

## Suspected cancer: recognition and referral guideline

### Review protocol for review question 1 Unexplained weight loss as a non-site-specific symptom in adults in primary care

ID	Field	Content
1.	Review title	Unexplained weight loss as a non-site-specific symptom in adults in primary care
2.	Review question	At what age thresholds should unexplained weight-loss be used to refer adults via a suspected cancer pathway?
3.	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.
4.	Searches	<p>The following databases will be searched:</p> <ul style="list-style-type: none"><li>• Clinical searches – Medline ALL, Embase, Epistemonikos, Cochrane CDSR</li><li>• Economic searches - Medline ALL, Embase and INAHTA</li></ul> <p>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.</p> <p>To ensure comprehensive coverage, the following will be done to supplement the database searches:</p> <ul style="list-style-type: none"><li>• Forward citation searching using a key paper that prompted the surveillance review for this question</li></ul>

		<ul style="list-style-type: none"> <li>• Backward citation searching using a key paper that prompted the surveillance review for this question</li> </ul> <p>Database functionality will be used, where available, to exclude:</p> <ul style="list-style-type: none"> <li>• Animal studies</li> <li>• Editorials, letters, news items and commentaries</li> <li>• Conference abstracts and posters</li> <li>• Registry entries for ongoing clinical trials or those that contain no results</li> <li>• Theses and dissertations</li> <li>• Papers not published in the English language.</li> <li>• Non-OECD countries</li> </ul> <p>Date limits: 2015 - present</p> <p>Search filters and classifiers:</p> <p>The following standard NICE filters will be used to limit results by study type:</p> <p>cost effectiveness studies</p> <p>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.</p> <p>The full search strategies for all databases will be published in the final review.</p>
5.	Condition or domain being studied	Age thresholds for referring adults with unexplained weight-loss for non-specific cancer sites.

6.	Population	<p>Inclusion: Adults (<math>\geq 18</math> years old) presenting to primary care* with unexplained weight loss as a non-specific symptom.</p> <p>*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.</p> <p>Exclusion:</p> <ul style="list-style-type: none"> <li>• Adults with a history of any type of cancer</li> </ul>
7.	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.
8.	Reference standard	Cancer diagnosis within six months following a referral via a suspected cancer pathway.
9.	Types of study to be included	<p>Include published full-text papers:</p> <ul style="list-style-type: none"> <li>• Prospective cohort studies</li> <li>• Retrospective cohort studies</li> <li>• Diagnostic accuracy studies</li> <li>• Systematic reviews of these studies</li> </ul> <p>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.</p>

10.	Other exclusion criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> <li>• All other study types</li> <li>• Full text papers</li> <li>• OECD countries - UK based studies will be prioritised, but publications from other OECD countries will be considered</li> </ul> <p>Exclusion:</p> <ul style="list-style-type: none"> <li>• Conference abstracts</li> <li>• 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</li> <li>• Studies using qualitative methods only</li> <li>• Studies where multivariate regression analysis was not conducted, or where important confounders were not adjusted for in the analysis, will be excluded.</li> <li>• Non-English language articles</li> </ul>
11.	Context	<p>In March 2025, an <a href="#">exceptional surveillance review</a> of the <a href="#">suspected cancer: recognition and referral guideline</a> (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.</p>
12.	Primary outcomes	<p>Accuracy of age thresholds for non-site specific cancer diagnosis within 6 months based on unexpected weight loss:</p> <ul style="list-style-type: none"> <li>• Sensitivity</li> </ul>

		<ul style="list-style-type: none"> <li>• Specificity</li> <li>• Positive predictive value</li> <li>• False negative rate</li> </ul> <p>The suggested thresholds for sensitivity and specificity are:</p> <ul style="list-style-type: none"> <li>• Sensitivity – upper 90, lower 10</li> <li>• Specificity – upper 80, lower 50</li> </ul>
13.	Secondary outcomes	Not applicable
14.	Data extraction (selection and coding)	<p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.</p>

15.	Risk of bias (quality) assessment	<p>Quality assessment of individual studies will be performed using the following checklists:</p> <ul style="list-style-type: none"> <li>• ROBIS tool for systematic reviews</li> <li>• QUADAS-2 for diagnostic accuracy studies</li> </ul> <p>The quality assessment will be performed by one reviewer, and this will be quality assessed by a senior reviewer.</p>
16.	Strategy for data synthesis	<p>Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively.</p> <p>For each reported age threshold, the 2-by-2 table (consisting of the number of true/false positives/negatives) will be extracted when possible. If more than two studies report 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 &gt;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.</p> <p>Where appropriate, meta-analysis of diagnostic test accuracy will be performed using the metaDTA app (<a href="https://crsu.shinyapps.io/MetaDTA/">https://crsu.shinyapps.io/MetaDTA/</a>). Cochrane Review Manager software may be used to help with visually displaying information.</p> <p>Sensitivity, specificity, positive predictive value and false negative rate 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.</p> <p>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</p>

		Evaluation (GRADE) toolbox' developed by the international GRADE working group: <a href="http://www.gradeworkinggroup.org/">http://www.gradeworkinggroup.org/</a>
17.	Analysis of sub-groups	<p>Evidence will be stratified by:</p> <ul style="list-style-type: none"> <li>• Cancer site</li> </ul> <p>Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes:</p> <ul style="list-style-type: none"> <li>• Groups identified in the equality and health inequalities assessment (EHIA) as outlined in the scope including: <ul style="list-style-type: none"> <li>○ socioeconomic and geographical factors</li> <li>○ age</li> <li>○ ethnicity</li> <li>○ disabilities</li> <li>○ people for whom English is not their first language or who have other communication needs.</li> <li>○ trans people</li> <li>○ non-binary people</li> </ul> </li> </ul> <p>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.</p> <p>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</p>

		consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.		
18.	Type and method of review	<input type="checkbox"/> Intervention <input checked="" type="checkbox"/> Diagnostic <input type="checkbox"/> Prognostic <input type="checkbox"/> Qualitative <input type="checkbox"/> Epidemiologic <input type="checkbox"/> Service Delivery <input type="checkbox"/> Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	20/08/2025		
22.	Anticipated completion date	01/10/2025		
23.	Stage of review at time of this submission	<b>Review stage</b>	<b>Started</b>	<b>Completed</b>
		Preliminary searches	<input type="checkbox"/>	<input type="checkbox"/>
		Piloting of the study selection process	<input type="checkbox"/>	<input type="checkbox"/>

		Formal screening of search results against eligibility criteria	<input type="checkbox"/>	<input type="checkbox"/>
		Data extraction	<input type="checkbox"/>	<input type="checkbox"/>
		Risk of bias (quality) assessment	<input type="checkbox"/>	<input type="checkbox"/>
		Data analysis	<input type="checkbox"/>	<input type="checkbox"/>
24.	Named contact	<p><b>5a. Named contact</b> NICE</p> <p><b>5b Named contact e-mail</b> <a href="mailto:SuspectedCancer@nice.org.uk">SuspectedCancer@nice.org.uk</a></p> <p><b>5e Organisational affiliation of the review</b> National Institute for Health and Care Excellence (NICE)</p>		
25.	Review team members	<ul style="list-style-type: none"> <li>• Robby Richey – Topic lead</li> <li>• Steven Barnes – Technical advisor</li> <li>• James Jagroo – Senior technical analyst</li> <li>• Yolanda Martinez - Technical analyst</li> <li>• James Hawkins - Health economist</li> <li>• Amy Finnegan - Information specialist</li> </ul>		

		<ul style="list-style-type: none"> <li>• Jon Littler – Project manager</li> </ul>
26.	Funding sources/sponsor	This systematic review is being completed by NICE which receives funding from the Department of Health and Social Care.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of <a href="#">Developing NICE guidelines: the manual</a> . Members of the guideline committee are available on the NICE website: <a href="#">[NICE guideline webpage]</a> .
29.	Other registration details	N/A
30.	Reference/URL for published protocol	<a href="#">[Give the citation and link for the published protocol, if there is one.]</a>
31.	Dissemination plans	<p>NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:</p> <ul style="list-style-type: none"> <li>• notifying registered stakeholders of publication</li> <li>• publicising the guideline through NICE's newsletter and alerts</li> <li>• 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.</li> </ul>
32.	Keywords	Age thresholds, non-site-specific symptoms, unexplained weight-loss, suspected cancer referral.

33.	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.
34.	Current review status	<input checked="" type="checkbox"/> Ongoing <input type="checkbox"/> Completed but not published <input type="checkbox"/> Completed and published <input type="checkbox"/> Completed, published and being updated <input type="checkbox"/> Discontinued
35..	Additional information	N/A
36.	Details of final publication	<a href="http://www.nice.org.uk">www.nice.org.uk</a>