National Institute for Health and Care Excellence

Suspected cancer: recognition and referral

[D] Evidence review (diagnostic) for unexplained weight loss as a non-site specific symptom in adults in primary care

NICE guideline NG12

Evidence underpinning recommendation 1.13.2

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Unexplained weight loss as a non-site specific symptom in adults in primary care

1.1 Review question

At what age thresholds should unexplained weight-loss be used to refer adults via a suspected cancer pathway?

1.1.1 Summary of the protocol

Table 1: Summary of the protocol

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[1] 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.
Diagnosis of interest	Cancer diagnosis Primary outcomes: Accuracy of age thresholds for non-site specific cancer diagnosis within 6 months based on unexpected[1] weight loss: • Sensitivity • Specificity • Positive predictive value • False negative rate
Study type	• Prospective cohort studies • Retrospective cohort studies • Diagnostic accuracy studies • Systematic reviews of these studies
1 Unexpected and unexplained both refer to a >5% mean weight loss within a 6-month period.	

For the full protocol see appendix A in the technical appendices document.

1.1.2 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol and in appendix J in the technical appendices document.

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

1.1.2.1 Search methods

The searches for the effectiveness evidence were run on 15 September 2025. The following databases were searched: Cochrane CDSR (Wiley), Embase (Ovid), Epistimonikos and Medline ALL (Ovid) Limits were applied to remove animal papers, non-English language papers and conference abstracts. Filters were used to limit to OECD countries. A date limit was applied from January 2015 to September 2025

The database searches were supplemented with additional search methods. Backward and forward citation searching were conducted on Citation Chaser (Lens.org) using a seed reference identified from the surveillance review.

The searches for the cost effectiveness evidence were run on 15 September 2025. The following databases were searched: Embase (Ovid), International Health Technology Assessment Database (INAHTA), Medline ALL (Ovid). Limits were applied to remove animal papers, non-English language papers and conference abstracts. Filters were used to limit to cost effectiveness studies. A date limit was applied from January 2015 to September 2025.

A NICE Senior Information Specialist (SIS) conducted the searches. The MEDLINE strategy was quality assured by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement. Further details and full search strategies for each database are provided in appendix B.

1.1.3 Diagnostic evidence

1.1.3.1 Included studies

Study selection

A systematic search was carried out to identify potentially relevant studies as detailed in appendix J in the technical appendices document. See appendix B in the technical appendices document for the literature search strategy. The study selection process is presented as a PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram in appendix C in the technical appendices document.

Two studies were included. For a summary of included studies see Table 2 and for full references see the list of included studies (section 1.1.12).

1.1.3.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion, are given in appendix I.

1.1.4 Summary of studies included in the diagnostic evidence

Table 2 Summary of studies included in the diagnostic evidence

Study details	Setting/Location/Funding	Population	Index test	Reference standard	Outcomes	Risk of bias Applicability
Nicholson 2024 N=117 769 (participants with no signs or symptoms) Study type: Retrospective cohort study Time between tests: 6 months	Setting: primary care Location: UK Funding source: Non-industry funded	≥18 years old people with at least one code for unexpected weight loss and at least 12 months of data before the first recorded unexpected weight loss code (index date) and without a cancer diagnosis before the index date Target condition: suspected cancer	Unexpected weight loss visit to primary care (a mean weight loss of ≥5% within a six month period)	Cancer diagnosis recorded in CPRD and linked NCRAS data within 6 months of index date	PPV	Low Directly applicable
Lee 2025 N=13 306	Setting: primary care Location: Australia Funding source: This study has been partly supported by funding from the Bupa	≥18 years old people with at least one presentation in primary care for unexpected weight loss during the	Unexpected weight loss visit to primary care	Cancer diagnosis recorded in Victorian Cancer Registry	PPV	Low Partially applicable

Study details	Setting/Location/Funding	Population	Index test	Reference standard	Outcomes	Risk of bias Applicability
Study type: Retrospective cohort study Time between tests: 6 months	Health Foundation; State Government of Victoria, Department of Health and the Victorian Comprehensive Cancer Centre Alliance	study period and without a previous diagnosis of cancer Target condition: suspected cancer		within 6 months of index test		

Abbreviations: CPRD: Clinical Practice Research Datalink; NCRAS: National Cancer Registrations and Analysis Service; PPV: positive predictive value

See appendix D for full evidence tables.

1.1.5 Summary of diagnostic evidence

Sensitivity is the proportion of those with the target condition who test positive for the condition, Specificity is the proportion of those without the target condition who test negative for the condition. The interpretation for the diagnostic ability of each index test was based on the agreed clinical decision-making thresholds. Sensitivity and specificity were rated as high, moderate or low based on the following:

- High: Point estimate is greater than or equal to the upper clinical decision-making threshold (≥90% for sensitivity and ≥80% for specificity).

- Moderate: Point estimate greater than or equal to the lower clinical decision-making threshold but lower than the upper clinical decision-making threshold (≥10% to <90% for sensitivity and ≥50% to <80% for specificity).
- Low: Point estimate is less than the lower clinical decision-making threshold (<10% for sensitivity and <50% for specificity).

A test with high sensitivity will classify more people as having the disease, thereby being good at ruling out the condition in people with a negative test result. A test with high specificity will classify fewer people as having the disease, thereby being good at ruling in the condition in people with a positive test result.

A minimum of 3 studies is required to estimate the parameters needed for bivariate meta-analysis. As only 2 studies have been included no meta-analysis was carried out.

Table 3 Summary of findings for diagnostic accuracy of 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	Sample size[1]	Effect size (95% CI)[2]	PPV (%)	FNR[2] (%)	Certainty	Interpretation of diagnostic ability
1 (Nicholson 2024) **Age group**: 18 to 39	37 574	Sensitivity: NR Specificity: NR	0.14 (0.10 to 0.18)	NR	LOW	Low certainty. There is a 0.14% probability that people 18 to 39 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Nicholson 2024) **Age group**: 40 to 49	17 489	Sensitivity: NR Specificity: NR	0.65 (0.53 to 0.78)	NR	LOW	Low certainty. There is a 0.65% probability that people 40 to 49 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.

1 (Nicholson 2024) **Age group**: 50 to 59	17 194	Sensitivity: NR Specificity: NR	2.15 (1.93 to 2.37)	NR	LOW	Low certainty. There is a 2.15% probability that people 50 to 59 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Nicholson 2024) **Age group**: 60 to 69	15 482	Sensitivity: NR Specificity: NR	4.82 (4.49 to 5.17)	NR	LOW	Low certainty. There is a 4.82% probability that people 60 to 69 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Nicholson 2024) **Age group**: 70 to 79	15 823	Sensitivity: NR Specificity: NR	7.17 (6.78 to 7.59)	NR	LOW	Low certainty. There is a 7.17% probability that people 70 to 79 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Nicholson 2024) **Age group**: 80 or older	14 207	Sensitivity: NR Specificity: NR	6.29 (5.90 to 6.70)	NR	LOW	Low certainty. There is a 6.29% probability that people 80 years and older with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.

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.

Table 4 Summary of findings for diagnostic accuracy of 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	Sample size	Effect size (95% CI)[1]	PPV (%)	FNR[1] (%)	Certainty	Interpretation of diagnostic ability
1 (Lee 2025) **Age group**: 40 to 49	1 916	Sensitivity: NR Specificity: NR	0.26 (0.09 to 0.61)	NR	VERY LOW	Very low certainty. There is a 0.26% probability that people 40 to 49 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Lee 2025) **Age group**: 50 to 59	1 823	Sensitivity: NR Specificity: NR	1.77 (1.21 to 2.49)	NR	VERY LOW	Very low certainty. There is a 1.77% probability that people 50 to 59 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Lee 2025) **Age group**: 60 to 69	1 563	Sensitivity: NR Specificity: NR	2.19 (1.52 to 3.05)	NR	VERY LOW	Very low certainty. There is a 2.19% probability that people 60 to 69 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Lee 2025) **Age group**: 70 to 79	1 510	Sensitivity: NR Specificity: NR	4.41 (3.43 to 5.58)	NR	VERY LOW	Very low certainty. There is a 4.41% probability that people 70 to 79 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Lee 2025) **Age group**: 80 or older	2 351	Sensitivity: NR Specificity: NR	3.94 (3.18 to 4.82)	NR	VERY LOW	Very low certainty. There is a 3.94% probability that people 80 years and older with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.

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.

Table 5 Summary of findings for diagnostic accuracy of 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	Sample size[1]	Effect size (95% CI)[2]	PPV (%)	FNR[2] (%)	Certainty	Interpretation of diagnostic ability
1 (Nicholson 2024) **Age group**: 18 to 39	22 508	Sensitivity: NR Specificity: NR	0.11 (0.07 to 0.16)	NR	LOW	Low certainty. There is a 0.11% probability that women 18 to 39 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Nicholson 2024) **Age group**: 40 to 49	8 704	Sensitivity: NR Specificity: NR	0.48 (0.35 to 0.65)	NR	LOW	Low certainty. There is a 0.48% probability that women 40 to 49 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Nicholson 2024) **Age group**: 50 to 59	7 969	Sensitivity: NR Specificity: NR	1.47 (1.22 to 1.76)	NR	LOW	Low certainty. There is a 1.47% probability that women 50 to 59 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Nicholson 2024) **Age group**: 60 to 69	7 249	Sensitivity: NR Specificity: NR	3.57 (3.16 to 4.03)	NR	LOW	Low certainty. There is a 3.57% probability that women 60 to 69 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Nicholson 2024) **Age group**: 70 to 79	8 103	Sensitivity: NR Specificity: NR	4.89 (4.43 to 5.38)	NR	LOW	Low certainty. There is a 4.89% probability that women 70 to 79 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Nicholson 2024)	8 876	Sensitivity: NR	4.48 (4.06 to 4.94)	NR	LOW	Low certainty.

Age group: 80 or older		Specificity: NR				There is a 4.48% probability that women 80 years and older with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.

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.

Table 6 Summary of findings for diagnostic accuracy of 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	Sample size	Effect size (95% CI)[1]	PPV (%)	FNR[1] (%)	Certainty	Interpretation of diagnostic ability
1 (Lee 2025) **Age group**: 40 to 49	NR[2]	Sensitivity: NR Specificity: NR	0.08 (0.00 to 0.44)	NR	VERY LOW	Very low certainty. There is a 0.08% probability that women 40 to 49 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Lee 2025) **Age group**: 50 to 59	NR[2]	Sensitivity: NR Specificity: NR	1.59 (0.95 to 2.51)	NR	VERY LOW	Very low certainty. There is a 1.59% probability that women 50 to 59 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.

1 (Lee 2025) **Age group**: 60 to 69	NR[2]	Sensitivity: NR Specificity: NR	1.61 (0.88 to 2.69)	NR	VERY LOW	Very low certainty. There is a 1.61% probability that women 60 to 69 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Lee 2025) **Age group**: 70 to 79	NR[2]	Sensitivity: NR Specificity: NR	2.74 (1.76 to 4.05)	NR	VERY LOW	Very low certainty. There is a 2.74% probability that women 70 to 79 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Lee 2025) **Age group**: 80 or older	NR[2]	Sensitivity: NR Specificity: NR	3.00 (2.20 to 3.99)	NR	VERY LOW	Very low certainty. There is a 3.00% probability that women 80 years and older with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.

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.

Table 7 Summary of findings for diagnostic accuracy of 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	Sample size[1]	Effect size (95% CI)[2]	PPV (%)	FNR[2] (%)	Certainty	Interpretation of diagnostic ability
1 (Nicholson 2024) **Age group**: 18 to 39	15 066	Sensitivity: NR Specificity: NR	0.18 (0.12 to 0.26)	NR	LOW	Low certainty. There is a 0.18% probability that men 18 to 39 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Nicholson 2024)	8 785	Sensitivity: NR	0.81 (0.63 to 1.02)	NR	LOW	Low certainty.

Age group: 40 to 49		Specificity: NR				There is a 0.81% probability that men 40 to 49 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Nicholson 2024) **Age group**: 50 to 59	9 225	Sensitivity: NR Specificity: NR	2.73 (2.41 to 3.09)	NR	LOW	Low certainty. There is a 2.73% probability that men 50 to 59 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Nicholson 2024) **Age group**: 60 to 69	8 233	Sensitivity: NR Specificity: NR	5.93 (5.43 to 6.46)	NR	LOW	Low certainty. There is a 5.93% probability that men 60 to 69 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Nicholson 2024) **Age group**: 70 to 79	7 720	Sensitivity: NR Specificity: NR	9.57 (8.93 to 10.25)	NR	LOW	Low certainty. There is a 9.57% probability that men 70 to 79 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Nicholson 2024) **Age group**: 80 or older	5 331	Sensitivity: NR Specificity: NR	9.30 (8.54 to 10.12)	NR	LOW	Low certainty. There is a 9.30% probability that men 80 years and older with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.

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.

Table 8 Summary of findings for diagnostic accuracy of 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	Sample size	Effect size (95% CI)[1]	PPV (%)	FNR[1] (%)	Certainty	Interpretation of diagnostic ability
1 (Lee 2025) **Age group**: 40 to 49	NR[2]	Sensitivity: NR Specificity: NR	0.63 (0.17 to 1.61)	NR	VERY LOW	Very low certainty. There is a 0.63% probability that men 40 to 49 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Lee 2025) **Age group**: 50 to 59	NR[2]	Sensitivity: NR Specificity: NR	2.07 (1.13 to 3.45)	NR	VERY LOW	Very low certainty. There is a 2.07% probability that men 50 to 59 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Lee 2025) **Age group**: 60 to 69	NR[2]	Sensitivity: NR Specificity: NR	2.94 (1.80 to 4.50)	NR	VERY LOW	Very low certainty. There is a 2.94% probability that men 60 to 69 years old with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.
1 (Lee 2025) **Age group**: 70 to 79	NR[2]	Sensitivity: NR Specificity: NR	6.79 (4.93 to 9.06)	NR	VERY LOW	Very low certainty. There is a 6.79% probability that men 70 to 79 years old with unexpected weight loss will have a cancer

						diagnosis within six months following a referral via a suspected cancer pathway.
1 (Lee 2025) **Age group**: 80 or older	NR[2]	Sensitivity: NR Specificity: NR	5.75 (4.22 to 7.61)	NR	VERY LOW	Very low certainty. There is a 5.75% probability that men 80 years and older with unexpected weight loss will have a cancer diagnosis within six months following a referral via a suspected cancer pathway.

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.

See **appendix F** for full GRADE tables. No data was found on the rest of subgroups listed in the protocol: cancer site, socioeconomic and geographical factors, ethnicity, disabilities, people for whom English is not their first language or who have other communication needs, trans people, and non-binary people.

1.1.6 Economic evidence

1.1.6.1 Included studies

A search was performed to identify published economic evaluations of relevance to this review question. See the literature search strategy in **appendix B** in the technical appendices document.

No economic studies were identified which were applicable to this review question. (see economic study selection flow chart in **appendix G** in the technical appendices document).

1.1.6.2 Excluded studies

No economic studies were reviewed at full text and excluded from this review.

1.1.7 Economic model

A decision analytic economic model was developed to assess the costs and consequences of different age-related referral thresholds in people with unexplained weight loss with no other signs or symptoms. A summary of the guideline model characteristics is provided in Table 11.

The costing analysis compared a baseline scenario representing NICE's current recommendations for referral, to two alternative referral strategies. Current recommendations are to refer everyone presenting to primary care with unexplained weight loss for investigation. The underlying evidence in the analysis is based on the numbers in the work by Nicholson and colleagues (2024), focusing on the group with no other signs or symptoms.

- In the first analysis, the baseline scenario was compared to a scenario where people over the age of 60 are referred for investigation. In the Nicholson (2024) study, the mean PPV and confidence interval around PPV are greater than 3 in these age groups, so there is more certainty of the association between unexplained weight loss and cancer.

- In a second analysis, the baseline scenario was compared to a scenario where men over 50 and women over 60 are referred for

investigation. In the Nicholson (2024) study, the confidence interval for PPV includes values over 3 for these age groups, but the mean PPV may be less than 3. There is less certainty of the association between unexplained weight loss and cancer.

To estimate the number of referrals for each age band, and subsequently the potential avoided referrals in each scenario, numbers of cases of unexplained weight loss provided by Nicholson (2024) were adjusted to reflect the annual number of cases in England (Table 9). The CRPD dataset on which the Nicholson analysis was based represents 28% of the English population (in mid-2024, when the analysis was undertaken), so this was scaled up to provide representative numbers for England. The dataset was further adjusted to only include those who are eligible for data linkage with other datasets in order to perform the analysis (74%). The analysis included data from a 20-year period, so the numbers were converted to an annual rate, assuming an equal rate of cancer and presentation with unexplained weight loss to primary care over the time frame of the dataset.

Table 9: Number of cases of unexplained weight loss

Age group	Cases of UWL (Nicholson) [1]		Cases of UWL (estimated) [2]	
	Female	Male	Female	Male
18-39	22,508	15,066	5,512	3,689
40-49	8,704	8,785	2,131	2,151
50-59	7,969	9,225	1,951	2,259
60-69	7,249	8,233	1,775	2,016
70-79	8,103	7,720	1,984	1,890
>80	8,876	5,331	2,174	1,305

Abbreviations: UWL, unexplained weight loss.
1. Number of cases of unexplained weight loss in the CPRD dataset between 2000-2020. 2. Number of cases of unexplained weight loss estimated for England each year.

People with unexplained weight loss can be referred to Acute Diagnostic Oncology Clinics (ADOC) by their GP, which are part of the National Rapid Diagnostic Centre programme, where there is a suspicion of a new cancer diagnosis but the patient does not meet an alternative tumour specific

pathway. In order to be referred to ADOC, patients must have investigations in primary care consisting of a chest x-ray, faecal immunochemical test (FIT), and blood tests. The unit costs of these primary care tests were obtained from NHS Cost Collection (2024), and the total cost of tests per person was estimated as £54 per person (Table 10). This cost was combined with the number of avoided referrals to estimate the potential cost savings in each scenario. In a costing scenario analysis, the proportion of people who receive investigation in clinical practice was arbitrarily assumed to be 50%, instead of 100%.

Table 10: Unit costs of primary care tests to investigate unexplained weight loss

Item	Cost	Code
Chest x-ray	£35	Plain Film. DADS, Service Code 800 Clinical Oncology Service
FIT	£6	Clinical biochemistry. DAPS, Service Code 800 Clinical Oncology Service
Blood test	£7	Haematology. DAPS, Service Code 800 Clinical Oncology Service
	£6	Phlebotomy. DAPS, Service Code 999 Unknown

Abbreviations: DAPS, direct access pathology service; DADS, direct access diagnostic service; FIT, Faecal Immunochemical Test.
Source: NHS Cost Collection (2024)

The impact on patient outcomes was estimated as the number of potentially missed cancers in each scenario, which would occur in age groups where they no longer receiving investigations. This was estimated using the PPV for each gender and age band, where PPV represents the probability that someone with unexpected weight loss will have a cancer diagnosis within six months.

The economic model evidence summary and a description of the costing analysis results is shown in Table 12. The analysis estimated that referring people over the age of 60 instead of all people with unexplained weight loss alone would be associated with cost savings of just under £1M per year in England. Referring men over 50 and women over 60 with unexplained weight loss alone would be associated with slightly lower cost savings per year.

Assuming that 50% of people under 60 years would usually receive further investigation, the costing analysis estimated that the cost savings could be around £0.5M per year in England.

However, avoided investigations were also associated with missed cancer diagnoses. Referring people over the age of 60 instead of all people with unexplained weight loss alone would be associated with 131 cases of cancer missed, per year in England. Referring men over 50 and women over 60 with unexplained weight loss alone would be associated with 69 cases of cancer missed, per year in England.

Table 11: Summary of characteristics of the guideline economic model

Study design and type of analysis	Population	Interventions and comparators	Perspective	Primary outcome	Time horizon
Study design: Decision analytic model Type of analysis: cost analysis	People with unexplained weight loss, and no other signs and symptoms for suspected cancer	(1) Refer everyone with unexplained weight loss for investigation (current recommendation) (2) Refer people over 60 with unexplained weight loss for investigation (3) Refer men over 50 and women over 60 with unexplained weight loss for investigation	NHS/PSS	Investigations avoided, cancers missed	1 year

Abbreviations: PSS: personal social services

Table 12: Guideline economic model evidence summary table

Applicability and limitations	Incremental costs	Incremental effects	Cost effectiveness	Uncertainty	Economic evidence statement
Directly applicable Potentially serious limitations[1]	Costs due to investigations per year in England: (2) vs (1): -£955,468 (3) vs (1): -£833,484	Avoided investigations per year in England: (2) vs (1): 17,694 (3) vs (1): 15,435	NA	Cost due to investigations per year in England: scenario where 50% patients get investigation in practice (2) vs (1): -£477,734	• Cost-effectiveness unclear (different outcome measure used)

Applicability and limitations	Incremental costs	Incremental effects	Cost effectiveness	Uncertainty	Economic evidence statement
	Cost year: 2025	Missed cancers per year in England: (2) vs (1): 131 (3) vs (1): 69		(3) vs (1): -£416,742	

1. 1-year time frame, quality-adjusted life years (QALYs) not estimated, probabilistic analysis not undertaken

1.1.8 Committee discussion and interpretation of the evidence

1.1.8.1 Is the problem a priority

The NICE guideline on suspected cancer has recommendations on several types of cancer with specific factors for referral where age thresholds and weight loss are some of those factors. However, the recommendation on unexplained weight loss as a non-site-specific symptom does not have any age thresholds. The potential benefit of age thresholds for unexplained weight loss could be to minimise the number of people without cancer who get inappropriately referred whilst maximising the number of people with cancer who get appropriately referred.

The committee agreed that positive predictive values were the primary diagnostic accuracy measures for this review. Positive predictive values provide information on the probability of having a diagnosis of cancer within six months following a referral via a suspected cancer pathway in a person who had more than 5% mean unexplained weight loss within a 6-month period before the referral. Sensitivity, specificity, and false negative rate were also primary diagnostic measures for this review, but the included studies did not report evidence on these measures.

The committee was concerned that unexplained weight loss on its own was rare. They were reassured that the recommendation on unexplained weight loss also recommends carrying out assessment for additional symptoms, signs or findings. This guideline also contains recommendations 1.15.1 and 1.15.2 on safety netting within the guideline on suspected cancer.

1.1.8.2 Test accuracy and certainty in the test accuracy

The committee agreed to retain from the previous guideline a positive predictive value of 3% or above to make recommendations, this has been consistently used within this guideline as a threshold at which the advantages of a suspected cancer pathway referral in those adults with cancer outweighed the disadvantages to those adults without.

The evidence was rated as very low to low certainty. The evidence was assessed for the risk of bias and directness using the QUADAS-2 tool. The risk of bias was considered to be low for the included studies. The evidence from one of the included studies (Lee et al. 2025) was downgraded for indirectness because the index test did not fully represent the one in the protocol. The study did not have thresholds for unexpected weight loss (this means that not all participants had more than 5% mean unexpected weight loss within 6 months in the study). Additionally, Lee et al. (2025) did not report whether participants had signs and symptoms as well as unexpected weight loss. This could have affected the accuracy of the index test because it was not possible to separate participants with only unexpected weight loss from participants with additional signs and symptoms. Based on these limitations, Lee et al. (2025) was reported separately. The evidence was downgraded for inconsistency because the included studies could not be combined. The included studies only reported positive predictive values and did not report sensitivity, specificity, false negative rate or any data to calculate these outcomes. The evidence was downgraded for imprecision because positive predictive values can not be used to assess imprecision in GRADE.

1.1.8.3 Balance of effects

The evidence showed that positive predictive values of 3% or above were seen in people 60 years and older who had a record of unexpected weight loss (more than 5% mean weight loss within a 6-month period) in primary care and who also had a cancer diagnosis record within 6 months of the primary care visit. The committee noticed that although positive predictive values were higher for men compared to women all the positive predictive values of 3% or above, which was the agreed threshold for recommending an urgent referral for suspected cancer, were in people 60 years and older, irrespective of their sex. They agreed to add this age for all people and unexplained weight loss thresholds to the existing recommendation. The certainty of the evidence was low but it was from a well conducted study and directly applicable to the UK, and with a sufficiently big sample size (n=117,769). Although the PPVs were different in the two studies (due to the lower prevalence in Austrailia) the

change in PPV across the same 10 year age groups was similar in both included studies. The committee agreed that a potential benefit of this recommendation would be to identify those people with cancer more rapidly.

1.1.8.4 Resources and cost-effectiveness

There was no published economic evidence to support the committee's decision making. Therefore, the committee considered the potential cost savings per year in England that could be realised through reducing the amount of tests conducted in primary care when someone presents to their GP with unexplained weight loss. They balanced this against the potential number of missed cancer cases if people presenting with unexplained weight loss were not investigated further.

The cost analysis, assuming that further investigations in primary care would comprise a direct access chest x-ray, faecal immunochemical test (FIT) and a complete blood test, estimated that referring people over the age of 60 instead of all people with unexplained weight loss alone would be associated with cost savings to the NHS of just under £1M per year in England that are due to a reduction in the number of investigations. This assumes that everyone presenting with unexplained weight loss alone would receive further investigation. The committee explained that these tests are required for referral to ADOC, and that the majority of people over 50 years of age (approximately 90% based on their experience) would usually have these tests conducted. However, given that the incidence of cancer in people under 60 is known to be much lower and non-cancer pathologies are more common causes of unexplained weight loss, they explained that people in this age group may not usually receive these tests or it might take longer to refer them. Assuming that 50% of people under 60 years would usually receive further investigation, the costing analysis estimated that the cost savings could be around £0.5M per year in England.

However, not investigating people under the age of 60 who present with with unexplained weight loss alone may result in missed cancer diagnoses. The committee acknowledged the results of the costing analysis and

considered their own experience, and noted how the incidence of cancer in this age group presenting with unexplained weight loss alone is rare.

As such, the committee's recommendation to investigate unexplained weight loss in people over the age of 60 are associated with a saving of NHS resources, as people should only be investigated further when they are over the age of 60 where there is good evidence that this symptom is associated with underlying cancer. The committee agreed that the use of urgent investigation or a suspected cancer pathway referral or a non-specific symptoms pathway referral should be made, and that the choice of and use of both these referral pathways is related to the person presenting to primary care and clinical judgement. There was not expected to be additional resources through missing cancers in people under the age of 60, due to the low incidence of cancer in this age group. The committee explained that unexplained weight loss is generally more indicative of advanced (stage 4) cancer, which is less likely to be treatable. 'Safety netting' recommendations elsewhere in the guideline means that if they develop additional symptoms suggestive of cancer then they will be detected, minimising the risk that their cancer would require additional resources to manage or have worse outcomes.

1.1.8.5 Equity

The committee acknowledged adults 18 to 59 years of age are not covered by the updated recommendation on unexplained weight loss as a non-site-specific symptom. They were reassured that the guideline on suspected cancer has guidance on ‘safety netting’ recommendations to consider a review for people with any symptom associated with increased cancer risk who do not meet the criteria for referral or investigative action (see recommendation 1.15.2). These ‘safety netting’ recommendations were made to identify people with any symptom that is associated with an increased risk of cancer, but who do not meet the criteria for referral or other investigative action. The committee were aware that there are patient safety initiatives within the NHS to improve diagnosis and treatment regardless of the person’s age (for example Jess’s Rule).

1.1.8.6 Feasibility

Unexplained weight loss is routinely recorded in primary care. However, it might take time to diseminate to general practices the new age threshold recommended here for referral.

1.1.9 Recommendations supported by this evidence review

This evidence review supports recommendation 1.13.2.

1.1.10 References

1.1.10.1 Effectiveness evidence

Lee, Alex, de Mendonca, Lucas, McCarthy, Damien et al. (2025) Primary care patients presenting with unexpected weight loss in Australian general practices: replication of a diagnostic accuracy study. BMJ open 15(7): e104690

Nicholson BD, Virdee P, Aveyard P et al. (2024) Prioritising primary care patients with unexpected weight loss for cancer investigation: diagnostic accuracy study (update). BMJ (Clinical research ed.) 387: e080199

1.1.10.2 Economic evidence

None

1.1.11 Miscellaneous

None