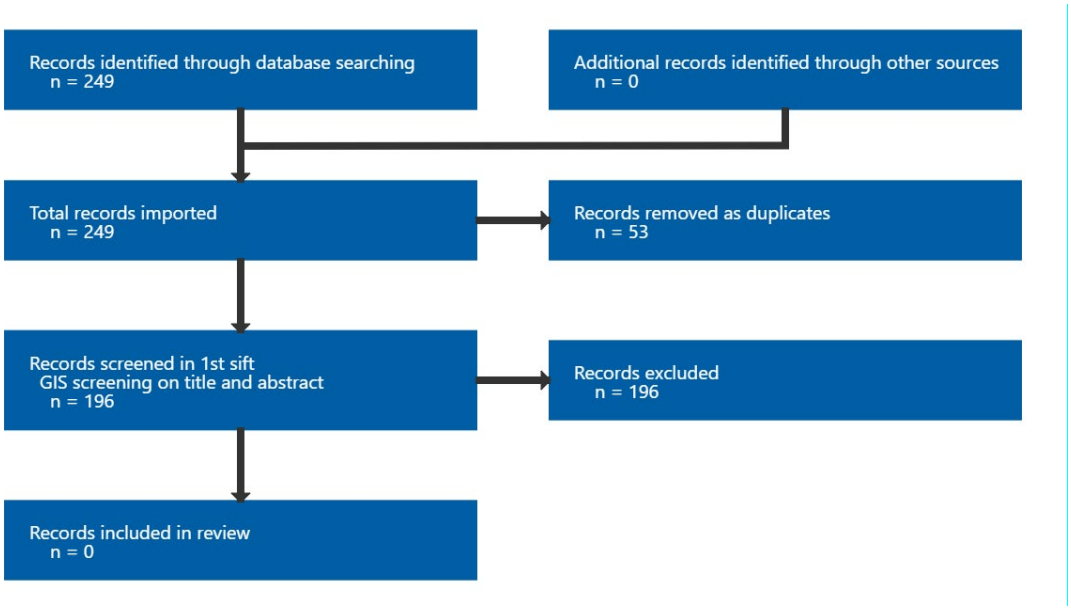
No of studies	Study design	Sample size	Effect size (95% CI)[1]	PPV % (95% CI)	FNR[1] (%)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
1 (Lee 2025) **Age group**: 40 to 49	Retrospective cohort	NR[2]	Sensitivity: NR Specificity: NR	0.63 (0.17 to 1.61)	NR	Not serious	Serious[3]	Serious[4]	Serious[5]	VERY LOW
1 (Lee 2025) **Age group**: 50 to 59	Retrospective cohort	NR[2]	Sensitivity: NR Specificity: NR	2.07 (1.13 to 3.45)	NR	Not serious	Serious[3]	Serious[4]	Serious[5]	VERY LOW
1 (Lee 2025) **Age group**: 60 to 69	Retrospective cohort	NR[2]	Sensitivity: NR Specificity: NR	2.94 (1.80 to 4.50)	NR	Not serious	Serious[3]	Serious[4]	Serious[5]	VERY LOW
1 (Lee 2025) **Age group**: 70 to 79	Retrospective cohort	NR[2]	Sensitivity: NR Specificity: NR	6.79 (4.93 to 9.06)	NR	Not serious	Serious[3]	Serious[4]	Serious[5]	VERY LOW

1 (Lee 2025) **Age group**: 80 or older	Retrospective cohort	NR[2]	Sensitivity: NR Specificity: NR	5.75 (4.22 to 7.61)	NR	Not serious	Serious[3]	Serious[4]	Serious[5]	VERY LOW

Abbreviations: CI: confidence interval; FNR: false negative rate; NR: not reported; PPV: positive predictive value.
Meta-analysis was not possible as a minimum of 3 studies are needed for bivariate meta-analysis.
1. Included studies did not report sensitivity, specificity, false negative rate or data to calculate those outcomes.
2. The total population of men was reported (n=4 600) but the population of men per age group was not reported.
3. Single study - downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default.
4. Serious indirectness - downgraded once, no threshold was specified for unexpected weight loss. Therefore, not all participants had >5% mean weight loss within a 6-month period.
5. Serious imprecision - downgraded once, study did not report sensitivity and specificity. Positive predictive value can not be used to grade the evidence.

Appendix G Economic evidence study selection

Figure 2: Economic evidence study selection flow chart



Appendix H Economic evidence tables

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

Appendix I Excluded studies

Diagnostic

Table 9 Studies excluded from the diagnostic review

Study	Reason for exclusion
Barclay, M., Renzi, C., Harrison, H. et al. (2024) Cancer incidence and competing mortality risk following 15 presenting symptoms in primary care: a population-based cohort study using electronic healthcare records. medRxiv	- Duplicate reference
Barclay, Matthew E, Renzi, Cristina, Harrison, Hannah et al. (2024) Cancer incidence and competing mortality risk following 15 presenting symptoms in primary care: a population-based cohort study using electronic healthcare records. BMJ oncology 3(1): e000500	- Study does not contain any relevant index tests Weight loss was reported as one of the symptoms for cancer diagnosis, but percentage of weight loss was not reported to match the 5% in our protocol
Jensen, Ellen, Kristensen, Jette Kolding, Bjerglund, Rikke Tveden et al. (2022) The pathway and characteristics of patients with non-specific symptoms of cancer: a systematic review. BMC cancer 22(1): 574	- Study does not contain any relevant index tests Weight loss was associated with cancer, but percentage of weight loss was not reported to match the 5% in our protocol
Nicholson, Brian D, Hamilton, William, O'Sullivan, Jack et al. (2018) Weight loss as a predictor of cancer in primary care: a systematic review and meta-analysis. The British journal of general practice : the journal of the Royal College of General Practitioners 68(670): e311-e322	- Not a relevant study design Systematic review included case-control studies. Cohort studies included in the systematic review were published before 2015.
Nicholson, Brian D, Hamilton, Willie, Koshiaris, Constantinos et al. (2020) The association between unexpected weight loss and cancer diagnosis in primary care: a matched cohort analysis of 65,000 presentations. British journal of cancer 122(12): 1848-1856	- More recent publication included that covers the same population over a longer time (2000 to 2019)

Study	Reason for exclusion
Nicholson, Brian David, Thompson, Matthew James, Hobbs, Frederick David Richard et al. (2022) Measured weight loss as a precursor to cancer diagnosis: retrospective cohort analysis of 43 302 primary care patients. Journal of cachexia, sarcopenia and muscle 13(5): 2492-2503	- Data on positive predictive value was not reported separately for people with or without history of cancer
Rao, Goutham, Ufholz, Kelsey, Saroufim, Paola et al. (2023) Recognition, diagnostic practices, and cancer outcomes among patients with unintentional weight loss (UWL) in primary care. Diagnosis (Berlin, Germany) 10(3): 267-274	- Study does not contain any relevant index tests Unexpected weight loss was not reported by age thresholds.
Wang, Qiao-Li, Babic, Ana, Rosenthal, Michael H et al. (2024) Cancer Diagnoses After Recent Weight Loss. JAMA 331(4): 318-328	- Study does not contain any relevant index tests Study does not report unexpected weight loss

Economic

No economic study was reviewed at full text and excluded from this review.

Appendix J Methods

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.

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

Developing the review questions and outcomes

The review question developed for this guideline were based on the key areas identified in the guideline scope. They were drafted by the NICE guideline development team and refined and validated by the guideline committee.

The review question was based on the following frameworks:

Population, index test(s), reference standard and outcome for reviews of diagnostic and predictive accuracy

Full literature searches, critical appraisals and evidence reviews were completed for all review questions.

Reviewing research evidence

Review protocols

Review protocol was developed with the guideline committee to outline the inclusion and exclusion criteria used to select studies for the evidence review.

Searching for evidence

Evidence was searched for the review question using the methods specified in Developing NICE guidelines: the manual.

Selecting studies for inclusion

All references identified by the literature searches and from other sources (for example, previous versions of the guideline or studies identified by committee

members) were uploaded into EPPI reviewer software (version 5) and de-duplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. At least 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies.

Data synthesis for diagnostic accuracy data

In this guideline, diagnostic test accuracy (DTA) data are classified as any data in which a feature – be it a symptom, a risk factor, a test result or the output of some algorithm that combines many such features – is observed in some people who have the condition of interest at the time of the test and some people who do not. Such data either explicitly provide, or can be manipulated to generate, a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly have the condition) and false positives and true negatives (in people who, according to the reference standard, do not).

The 'raw' 2x2 data can be summarised in a variety of ways. Those that were used for decision making in this guideline were as follows:

Sensitivity is the probability that the feature will be positive in a person with the condition.

- sensitivity = TP/(TP+FN)

Specificity is the probability that the feature will be negative in a person without the condition.

- specificity = TN/(FP+TN)

False negative rate (FNR) describes the proportion of actual positives that are incorrectly classified as negatives and describes how often a test fails to

detect something. A high FNR means the test is missing a lot of actual cases.

- FNR = 1 - sensitivity

Positive predictive values describe the probability that a person with a positive feature has the disease.

- PPV = TP/ (TP+FP)

Meta-analysis of the findings was not undertaken as only 2 studies were included for this review. Meta-analysis should not be performed on 2 studies as a minimum of 3 studies is needed to estimate the 5 parameters needed for a bivariate meta-analysis (mean and variance of logit sensitivity, mean and variance of logit specificity, and the correlation between logit sensitivity and logit specificity).

Appraising the quality of evidence

Diagnostic accuracy studies

Individual diagnostic accuracy studies were quality assessed using the QUADAS-2 tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, index features and/or reference standard in the study and how directly these

variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, index feature and/or reference standard.
- Partially indirect – Important deviations from the protocol in one of the population, index feature and/or reference standard.
- Indirect – Important deviations from the protocol in at least two of the population, index feature and/or reference standard.

GRADE for diagnostic accuracy evidence

Evidence from diagnostic accuracy studies was initially rated as high quality and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency, imprecision and indirectness) as detailed in Table 10 below.

The choice of primary outcome for decision making was determined by the committee and GRADE assessments were undertaken based on these outcomes.

In all cases, the downstream effects of diagnostic accuracy on patient-important outcomes were considered. This was done explicitly during committee deliberations and reported as part of the discussion section of the review detailing the likely consequences of true positive, true negative, false positive and false negative test results. In reviews where a decision model is being carried (for example, as part of an economic analysis), these consequences were incorporated here in addition.

GRADE assessments were only undertaken for sensitivity and specificity where available but results for positive predictive values and false negative rates are also presented alongside those data.

The committee were consulted to set 2 clinical decision thresholds for each measure: the value above which a test would be recommended, and a second

below which a test would be considered of no clinical use. These values were used to judge imprecision (see below).

If studies could not be pooled in a meta-analysis, GRADE assessments were undertaken for each study individually and reported as separate lines in the GRADE profile.

These criteria were used to apply preliminary ratings, but were overridden in cases where, in the view of the analyst or committee the uncertainty identified was unlikely to have a meaningful impact on decision making.

Table 10 Rationale for downgrading quality of evidence for diagnostic accuracy data

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious (don't downgrade): less than 50% overall weighting some concerns/high risk of bias Serious (downgrade 1 level): more than 50% some concerns/high risk of bias Very serious (downgrade 2 levels): more than 50% high risk of bias.
Indirectness	Not serious (don't downgrade): less than 50% of overall weighting partially direct or indirect. Serious (downgrade 1 level): more than 50% of overall weighting partially direct or indirect. Very serious (downgrade 2 levels): more than 50% of overall weighting indirect.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. Where data was pooled it was checked visually to identify inconsistency. Where there are apparent differences in effect size due consideration was given to the appropriateness of pooling studies.
Imprecision	The most appropriate primary pair of measures (for example: sensitivity/specificity, likelihood ratio) were used as described this in the review protocol. And appropriate thresholds with were discussed with the guideline committee.

Publication bias	If the review team became aware of evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of publication bias was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability.