National Institute for Health and Care Excellence

Final

Thyroid cancer: assessment and management

[B] Evidence review for indications for blood tests

NICE guideline NG230

Evidence reviews underpinning recommendations 1.2.1 to 1.2.5 and the research recommendation on thyroid peroxidase antibody testing in the NICE guideline

December 2022

Final

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Review question

1.1.1 What is the clinical and cost effectiveness of 1) measurement of thyroid peroxidase antibody (TPO), and 2) measurement of serum calcitonin, at initial presentation?

1.1.2 Introduction

This review seeks to assess the efficacy and cost-effectiveness of two commonly used blood tests, thyroid peroxidase antibody (TPO) and serum calcitonin in people with suspected thyroid cancer.

Thyroid Peroxidase (TPO) is a major thyroid microsomal antigen corresponding to anti-microsomal autoantibodies in thyroid autoimmune diseases such as Hashimoto's thyroiditis. The identification of the thyroid peroxidase (TPO) as the main antigen of the thyroid microsomal fraction has enabled the development of a sensitive and specific assay for detection of the corresponding autoantibodies. Serological and clinical information regarding the TPO levels helps with the cytological diagnosis, especially while interpreting indeterminate /Thy3a cytology in an ultrasound (US)/clinically non-suspicious thyroid nodule.

Calcitonin is a polypeptide hormone secreted by the parafollicular cells (also known as C cells) of the thyroid gland. Calcitonin is a sensitive and specific tumour marker for diagnosis and follow up of C cell disorder, including C cell hyperplasia (CCH) and medullary thyroid carcinoma (MTC). Whilst serum calcitonin measurement helps with early detection of medullary thyroid carcinoma in patients with suspicious thyroid nodules, it can also be falsely elevated in some other conditions. Awareness of serum calcitonin levels helps with the cytological diagnosis of medullary thyroid carcinoma which can occasionally be challenging on fine needle aspiration cytology (FNAC) specimens.

1.1.3 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	People aged 16 or over with clinical symptoms or signs suggesting possible thyroid cancer.
Interventions	• Thyroid antibody tests ○ Thyroid peroxidase antibody test (TPO) • Calcitonin
Comparison	Usual care (simply not doing the named test as part of the investigation of the nodule)
Outcomes	• Mortality • Quality of life (any validated scores) • Local cancer progression • Incidence of distant metastases • Cancer recurrence • Change in management
Study design	RCTs and SRs

1.1.4 Methods and process

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

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

1.1.5 Effectiveness evidence

1.1.5.1 Included studies

No relevant clinical studies comparing thyroid antibody tests or calcitonin tests with usual care were identified.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.5.2 Excluded studies

Twelve studies were identified for full text eligibility assessment. Of these, 2 were narrative reviews and 5 were systematic reviews. References were checked for potential inclusion however none were RCTs. Of the remaining 5 studies, all 5 were excluded as they were non-randomised studies.

See the excluded studies list in Appendix I.

1.1.6 Summary of studies included in the effectiveness evidence

No evidence was identified.

1.1.7 Summary of the effectiveness evidence

No evidence was identified.

1.1.8 Economic evidence

1.1.8.1 Included studies

No health economic studies were included.

1.1.8.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.1.9 Summary of included economic evidence

None.

1.1.10 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.11 Economic evidence statements

No relevant economic evaluations were identified.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1 The outcomes that matter most

Protocol-specified outcomes of mortality, quality of life, local cancer progression, incidence of distant metastases, and cancer recurrence were all deemed critical, and were therefore of equal importance in decision-making. The protocol stated that the longest follow-up time point available should be used.

1.1.12.2 The quality of the evidence

No evidence was found for this question, and so recommendations were made on the basis of consensus.

1.1.12.3 Benefits and harms

In the absence of review evidence, the committee used consensus to discuss benefits and harms and to form recommendations. This was done for each of the two parts of the question separately, and the discussion below has been separated accordingly.

Calcitonin testing

The committee discussed how calcitonin testing is used to detect medullary thyroid cancer (MTC). Although used extensively in certain parts of Europe as part of the normal assessment of any thyroid nodule, it tends to be far less used in the UK because of the cost of the test and an awareness of the high rates of false positives, that can cause serious harm from unnecessary treatments. For example, the committee were aware of some studies that suggest a borderline raised calcitonin level can spuriously occur because of Hashimoto's disease or can arise because of certain drugs, and the subsequent over-treatment due to such false-positive results may lead to high levels of morbidity. The relatively high level of false positive results is made more important by the relative rarity of medullary cancer, with only 100-150 new cases of MTC per year in the UK. This means that the positive predictive value of calcitonin testing is likely to be very low indeed. The committee agreed that for most patients it would therefore be more useful, and less harmful, not to use calcitonin testing, but to rely upon other methods of assessment such as FNAC instead.

However, it was also agreed that there were some patients for whom calcitonin testing would be highly useful, where the benefits might exceed the harms. These would include people at higher risk of medullary cancer, where the risks of false negatives would outweigh the risks of false positives at a population level. Such people at higher risk would include, but would not be restricted to: those with a family history of medullary cancer; those with multiple endocrine neoplasms; those with suspicion or diagnosis of medullary cancer as a result of cytopathology, core biopsy, or other histopathology; and those with C cell hyperplasia.

Therefore, the recommendation was made that calcitonin should not be tested routinely, unless there were prior reasons to suspect medullary thyroid cancer.

Thyroid peroxidase antibody (TPO)

The committee discussed how TPO test results can facilitate interpretation of FNAC results. For example, if the FNAC result is suggestive of benign thyroiditis then a positive TPO may help to confirm this. In addition, a positive TPO may allow the downgrading of an indeterminate result (such as a Thy3a or 3f) to a benign reading (Thy2). Therefore, in cases

where there is uncertainty about the FNAC result, the committee agreed that TPO has clinical use because of its capacity to facilitate interpretation, and it should be utilised in that situation. However, in cases where there is little uncertainty about the FNAC result, the benefits of TPO testing were not regarded by the committee as sufficient to justify the practice. Therefore, the recommendation was made that TPO should not be routinely measured, but could be usefully used when there was indeterminate cytopathology.

1.1.12.4 Cost effectiveness and resource use

No health economics evidence was found for this question.

This question can essentially be divided into two different questions: Calcitonin test and Thyroid peroxidase antibody (TPO).

Calcitonin tests are routinely offered in some European countries as it is effective in detecting medullary cancer, a rare form of thyroid cancer that may be harder to diagnostic otherwise. Its high cost and the rare prevalence of medullary cancers (around 100-150 of new cases per year in the UK) makes its routine use unlikely to be cost effective. However, the committee agreed that for people at high risk of medullary cancer the benefits outweigh the harms. Hence, the committee made the recommendation not to offer calcitonin tests routinely unless family history and other patient's characteristics raise suspicion of a medullary cancer. This targeted approach reflects current practice in the UK as BTA guidelines do not recommend calcitonin routinely if medullary thyroid cancer is not suspected. Hence, this recommendation is not expected to lead to any significant resource impact. Moreover, this is likely to represent a cost-effective use of NHS resource as the test, although expensive, would be offered only to people with a high probability of needing it.

The committee argued that antibody tests may be helpful in providing additional elements during MDT discussions for some cytologies of difficult interpretation. This could avoid people with Hashimoto's disease, for instance, undergoing unnecessary surgery for thyroid cancer following a false positive FNA cytology. Therefore, the committee made a consider recommendation for TPO when interpreting indeterminate cytopathology. This should have a limited NHS resource use and enhance the overall accuracy of the diagnosis, thus leading to fewer unnecessary thyroidectomies and ultimately improving the efficiency of the NHS.

1.1.12.5 Other factors the committee took into account

In order to consider the pathway in full, the committee discussed the other initial blood tests that should be done at initial presentation, whilst acknowledging that they were not in the scope of the review question. Thyroid function tests (usually comprising TSH, thyroxine [T4] and sometimes tri-iodothyronine [T3]) were regarded as a vital component of initial testing as they assist in interpretation of other tests. In their opinion testing for thyroglobulin antibodies or thyroglobulin at initial presentation was not useful and should not be practiced.

A research recommendation was not made for calcitonin testing as the committee agreed that appropriately rigorous studies (RCTs) would unlikely be practical since the number of people eventually diagnosed with medullary cancer would be so low that very large initial samples would be needed. Together with the committee's view that their confidence in the validity of their consensus recommendations would probably be shared by external parties, this made it seem highly unlikely that a research recommendation on calcitonin would be followed up.

However, as TPO tests have the potential to improve interpretation of FNAC and increase its accuracy, a research recommendation was made on this test.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.2.1 to 1.2.5 and the research recommendation on thyroid peroxidase antibody testing.

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Appendices

Appendix A – Review protocols

1.1.13.1 Review protocol for Blood tests

Field	Content
PROSPERO registration number	CRD42021283297
Review title	The clinical and cost-effectiveness of 1) measurement of thyroid peroxidase antibody, and 2) measuring serum calcitonin, at initial presentation.
Review question	What is the clinical and cost effectiveness of 1) measurement of thyroid peroxidase antibody (TPO), and 2) measurement of serum calcitonin, at initial presentation?
Objective	To assess the efficacy and cost-effectiveness of two commonly used blood tests. This is two questions encapsulated into one protocol
Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE

Field	Content
	Searches will be restricted by: • English language • Human studies • Letters and comments are excluded. Other searches: • Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
Condition or domain being studied	Thyroid cancer
Population	Inclusion: People aged 16 or over with clinical symptoms or signs suggesting possible thyroid cancer.

Field	Content
	Exclusion: Children under 16
Intervention	1) thyroid antibody tests • Thyroid peroxidase antibody test (TPO) 2) Calcitonin These interventions will NOT be compared to each other. Each is to be compared separately to usual care (thus making 2 essentially separate questions).
Comparator	Usual care (simply not doing the named test as part of the investigation of the nodule)
Types of study to be included	RCTs and SRs There will be no drop-down to NRS if no RCTs exist.
Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
Context	Measurement of serum thyroid antibodies and calcitonin are both routinely performed as blood tests at initial presentation. However, it is unclear whether these tests are clinically beneficial, or whether they are cost effective. This review therefore aims to find out the clinical and cost effectiveness of these tests
Primary outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical:

Field	Content
(critical outcomes)	• mortality • quality of life (any validated scores) • local cancer progression • incidence of distant metastases • cancer recurrence • change in management Time of follow up: longest available. No minimum time selected.
Secondary outcomes (important outcomes)	Not applicable
Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will

Field	Content
	be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0)

Field	Content
Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.

Field	Content
Analysis of sub-groups	<u>Stratification</u> None <u>Sub-grouping</u> If serious or very serious heterogeneity (I2>50%) is present within any stratum, sub-grouping will occur according to the following strategies: • Family history (Y/N)
Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
Language	English
Country	England
Named contact	**Named contact** National Guideline Centre **Organisational affiliation of the review**

Field	Content
	National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
Review team members	From the National Guideline Centre: Carlos Sharpin, Guideline lead Mark Perry, Senior systematic reviewer Alfredo Mariani, Health economist Lina Gulhane, Head of Information specialists
Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
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-ng10150/documents

Field	Content
Other registration details	N/A
Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=283297
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	Thyroid cancer
Details of existing review of same topic by same authors	N/A
Additional information	N/A

Field	Content
Details of final publication	www.nice.org.uk

1.1.13.2 Review protocol health economic evidence

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see Appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2005, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[4] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion**

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2005 or later but that depend on unit costs and resource data entirely or predominantly from before 2005 will be rated as ‘Not applicable’.
- Studies published before 2005 will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health 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.

Appendix B – Literature search strategies

The literature searches for these reviews are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual, 2014 (updated 2020) https://www.nice.org.uk/process/pmg20/chapter/identifying-the-evidence-literature-searching-and-evidence-submission.

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

1.2 Blood Tests

Clinical literature search strategy

This literature search strategy was used for the following review:

- What is the clinical and cost effectiveness of 1) measurement of thyroid peroxidase antibody (TPO), and 2) measurement of serum calcitonin, at initial presentation?

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 2: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	1946 – 13 January 2022	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, children) English language
Embase (OVID)	1974 – 13 January 2022	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts, children) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 12 of 12, December 2021 Cochrane Central Register of Controlled Trials to Issue 12 of 12, December 2021	Exclusions (clinical trials, conference abstracts)

Medline (Ovid) search terms

1.	exp Thyroid Neoplasms/
2.	(thyroid adj3 (cancer* or carcinom* or microcarcinoma* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or node* or nodul* or nodal or lump* or papillar* or swollen or swell* or anaplastic or sarcoma* or cyst* or malignan*)).ti,ab.
3.	DTC.ti,ab.
4.	((papillar* or anaplastic) adj2 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nodul* or node* or lump*)).ti,ab.
5.	or/1-4
6.	letter/
7.	editorial/
8.	news/
9.	exp historical article/
10.	Anecdotes as Topic/
11.	comment/
12.	case report/
13.	(letter or comment*).ti.
14.	or/6-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animals/ not humans/
18.	exp Animals, Laboratory/
19.	exp Animal Experimentation/
20.	exp Models, Animal/
21.	exp Rodentia/
22.	(rat or rats or mouse or mice or rodent*).ti.
23.	or/16-22
24.	5 not 23
25.	limit 24 to english language
26.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
27.	25 not 26
28.	Calcitonin/
29.	(calcitrin* or calcitoni* or cibalcin* or thyreocalcitonin* or thyrocalcitonin*).ti,ab,kf.
30.	exp Antibodies/
31.	exp Autoantibodies/
32.	Iodide Peroxidase/
33.	((antithyroid or thyroid or iodide) adj3 (antibod* or autoantibod*)).ti,ab,kf.
34.	((iodide or thyroid or antithyroid or autoantibod* or antibod*) adj3 (peroxidase* or oxidoreductase*)).ti,ab,kf.
35.	(thyroperoxidase* or deiodinase*).ti,ab,kf.
36.	(iodotyrosine adj2 (deiodase* or deiodinase* or desiodase*)).ti,ab,kf.
37.	(TPO or TPOAb).ti,ab,kf.
38.	or/28-37
39.	27 and 38
40.	randomized controlled trial.pt.
41.	controlled clinical trial.pt.
42.	randomi#ed.ab.

43.	placebo.ab.
44.	randomly.ab.
45.	clinical trials as topic.sh.
46.	trial.ti.
47.	or/40-46
48.	Meta-Analysis/
49.	Meta-Analysis as Topic/
50.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
51.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
52.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
53.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
54.	(search* adj4 literature).ab.
55.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
56.	cochrane.jw.
57.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
58.	or/48-57
59.	39 and (47 or 58)

Embase (Ovid) search terms

1.	exp Thyroid Cancer/
2.	(thyroid adj3 (cancer* or carcinom* or microcarcinoma* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or node* or nodul* or nodal or lump* or papillar* or swollen or swell* or anaplastic or sarcoma* or cyst* or malignan*)).ti,ab.
3.	DTC.ti,ab.
4.	((papillar* or anaplastic) adj2 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nodul* or node* or lump*)).ti,ab.
5.	or/1-4
6.	letter.pt. or letter/
7.	note.pt.
8.	editorial.pt.
9.	case report/ or case study/
10.	(letter or comment*).ti.
11.	(conference abstract or conference paper).pt.
12.	or/6-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice or rodent*).ti.
22.	or/14-21
23.	5 not 22
24.	limit 23 to english language

25.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
26.	24 not 25
27.	Calcitonin/
28.	(calcitrin* or calcitoni* or cibalcin* or thyreocalcitonin* or thyrocalcitonin*).ti,ab,kf.
29.	exp *Antibody/
30.	exp *Autoantibody/
31.	Iodide Peroxidase/
32.	((antithyroid or thyroid or iodide) adj3 (antibod* or autoantibod*)).ti,ab,kf.
33.	((iodide or thyroid or antithyroid or autoantibod* or antibod*) adj3 (peroxidase* or oxidoreductase)).ti,ab,kf.
34.	(thyroperoxidase* or deiodinase*).ti,ab,kf.
35.	(iodotyrosine adj2 (deiodase* or deiodinase* or desiodase*)).ti,ab,kf.
36.	(TPO or TPOAb).ti,ab,kf.
37.	or/27-36
38.	26 and 37
39.	random*.ti,ab.
40.	factorial*.ti,ab.
41.	(crossover* or cross over*).ti,ab.
42.	((doubl* or singl*) adj blind*).ti,ab.
43.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
44.	crossover procedure/
45.	single blind procedure/
46.	randomized controlled trial/
47.	double blind procedure/
48.	or/39-47
49.	systematic review/
50.	Meta-Analysis/
51.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
52.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
53.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
54.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
55.	(search* adj4 literature).ab.
56.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
57.	cochrane.jw.
58.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
59.	or/49-58
60.	38 and (48 or 59)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2.	(thyroid near/3 (cancer* or carcinom* or microcarcinoma* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or node* or nodul* or nodal or lump* or papillar* or swollen or swell* or anaplastic or sarcoma* or cyst* or malignan*)):ti,ab
#3.	DTC:ti,ab
#4.	((papillar* or anaplastic) near/2 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nodul* or node* or lump*)):ti,ab

#5.	#1 or #2 or #3 or #4
#6.	MeSH descriptor: [Calcitonin] explode all trees
#7.	(calcitrin* or calcitoni* or cibalcin* or thyreocalcitonin* or thyrocalcitonin*):ti,ab
#8.	MeSH descriptor: [Antibodies] explode all trees
#9.	MeSH descriptor: [Autoantibodies] explode all trees
#10.	MeSH descriptor: [Iodide Peroxidase] explode all trees
#11.	((antithyroid or thyroid or iodide) near/3 (antibod* or autoantibod*)):ti,ab
#12.	((iodide or thyroid or antithyroid or autoantibod* or antibod*) near/3 (peroxidase* or oxidoreductase*)):ti,ab
#13.	(thyroperoxidase* or deiodinase*):ti,ab
#14.	(iodotyrosine near/2 (deiodase* or deiodinase* or desiodase*)):ti,ab
#15.	(TPO or TPOAb):ti,ab
#16.	(or #6-#15)
#17.	#5 and #16
#18.	conference:pt or (clinicaltrials or trialsearch):so
#19.	#17 not #18

Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Thyroid Cancer population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 2: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 16 December 2021	Health economics studies Quality of life studies
	Quality of Life 1946 – 16 December 2021	Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
Embase (OVID)	Health Economics 1 January 2014 – 16 December 2021	Health economics studies Quality of life studies
	Quality of Life 1974 – 16 December 2021	Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
NHS Economic Evaluation Database (NHS EED)	Inception –31st March 2015	

Database	Dates searched	Search filters and limits applied
(Centre for Research and Dissemination - CRD)		
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 16 December 2021	English language

Medline (Ovid) search terms

1.	exp Thyroid Neoplasms/
2.	(thyroid adj4 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or papillar* or follicul* or lymphoma* or anaplastic)).ti,ab.
3.	((papillar* or follicul* or medullary or anaplastic) adj4 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or lymphoma*)).ti,ab.
4.	or/1-3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.
13.	or/5-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	limit 23 to english language
25.	economics/
26.	value of life/
27.	exp "costs and cost analysis"/
28.	exp Economics, Hospital/
29.	exp Economics, medical/
30.	Economics, nursing/
31.	economics, pharmaceutical/

32.	exp "Fees and Charges"/
33.	exp budgets/
34.	budget*.ti,ab.
35.	cost*.ti.
36.	(economic* or pharmaco?economic*).ti.
37.	(price* or pricing*).ti,ab.
38.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
39.	(financ* or fee or fees).ti,ab.
40.	(value adj2 (money or monetary)).ti,ab.
41.	or/25-40
42.	24 and 41
43.	quality-adjusted life years/
44.	sickness impact profile/
45.	(quality adj2 (wellbeing or well being)).ti,ab.
46.	sickness impact profile.ti,ab.
47.	disability adjusted life.ti,ab.
48.	(qal* or qtime* or qwb* or daly*).ti,ab.
49.	(euroqol* or eq5d* or eq 5*).ti,ab.
50.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/52-70
63.	24 and 62

Embase (Ovid) search terms

1.	exp Thyroid Cancer/
2.	(thyroid adj4 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or papillar* or follicul* or lymphoma* or anaplastic)).ti,ab.
3.	((papillar* or follicul* or medullary or anaplastic) adj4 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or lymphoma*)).ti,ab.
4.	or/1-3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9

11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to english language
23.	health economics/
24.	exp economic evaluation/
25.	exp health care cost/
26.	exp fee/
27.	budget/
28.	funding/
29.	budget*.ti,ab.
30.	cost*.ti.
31.	(economic* or pharmaco?economic*).ti.
32.	(price* or pricing*).ti,ab.
33.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
34.	(financ* or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/23-35
37.	22 and 36
38.	quality-adjusted life years/
39.	"quality of life index"/
40.	short form 12/ or short form 20/ or short form 36/ or short form 8/
41.	sickness impact profile/
42.	(quality adj2 (wellbeing or well being)).ti,ab.
43.	sickness impact profile.ti,ab.
44.	disability adjusted life.ti,ab.
45.	(qal* or qtime* or qwb* or daly*).ti,ab.
46.	(euroqol* or eq5d* or eq 5*).ti,ab.
47.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
48.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
49.	(hui or hui1 or hui2 or hui3).ti,ab.
50.	(health* year* equivalent* or hye or hyes).ti,ab.
51.	discrete choice*.ti,ab.
52.	rosser.ti,ab.
53.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
54.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
55.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
56.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
57.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.

58.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
59.	or/37-58
60.	22 and 59

NHS EED and HTA (CRD) search terms

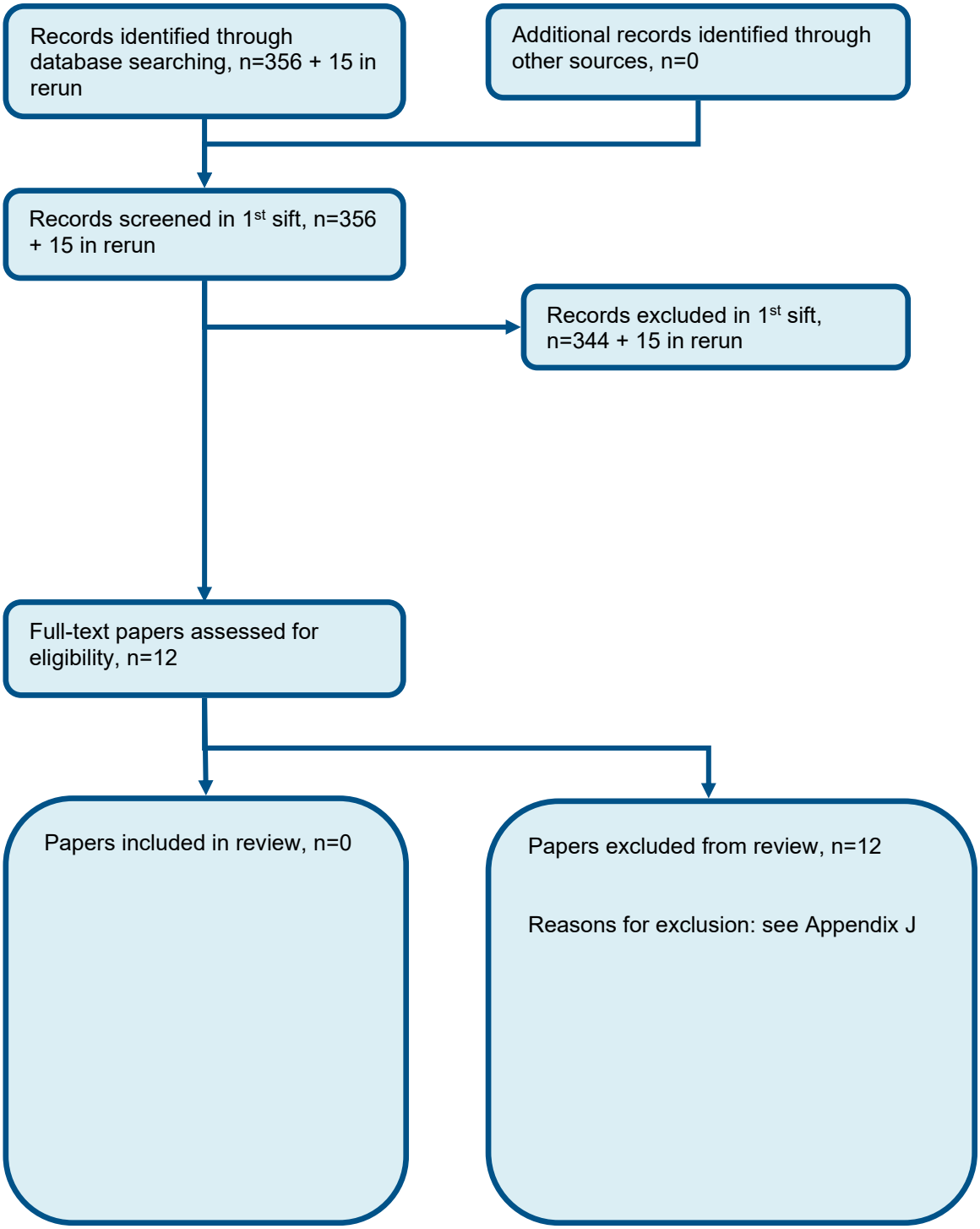
#1.	MeSH DESCRIPTOR Thyroid Neoplasms EXPLODE ALL TREES
#2.	((thyroid NEAR4 (cancer* or carcinom* or tumour* or tumor* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or papillar* or follicul* or lymphoma* or anaplastic)))
#3.	(((papillar* or follicul* or medullary or anaplastic) NEAR4 (cancer* or carcinom* or tumour* or tumor* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or lymphoma*)))
#4.	#1 OR #2 OR #3

INHATA search terms

1.	(Thyroid Neoplasms)[mh] OR (thyroid neoplasms) AND (thyroid cancers)

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of blood tests



Appendix D – Effectiveness evidence

No evidence was identified.

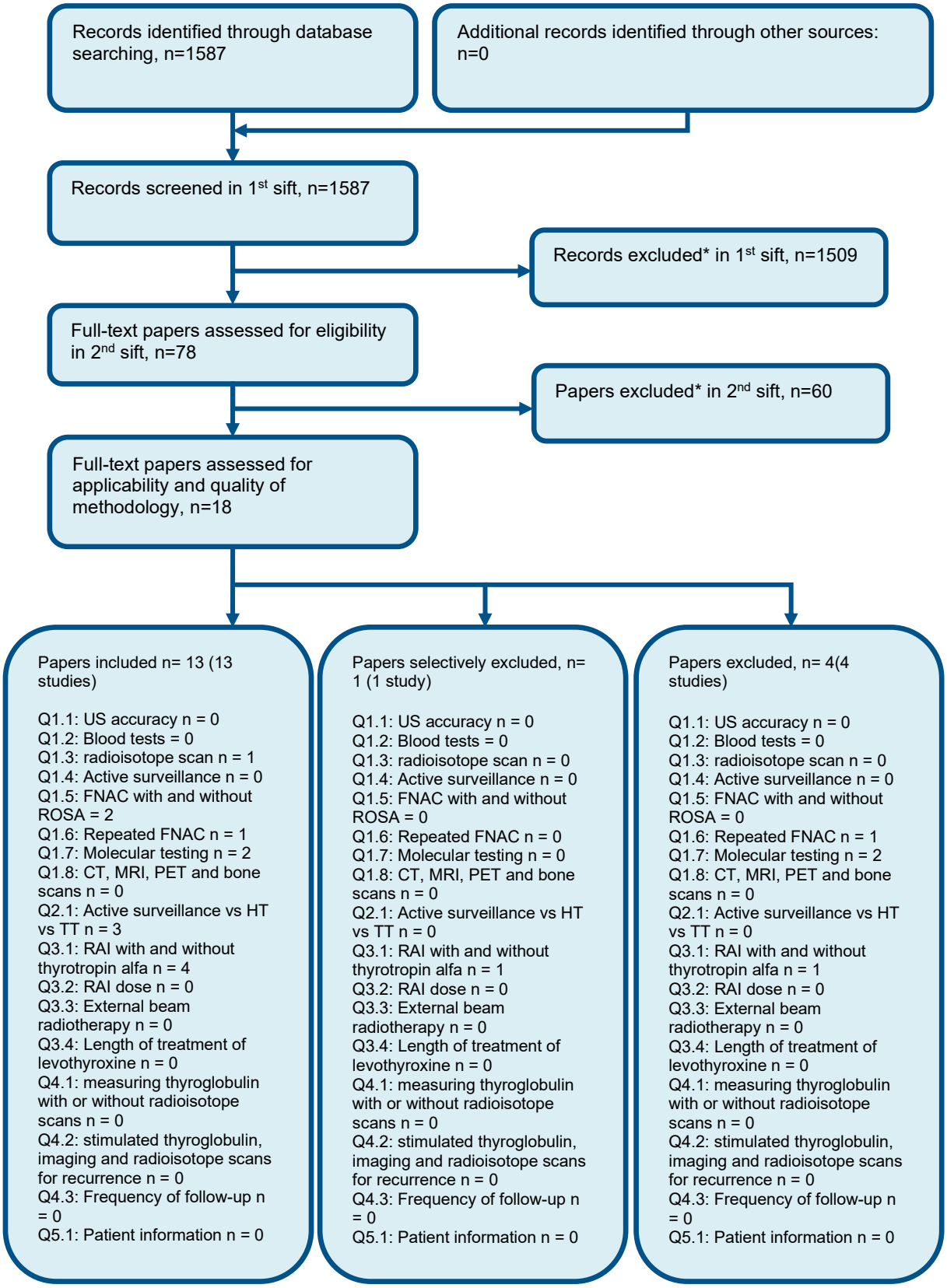
Appendix E – Forest plots

No evidence was identified.

Appendix F – GRADE tables

No evidence was identified.

Appendix G – Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H – Economic evidence tables

None.

Appendix I – Excluded studies

I.1 Clinical studies

Table 3: Studies excluded from the clinical review

Study	Exclusion reason
Bulow 2005[1]	Incorrect study design (non-randomised), incorrect population (randomly selected people from the Danish Civil Registration System)
Colombo 2012[2]	Incorrect study design (non-randomised), incorrect population (people with medullary thyroid cancer in remission or persistent, people with RET gene mutation, people with nodular goiters and healthy volunteers)
Karatzas 2016[3]	Incorrect study design (retrospective, non-randomised)
Spencer 2011[5]	Incorrect study design (narrative review, references have been checked)
Spencer 2011[6]	Duplicate
Trimboli 2015[8]	Systematic review: study designs inappropriate
Trimboli 2022[7]	Systematic review: study designs inappropriate
Vardarli 2021[9]	Systematic review: study designs inappropriate
Verbeek 2020[10]	Systematic review: study designs inappropriate
Vitale 2002[11]	Incorrect study design (non-randomised study), incorrect population (healthy individuals, people with medullary thyroid cancer with mildly or moderately increased basal calcitonin serum concentrations)
Wimalawansa 1993[12]	Incorrect study design (non-randomised study), incorrect population (people with proven medullary thyroid cancer, people with false positive increase in basal plasma immunoreactive calcitonin, people with true positive C cell hyperplasia and healthy volunteers)
Xiao 2019[13]	Systematic review: study designs inappropriate

I.2 Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2005 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.

Appendix J – Research recommendations

J.1.1 Research recommendation

For people with indeterminate cytopathology, what is the clinical and cost effectiveness of TPO testing?

J.1.2 Why this is important

In patients with indeterminate cytopathology, TPO testing may provide useful additional information that facilitates interpretation of cytopathology findings, and it may therefore lead to clinical benefits. However, there are currently no randomised controlled trials comparing clinical outcomes when TPO testing is used and not used in this group of people, and so there is a need for an RCT in this area.

J.1.3 Rationale for research recommendation

Importance to 'patients' or the population	Knowledge of any beneficial effects of TPO testing on quality of life may allow the introduction of TPO into standard care if these benefits can be shown to be cost effective. The possibility that this research recommendation could lead to the introduction of a management strategy that can improve quality of life is clearly of importance to patients.
Relevance to NICE guidance	The efficacy of TPO tests has been considered in this guideline, but we did not find any RCTs evaluating them. The development of such RCTs is therefore required.
Relevance to the NHS	TPO tests have the potential to improve interpretation of FNAC results and therefore should lead to improved accuracy of diagnosis. This will lead to a reduction in both the number of people who have a missed diagnosis and those that undergo unnecessary surgery. This may lead to better health outcomes for more patients.
National priorities	None known
Current evidence base	There is currently no RCT evidence.
Equality considerations	None known

J.1.4 Modified PICO table

Population	Patients with clinical symptoms or signs suggesting thyroid cancer and indeterminate cytopathology
Intervention	TPO testing
Comparator	Usual care

Outcome	Quality of life, progression, mortality
Study design	RCT
Timeframe	Long term
Additional information	This will be a randomised diagnostic trial, where diagnostic accuracy will not be directly evaluated. Instead, the indirect effects of more accurate determination of nodule status on downstream patient reported health outcomes will be evaluated.