British Thoracic Society

NICE National Institute for Health and Care Excellence

Healthcare Improvement Scotland | SIGN Makes sense of evidence

Draft for Consultation

Asthma: diagnosis, monitoring and chronic asthma management (update)

Evidence reviews for diagnostic accuracy of eosinophil blood count measures in the diagnosis of asthma

BTS/NICE/SIGN collaborative guideline <number>

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1. Eosinophil blood count measures

1.1 Review question

In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of eosinophil blood count measures?

1.1.1 Introduction

Eosinophils are white blood cells that are produced and recruited to tissues as part of the type 2 inflammatory response. They are measured routinely in the blood (as part of a full blood count).

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: People with suspected asthma (presenting with respiratory symptoms). Ages stratified into the following 2 groups: • Children/young people (5-16 years old) • Adults (≥17 years old) Stratified by smoking status: • Smokers • Non-smokers • Mixed populations Exclusion: • Children under 5 years old • People on steroid medication (washout period minimum of 4 weeks for inclusion)
Target condition	Asthma
Index test	Peripheral blood eosinophil count (may be part of FBC)
Reference standards	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) • FeNO Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold.

	Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis. Stratification: • Different reference standards Maximum interval between initial diagnosis and confirmation of asthma diagnosis: 12 months
Statistical measures	• Sensitivity (thresholds: upper 90%, lower 10%) • Specificity (thresholds: upper 80%, lower 50%) • Raw data to calculate 2x2 tables to calculate sensitivity and specificity • Negative predictive value (NPV), Positive predictive value (PPV)
Study design	• Cross sectional studies • Cohort studies

1.1.3 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.

1.1.4 Diagnostic evidence

1.1.4.1 Included studies

Seven observational studies were included in the review; (Bao, et al., 2021, Koca Kalkan, et al., 2021, Livnat, et al., 2015, Louis, et al., 2023, Nekoee, et al., 2020, Popovic-Grle, et al., 2002, Tilemann, et al., 2011) these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below in Table 5 and references in 1.3 References . The assessment of the evidence quality was conducted with emphasis on test sensitivity and specificity as both were identified by the committee as primary measures in guiding decision-making. The committee set clinical decision thresholds as sensitivity: upper= 90% and lower= 10%, specificity: upper= 80% and lower= 50%. Values above the upper threshold indicated a test would be recommended and values below the lower threshold indicated a test is of no clinical use.

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

1.1.4.2 Excluded studies

17 studies were excluded that were included in the previous NICE guidance on this topic. These studies were excluded due to containing a population that was not relevant to the current review protocol (most often due to a large proportion of the study population using inhaled corticosteroids) or not containing relevant diagnostic data (reporting mean blood eosinophil counts between different groups such as asthmatics vs controls or asthmatics with atopy vs without but no diagnostic accuracy data calculable).

1 See the excluded studies list in Appendix H.

2 ### 1.1.5 Summary of studies included in the diagnostic evidence

3 **Table 2: Summary of studies included in the evidence review**

Study	Population	Target condition	Index test	Reference standard	Comments
Bao 2021 (Bao et al., 2021)	Adults with an FEV1 >80%, normal CT scan results and recurrent variable symptoms of dyspnoea, cough, wheeze or chest tightness for >8 weeks referred to a pulmonary outpatient clinic N= 692 Mean age (SD): positive MCT; 43.90 (12.56), negative MCT: 43.80 (14.90) China	Airway hyperresponsiveness to methacholine	Eosinophils Cut-offs: 3.4% and 360 cells/µL	Airway hyperresponsiveness was diagnosed using methacholine challenge testing	Retrospective cross-sectional study Strata: Age: Adults ICS use: None within a month Smoking status: Non-smokers Indirectness: Downgraded by one increment due to reference standard (unclear clinician decision in diagnosis) indirectness
Koca Kalkan 2021 (Koca Kalkan et al., 2021)	Adults presenting with respiratory symptoms suggestive of asthma (cough, wheezing, dyspnoea, chest tightness) but with normal spirometric values and negative bronchodilator reversibility test. N=51 (n=19 eventually diagnosed with asthma) Median age (SD): 40.2 (12.3) years	Asthma	Absolute blood eosinophils count in peripheral blood Cut-off: 150/µl	Bronchial hyperactivity defined by the methacholine bronchial provocation tests	Retrospective cohort study Strata: Age: Adults ICS use not reported Smoking history n (%): never 36 (70.6%); ex-smoker 12 (23.5%), current smoker 3 (5.9%), pack years 4(1-60) Indirectness: Downgraded by two increments due to population (ICS use not reported and mixed smoking

Study	Population	Target condition	Index test	Reference standard	Comments
	Turkey				status) indirectness
Livnat 2015 (Livnat et al., 2015)	Children aged 6-18 years referred for MCT at the pulmonary outpatient clinic of a tertiary university-affiliated medical centre. N=131 (n=63 positive MCT; n=68 negative MCT) Mean age (SD): 12.66 (3.77) Israel	Bronchial hyper-responsiveness (BHR) assessed by the methacholine challenge test (MCT)	Peripheral blood eosinophil counts Cut-off: 500/mL	Methacholine Challenge Test performed according to published guidelines and manufacturer's instructions (threshold for positivity: <8mg/ml) ; assessments included medical history, assessment of BHR by MCT, determination of FeNO, and blood tests. Negative MCT: 10/17 (58.8%) had positive skin-prick test; Positive MCT: 24/30 (80%) had positive skin prick test	Prospective study Exposure to passive smoking: 28.2% Downgraded by one increment due to reference standard (unclear clinician decision in diagnosis) indirectness
Louis 2023 (Louis et al., 2023)	Adults seeking medical attention at an asthma clinic, in whom asthma was suspected N= 303; mean age; 51 (16) years Belgium	Asthma	Blood eosinophils Cut-off: 300 μL^{-1}	Asthma was diagnosed as per GINA guidelines, combining symptoms with bronchodilator reversibility and/or methacholine bronchial challenge tests	Prospective cross-sectional study Strata: Age: Adults ICS use: Treatment naïve Smoking status: Mixed Indirectness: Downgraded by one increment due to population (mixed smoking status) indirectness
Nekoee 2020 (Nekoee	Database record of patients who had been	Asthma	Eosinophils Cut-off: 4.4%	Asthma was diagnosed by a positive result with a	Retrospective cross-sectional study

Study	Population	Target condition	Index test	Reference standard	Comments
et al., 2020)	referred to an asthma clinic with respiratory symptoms suggestive of asthma by two respiratory physicians N= 702; mean age: 51 years Location not reported			bronchodilator test (≥12% and 200 mL) or methacholine challenge test (≥20% fall in FEV_1 with ⩽8 $mg \cdot mL^{-1}$)	Strata: Age: Adults ICS use: Treatment naïve Smoking status: Mixed (57% never, 24% ex, 19% current Indirectness: Downgraded by two increments due to population (mixed smoking status) and reference standard (unclear clinician decision in diagnosis) indirectness
Popovic 2002 (Popovic-Grle et al., 2002)	Adults outpatients with dyspnoea, treated for breathlessness; referred by GP due to suspected asthma. N=195 (final diagnosis n=141 asthma, n=17 COPD, n=29 rhinitis/sinusitis, n=8 unsolved so further examined) Mean age: 39 years Croatia	Asthma	Peripheral blood eosinophils Cut-off: not reported, defined as eosinophilia	Physician diagnosis based on questionnaire (medical history of occasional asthma attacks with wheezing and nocturnal wakening due to dyspnoea) and on the basis of bronchodilatio n test (reversible obstruction) with salbutamol.	Cross-sectional study Strata: Age: Adults ICS use not reported Current smokers: 20% Indirectness: Downgraded by two increments due to population (ICS use not reported and mixed smoking status) and index test (cut-off not reported) indirectness
Tilemann 2011 (Tileman n et al., 2011)	Adults presenting to their GP for the first time with complaints suggestive of obstructive airways	Asthma	Peripheral blood eosinophils Cut-off: 4.15%	Whole-body plethysmograp hy (patients with FEV1 <80% predicted repeated the test after	Prospective cross-sectional study Strata: Age: Adults

Study	Population	Target condition	Index test	Reference standard	Comments
	disease. Patients had dyspnoea, coughing and/or expectoration persisting for at least 2 months. Patients were referred to the lung function laboratory of a university hospital for further examination. N= 210 Mean age (SD): Asthma; 38.0 (14.6), COPD; 56.8 (11.7), Partial reversibility; 57.9 (11.2), No OAD: 42.3 (14.4) Germany			inhaling 400µg salbutamol). Asthma was diagnosed if reversibility was ≥12% and 200mL compared to baseline. If no obstruction in WBP, methacholine challenge using a cut-off of PC20 ≤16 mg/mL	ICS use: 5.2% receiving ICS Smoking status: 63 (30%) current smokers, 36 (17%) past smokers, 111 (53%) never smokers Indirectness: Downgraded by two increments due to population (5.2% receiving ICS, 12-hour washout and mixed smoking status), and reference standard (unclear clinician decision in diagnosis) indirectness

See Appendix D for full evidence tables

1.1.6 Summary of the diagnostic evidence

The assessment of the evidence quality was conducted with emphasis on [test sensitivity and specificity as this was identified by the committee as the primary measure in guiding decision-making. The committee set clinical decision thresholds as sensitivity: upper= 90% and lower= 10%, specificity: upper= 80% and lower= 50%. Values above the upper threshold indicated a test would be recommended and values below the lower threshold indicated a test is of no clinical use.

Table 3: Clinical evidence summary: diagnostic test accuracy for blood eosinophils in children and young people

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Peripheral blood eosinophil count (cut-off: 500/mL) vs methacholine bronchial challenge test							
1 prospective cross-sectional study	131	Serious[1]	Not serious	Serious[2]	Not serious	Sensitivity= 0.37 (0.25-0.50)	LOW
		Serious[1]	Not serious	Serious[2]	Serious[3]	Specificity= 0.91 (0.82-0.97)	VERY LOW

1. *Downgraded by one increment due to concerns arising from the interpretation of the index test and reference standard (unclear if blinded)*
2. *Downgraded by one increment due to reference standard (unclear clinician decision in diagnosis) indirectness*
3. *Downgraded by one increment due to the 95%CI overlapping the threshold corresponding to 'high specificity' (80%)*

Table 4: Clinical evidence summary: diagnostic test accuracy for blood eosinophils in non-smoking adults

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Eosinophils (cut-off: 3.4%) vs methacholine bronchial challenge test							
1 retrospective cross-sectional study	692	Very serious[1]	Not serious	Serious[2]	Not serious	Sensitivity= 0.56 (0.48-0.63)	VERY LOW
		Very serious[1]	Not serious	Serious[2]	Not serious	Specificity= 0.66 (0.62-0.70)	VERY LOW
Eosinophils (cut-off: 360 cells/μL) vs methacholine bronchial challenge test							
1 retrospective cross-sectional study	692	Very serious[1]	Not serious	Serious[2]	Not serious	Sensitivity= 0.42 (0.34-0.50)	VERY LOW
		Very serious[1]	Not serious	Serious[2]	Serious[3]	Specificity= 0.81 (0.77-0.84)	VERY LOW

1. *Downgraded by two increments due to concerns arising from the selection of participants (method not reported) and interpretation of the index test and reference standard (unclear if blinded)*
2. *Downgraded by one increment due to population (pre-study ICS use not reported)*
3. *Downgraded by one increment due to the 95%CI overlapping the threshold corresponding to 'high specificity' (80%)*

Table 5: Clinical evidence summary: diagnostic test accuracy for blood eosinophils in adults with mixed/unclear smoking status

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Eosinophils (cut-off: 150/μL) vs methacholine bronchial challenge test							
1 prospective cross-sectional study	51	Very serious[1]	Not serious	Very serious[2]	Serious[3]	Sensitivity= 0.79 (0.54-0.94)	VERY LOW
		Very serious[1]	Not serious	Very serious[2]	Serious[4]	Specificity= 0.66 (0.57-0.81)	VERY LOW
Eosinophils (cut-off: 4.4%) vs bronchodilator reversibility and/or methacholine bronchial challenge test							
1 prospective cross-sectional study	702	Very serious[5]	Not serious	Very serious[2]	Not serious	Sensitivity= 0.23 (0.19-0.28)	VERY LOW
		Very serious[5]	Not serious	Very serious[2]	Not serious	Specificity= 0.91 (0.87-0.94)	VERY LOW
Eosinophilia (cut-off not reported) vs clinician diagnosis and bronchodilator reversibility							
1 prospective cross-sectional study	195	Very serious[1]	Not serious	Very serious[6]	Serious[7]	Sensitivity= 0.15 (0.09-0.22)	VERY LOW
		Very serious[1]	Not serious	Very serious[6]	Serious[8]	Specificity= 0.39 (0.26-0.53)	VERY LOW
Eosinophils (cut-off: 4.15%) vs whole body plethysmography assessment of spirometry and bronchodilator reversibility or methacholine bronchial challenge test							

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
1 prospective cross-sectional study	197	Very serious[9]	Not serious	Very serious[10]	Not serious	Sensitivity= 0.36 (0.25-0.47)	VERY LOW
		Very serious[9]	Not serious	Very serious[10]	Serious[4]	Specificity= 0.83 (0.75-0.89)	VERY LOW
Eosinophils (cut-off: >300 μL^{-1}) vs clinician diagnosis with bronchodilator reversibility and/or methacholine bronchial challenge tests							
1 cross-sectional study	303	Very serious[11]	Not serious	Serious[12]	Not serious	Sensitivity= 0.22 (0.16-0.29)	VERY LOW
		Very serious[11]	Not serious	Serious[12]	Serious[4]	Specificity= 0.85 (0.77-0.91)	VERY LOW

1. *Downgraded by two increments due to concerns arising from the selection of participants (method not reported) and interpretation of the index test and reference standard (unclear if blinded)*
2. *Downgraded by two increments due to population (pre-study ICS use not reported and mixed smoking status)*
3. *Downgraded by one increment due to the 95%CI overlapping the threshold corresponding to 'high sensitivity' (90%)*
4. *Downgraded by two increments due to the 95%CI overlapping the threshold corresponding to 'high specificity' (80%)*
5. *Downgraded by two increments due to concerns arising from the selection of participants (method not reported), interpretation of the index test and reference standard (unclear if blinded) and the flow and timing of participants through the study (not all participants received the same reference standard)*
6. *Downgraded by two increments due to population (pre-study ICS use not reported and mixed smoking status) and index test (cut-off not reported) indirectness*
7. *Downgraded by one increment due to the 95%CI overlapping the threshold corresponding to 'low sensitivity' (10%)*
8. *Downgraded by one increment due to the 95%CI overlapping the threshold corresponding to 'low specificity (50%)*
9. *Downgraded by two increments due to concerns arising from the interpretation of the index test and reference standard (unclear if blinded) and the flow and timing of participants through the study (not all participants received the same reference standard)*
10. *Downgraded by two increments due to population (5.2% of participants were receiving ICS with no washout prior to testing and mixed smoking status) and reference standard (unclear clinician decision in diagnosis) indirectness*
11. *Downgraded by two increments due to concerns arising from the method of participant selection (method not reported) and interpretation of the index test and reference standard (unclear if blinded)*
12. *Downgraded by one increment due to population (mixed smoking status) indirectness*

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 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 F.

1.1.8 Summary of included economic evidence

None.

1.1.9 Economic model

A health economic model was conducted focusing on sequences and combinations of diagnostic tests. This is reported in Evidence review 1.11.

1.1.10 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 6: Eosinophil blood count cost

Resource	Unit costs	Source
Haematology	£2.96	NHS reference costs 2021/2022 DAPS05(NHS England, 2022)
Phlebotomy	£4.70	NHS reference costs 2021/2022 DAPS08(NHS England, 2022)
Emla 5% cream	£0.41 per g	BNF 2024(Joint Formulary Committee, 2024)
Total	£6.41	

1.1.11 Evidence statements

Economic

- No relevant economic evaluations were identified.

1.2 The committee's discussion and interpretation of the evidence

1.2.1 The outcomes that matter most

Test and treat studies

The outcomes considered for this review were: severe asthma exacerbations, mortality, quality of life, asthma control, hospital admissions, reliever/rescue medication use, lung function (change in FEV1 or morning PEF – average over at least 7 days for morning PEF), adverse events (linear growth, pneumonia frequency, adrenal insufficiency, bone mineral density), inflammatory markers; exhaled nitric oxide (continuous outcome at ≥8 weeks). For purposes of decision making, all outcomes were considered equally important and were therefore rated as critical by the committee. No relevant evidence was identified for any of the outcomes.

Diagnostic accuracy

The committee considered the diagnostic measures of sensitivity and specificity of eosinophil blood count measures for diagnosing asthma in children and young people as well as the positive and negative predictive values where these were reported by the studies. Clinical decision thresholds were set by the committee as sensitivity/specificity 0.9 and 0.8 above which a test would be recommended and 0.1 and 0.5 below which a test is of no clinical use.

1.2.2 The quality of the evidence

Test and treat studies

No relevant clinical studies were identified comparing the clinical effectiveness of diagnosis of asthma based on eosinophil blood count measures in terms of the clinical outcomes set in the protocol.

Diagnostic accuracy

Seven observational studies examining the diagnostic accuracy of peripheral blood eosinophil count for asthma were identified. Six of those studies were in adults and one study was in children and young people. One study excluded participants that smoked, providing evidence for the diagnostic accuracy of blood eosinophils in non-smokers. The rest of the evidence was in participants with a smoking status that was either mixed or not reported. The quality of the evidence for non-smoking adults was very low. This evidence was downgraded due to very serious concerns arising from the risk of bias assessment, namely due to an unclear recruitment method and unclear blinding in the assessment of the index test and reference standard. Furthermore, the evidence identified did not specify the prior use of ICS, resulting in downgrading due to indirectness.

Evidence for adults with mixed or unreported smoking status was very low quality. All evidence was downgraded by two increments due to risk of bias. This was most frequently due to concerns over the interpretation of the index test and reference standard, with a lack of clarity over blinding and a lack of detail on the method of participant selection. All evidence was downgraded by at least one increment due to containing participants with mixed or unreported smoking status, with the majority downgraded by a further increment due to not reporting pre-study ICS use or not reporting a specific cut-off for positivity of the index test.

The quality of the evidence for children and young people was low to very low. This evidence was downgraded due to serious concerns in the interpretation of the index test and reference standard as a result of a lack of information on blinding. This evidence was also downgraded due to serious indirectness because it was not clear how a clinician decision contributed to the reference standard diagnosis.

1.2.3 Benefits and harms

Non-smoking Adults

Very low-quality evidence from one study reported eosinophils using two separate cut-offs. The first was 3.4%, with a moderate sensitivity of 0.56 and moderate specificity of 0.66. Alternatively, a cut-off of 360 cells/μL resulted in a moderate sensitivity of 0.42 and a high specificity of 0.81 in the same population.

Adults with mixed or unreported smoking status

Very low-quality evidence from one study reported a cut-off of 150/μL, resulting in a moderate sensitivity of 0.79 and a moderate specificity of 0.66. The committee noted the limitations of this evidence, mainly due to the small number of participants in the study and the use of methacholine bronchial challenge tests as a reference standard without a clear clinician input into the diagnosis.

Very low-quality evidence from one study reported eosinophils with a cut-off of 4.4%, reporting a low sensitivity of 0.23, but a high specificity of 0.91. The committee acknowledged the high specificity of this test and that a relatively large number of participants were included, indicating a potentially useful objective test for ruling asthma in. However, the ICS status of the participants was unclear as was the extent of clinician input into the reference standard asthma diagnosis.

Very low-quality evidence from another study also showed very low sensitivity (0.15) and specificity (0.39) of peripheral blood eosinophils when the cut-off used was not specified, instead reported as “eosinophilia”. The committee noted the very limited usefulness of this evidence due to the lack of a clear cut-off point.

Very low-quality evidence from one study showed peripheral blood eosinophils using a cut-off of 4.15% had very low sensitivity (0.36) but high specificity (0.83). The committee highlighted 4.15% cut-off is around the top-end of the normal range.

Very low-quality evidence from one study reported eosinophils using a cut-off of >300 μL^{-1}, resulting in a low sensitivity of 0.22, but a high specificity of 0.85. The committee again acknowledged the potential utility of eosinophils as a confirmatory test but agreed that this evidence strengthened their opinion that it may not be an appropriate test for ruling out an asthma diagnosis.

Children and young people

Low to very low-quality evidence from one study showed that peripheral blood eosinophils using a cut-off of 500/mL had low sensitivity (0.37) and high specificity (0.91) to detect bronchial hyperresponsiveness in children and young people. The committee noted that the outcome measure was not asthma per se, although the methacholine bronchial challenge test used in this evidence is a relatively strong indicator of asthma.

Summary

Overall, the committee noted the variability in the cut-offs used by the studies, although in most cases the cut-off was around the upper limit of the normal range for eosinophils. The committee agreed peripheral eosinophil count does not offer a sufficiently good balance between sensitivity and specificity ratio to inform a diagnosis of asthma as a standalone test. However, the committee agreed that peripheral blood eosinophil counts could be part of the battery of tests used to establish a diagnosis of asthma. They noted that peripheral blood eosinophil count is a simple measure to obtain, and it can be routinely collected in full-blood count in adults, although the need for venepuncture makes the test less easy to carry out in children.

The committee concluded that peripheral blood eosinophils could be of use when performed alongside other diagnostic tests for asthma but noted that the current evidence did not support a specific cut-off for diagnosis. There are slight variations between the normal ranges quoted by different laboratories and their consensus view was that the upper limit of the relevant lab's range should be used.

1.2.4 Cost effectiveness and resource use

No relevant published health economic analyses were identified for this review question. The unit cost of a blood eosinophil test was presented to aid committee consideration of cost effectiveness. The unit cost of undertaking a blood eosinophil test was estimated to be £7.66 in adults including the haematology (£2.96) and phlebotomy (£4.70). In children, it was assumed that a further cost of £0.41 for local anaesthetic would be incurred.

The committee considered blood eosinophils alongside or in combination with a variety of tests for asthma within a diagnostic algorithm for both adults and children (see evidence review 1.11). Blood eosinophil was found to be a cost-effective initial test in adults and therefore a recommendation was made to include either blood eosinophil or FeNO in their diagnostic pathway.

1.2.5 Other factors the committee took into account

The committee emphasised that caution is needed in the interpretation of the test results as the eosinophil level can depend on the timing of the test, for example on whether or not people are experiencing symptoms at the time blood samples are collected. In addition, the committee emphasised that factors such as inflammation due to a different illness or infection, as well as some medication, can affect the eosinophil level. It is therefore important to interpret the result in the light of the clinical picture, which needs to be suggestive of asthma, and to allow for potential confounding factors.

1.2.6 Recommendations supported by this evidence review

No recommendations were made from this evidence review.

1.3 References

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Appendices

Appendix A – Review protocol

Review protocol for diagnostic accuracy of blood eosinophils for the diagnosis of asthma

Field	Content
PROSPERO registration number	CRD42023438229
Review title	Accuracy of eosinophil blood count measures in the diagnosis of asthma
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of eosinophil blood count measures?
Objective	To evaluate the diagnostic test value of eosinophil blood count in diagnosing asthma. This evidence review will have two stages: (1) Identify the clinical and cost effectiveness of diagnosis with the test (test plus treatment) (2) If evidence on clinical effectiveness is limited, the diagnostic accuracy will instead be determined
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos

	Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the 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	Asthma
Population	Inclusion: People with suspected asthma (presenting with respiratory symptoms). Ages stratified into the following 2 groups: • Children/young people (5-16 years old) • Adults (≥17 years old)

	Exclusion: • Children under 5 years old • People on steroid medication(washout period minimum of 4 weeks for inclusion) • Stratification: smokers vs non-smokers vs mixed population
Test	Peripheral blood eosinophil count (may be part of FBC)
Reference standard	Effectiveness (test-and-treat) • Compare to each-other Diagnostic accuracy: Reference standard: Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) • FeNO Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold. Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.

	Stratification: • Different reference standard Maximum interval between initial diagnosis and confirmation of asthma diagnosis: 12 months
Types of study to be included	Clinical effectiveness (test and treat): • Systematic reviews of RCTs • Parallel RCTs Published NMAs and IPDs will be considered for inclusion. Diagnostic test accuracy: • Cross sectional studies • Cohort studies will be included
Other exclusion criteria	• Non-English language studies. • Non comparative cohort studies • Before and after studies • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available. • Not looking at occupational asthma /allergens • Not looking at validation studies, or studies comparing different methods of measuring eosinophil blood counts.

	• Not looking at factors which influence eosinophil measurements • Studies in which >10% of people are on inhaled and/or systemic corticosteroid treatment • Cross-sectional studies only included if they report sensitivity/specificity or the sensitivity and specificity can be calculated.
Context	Primary, secondary and community care settings
Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making a therefore have all been rated as critical: Clinical effectiveness (test and treat) outcomes: • Severe asthma exacerbations (defined as asthma exacerbations requiring oral corticosteroid use (dichotomous outcome at ≥6 months) • Mortality (dichotomous outcome at ≥6 months) • Quality of life (QOL; validated scale, including asthma specific questionnaires AQLQ; health-related) (continuous outcome at ≥3 months) • Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months) • Hospital admissions (dichotomous outcome at ≥6 months) • Reliever/rescue medication use (continuous outcome at ≥3 months) • Lung function (change in FEV1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 months). *Note: Extract FEV1 %pred over litres if both are reported. If only litres is reported, extract and analyse separately (do not extract both). For children, only use FEV1 %pred.*

	• Adverse events
	  ○ Linear growth (continuous outcome at ≥1 year),
	  ○ Pneumonia frequency (dichotomous outcome at ≥3 months)
	  ○ Adrenal insufficiency as defined by study, including short synacthen test and morning cortisol (dichotomous outcome at ≥3 months)
	  ○ Bone mineral density (continuous outcome at ≥6 months)
	• Inflammatory markers; exhaled nitric oxide (continuous outcome at ≥8 weeks)
	
	Diagnostic accuracy outcomes: Asthma diagnosis
	• Sensitivity
	thresholds: upper 90, lower 10
	• Specificity
	thresholds: upper 80, lower 50
	• Raw data to calculate 2x2 tables to calculate sensitivity and specificity
	• Negative predictive value (NPV), Positive predictive value (PPV)

Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).

	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. Study investigators may be contacted for missing data where time and resources allow.
Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • QUADAS-2 checklist
Strategy for data synthesis	<u>Diagnostic intervention (test and treat):</u> Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered 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 pooled using random-effects.

	GRADEpro will be used to assess the quality of evidence for 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 will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. WinBUGS will be used for network meta-analysis, if possible given the data identified. Diagnostic accuracy: Where possible data will be meta-analysed where appropriate (if at least 3 studies reporting data at the same diagnostic threshold) in WinBUGS. Summary diagnostic outcomes will be reported from the meta-analyses with their 95% confidence intervals in adapted GRADE tables. Heterogeneity will be assessed by visual inspection of the sensitivity and specificity plots and summary area under the curve (AUC) plots. Particular attention will be placed on specificity determined by the committee to be the primary outcome for decision making. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software.	
Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Different reference standards	
Type and method of review	☒	Intervention

	☒	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	
Country	England	
Anticipated or actual start date		
Anticipated completion date	31 July 2024	

Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	☑	☑
	Piloting of the study selection process	☐	☐
	Formal screening of search results against eligibility criteria	☐	☐
	Data extraction	☐	☐
	Risk of bias (quality) assessment	☐	☐
	Data analysis	☐	☐

Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail asthmachronicmanagement@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre
Review team members	From the National Guideline Centre: Bernard Higgins (Guideline lead) Sharon Swain (Guideline lead) Qudsia Malik (Senior systematic reviewer) Toby Sands (Systematic reviewer) Alfredo Mariani (Senior health economist) Lina Gulhane (Head of information specialists) Stephen Deed (Information specialist) Amy Crisp (Senior project manager) Melina Vasileiou (Senior systematic reviewer)
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-ng10186	
Other registration details	N/A	
Reference/URL for published protocol		
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	N/A	
Details of existing review of same topic by same authors	N/A	
Current review status	x	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated

	☐	Discontinued
Additional information	N/A	
Details of final publication	www.nice.org.uk	

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2 **Health economic review protocol**

3 **Table 7: Health economic review protocol**

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 2006, 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).(National Institute for Health and Care Excellence) **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 2006 or later but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as 'Not applicable'. • Studies published before 2006 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.

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Appendix B – Literature search strategies

Clinical search literature search strategy

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 as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 8: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 20 Dec 2023	Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 20 Dec 2023	Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies Exclusions (conference abstracts, animal studies, letters, comments, editorials, case studies/reports) English language
The Cochrane Library (Wiley)	Cochrane Reviews to 2023 Issue 12 of 12 CENTRAL to 2023 Issue 12 of 12	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 20 Dec 2023	Exclusions (Cochrane reviews) English language

Medline (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/
6.	news/

7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case reports/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/
19.	exp Rodentia/
20.	(rat or rats or mouse or mice or rodent*).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language
24.	*Eosinophils/
25.	*Eosinophilia/
26.	(eosinophil* or eosinophyl* or acidophil* or hypereosinophil*).ti,ab,kf.
27.	or/24-26
28.	23 and 27
29.	exp "sensitivity and specificity"/
30.	(sensitivity or specificity).ti,ab.
31.	((pre test or pretest or post test) adj probability).ti,ab.
32.	(predictive value* or PPV or NPV).ti,ab.
33.	likelihood ratio*.ti,ab.
34.	likelihood function/
35.	((area under adj4 curve) or AUC).ti,ab.
36.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
37.	gold standard.ab.
38.	exp Diagnostic errors/
39.	(false positiv* or false negativ*).ti,ab.
40.	Diagnosis, Differential/
41.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab.
42.	or/29-41
43.	Epidemiologic studies/
44.	Observational study/
45.	exp Cohort studies/
46.	(cohort adj (study or studies or analys* or data)).ti,ab.
47.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.

48.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
49.	Controlled Before-After Studies/
50.	Historically Controlled Study/
51.	Interrupted Time Series Analysis/
52.	(before adj2 after adj2 (study or studies or data)).ti,ab.
53.	exp case control study/
54.	case control*.ti,ab.
55.	Cross-sectional studies/
56.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
57.	or/43-56
58.	randomized controlled trial.pt.
59.	controlled clinical trial.pt.
60.	randomi#ed.ab.
61.	placebo.ab.
62.	randomly.ab.
63.	clinical trials as topic.sh.
64.	trial.ti.
65.	or/58-64
66.	Meta-Analysis/
67.	Meta-Analysis as Topic/
68.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
69.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
70.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
71.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
72.	(search* adj4 literature).ab.
73.	(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.
74.	cochrane.jw.
75.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
76.	or/66-75
77.	42 or 57 or 65 or 76
78.	28 and 77

Embase (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.
7.	case report/ or case study/
8.	(letter or comment*).ti.

9.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
10.	or/4-9
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 or rodent*).ti.
20.	or/12-19
21.	3 not 20
22.	limit 21 to English language
23.	eosinophil/
24.	*eosinophilia/ or *hypereosinophilia/ or *hypereosinophilic syndrome/
25.	(eosinophil* or eosinophyl* or acidophil* or hypereosinophil*).ti,ab,kf.
26.	or/23-25
27.	22 and 26
28.	exp "sensitivity and specificity"/
29.	(sensitivity or specificity).ti,ab.
30.	((pre test or pretest or post test) adj probability).ti,ab.
31.	(predictive value* or PPV or NPV).ti,ab.
32.	likelihood ratio*.ti,ab.
33.	((area under adj4 curve) or AUC).ti,ab.
34.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
35.	diagnostic accuracy/
36.	diagnostic test accuracy study/
37.	gold standard.ab.
38.	exp diagnostic error/
39.	(false positiv* or false negativ*).ti,ab.
40.	differential diagnosis/
41.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab.
42.	or/28-41
43.	Clinical study/
44.	Observational study/
45.	Family study/
46.	Longitudinal study/
47.	Retrospective study/
48.	Prospective study/
49.	Cohort analysis/
50.	Follow-up/

51.	cohort*.ti,ab.
52.	50 and 51
53.	(cohort adj (study or studies or analys* or data)).ti,ab.
54.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
55.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
56.	(before adj2 after adj2 (study or studies or data)).ti,ab.
57.	exp case control study/
58.	case control*.ti,ab.
59.	cross-sectional study/
60.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
61.	or/43-49,52-60
62.	random*.ti,ab.
63.	factorial*.ti,ab.
64.	(crossover* or cross over*).ti,ab.
65.	((doubl* or singl*) adj blind*).ti,ab.
66.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
67.	crossover procedure/
68.	single blind procedure/
69.	randomized controlled trial/
70.	double blind procedure/
71.	or/62-70
72.	Systematic Review/
73.	Meta-Analysis/
74.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
75.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
76.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
77.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
78.	(search* adj4 literature).ab.
79.	(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.
80.	cochrane.jw.
81.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
82.	or/72-81
83.	42 or 61 or 71 or 82
84.	27 and 83

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Asthma] explode all trees
#2.	asthma*:ti,ab
#3.	#1 or #2

#4.	conference:pt or (clinicaltrials or trialsearch):so
#5.	#3 not #4
#6.	MeSH descriptor: [Eosinophils] this term only
#7.	MeSH descriptor: [Eosinophilia] this term only
#8.	(eosinophil* or eosinophyl* or acidophil* or hypereosinophil*):ti,ab
#9.	#6 or #7 or #8
#10.	#5 and #9

Epistemonikos search terms

1.	(title:(eosinophil* OR eosinophyl* OR acidophil* OR hypereosinophil*) OR abstract:(eosinophil* OR eosinophyl* OR acidophil* OR hypereosinophil*)) AND (title:(asthma*) OR abstract:(asthma*))

Health economic literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Asthma 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 and modelling.

Table 9: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 29 Dec 2023	Health economics studies Quality of life studies Modelling Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Quality of Life 1946 – 29 Dec 2023	
	Modelling 1946 – 29 Dec 2023	
Embase (OVID)	Health Economics 1 January 2014 – 29 Dec 2023	Health economics studies Quality of life studies Modelling Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts)
	Quality of Life 1974 – 29 Dec 2023	

Database	Dates searched	Search filters and limits applied
	Modelling 1974 – 29 Dec 2023	English language
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
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 - 29 Dec 2023	English language

Medline (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/
6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case reports/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/
19.	exp Rodentia/
20.	(rat or rats or mouse or mice or rodent*).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language

24.	quality-adjusted life years/
25.	sickness impact profile/
26.	(quality adj2 (wellbeing or well being)).ti,ab.
27.	sickness impact profile.ti,ab.
28.	disability adjusted life.ti,ab.
29.	(qal* or qtime* or qwb* or daly*).ti,ab.
30.	(euroqol* or eq5d* or eq 5*).ti,ab.
31.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
32.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
33.	(hui or hui1 or hui2 or hui3).ti,ab.
34.	(health* year* equivalent* or hye or hyes).ti,ab.
35.	discrete choice*.ti,ab.
36.	rosser.ti,ab.
37.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
38.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
39.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
40.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
41.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
42.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
43.	or/24-42
44.	exp models, economic/
45.	*Models, Theoretical/
46.	*Models, Organizational/
47.	markov chains/
48.	monte carlo method/
49.	exp Decision Theory/
50.	(markov* or monte carlo).ti,ab.
51.	econom* model*.ti,ab.
52.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
53.	or/44-52
54.	Economics/
55.	Value of life/
56.	exp "Costs and Cost Analysis"/
57.	exp Economics, Hospital/
58.	exp Economics, Medical/
59.	Economics, Nursing/
60.	Economics, Pharmaceutical/
61.	exp "Fees and Charges"/
62.	exp Budgets/

63.	budget*.ti,ab.
64.	cost*.ti.
65.	(economic* or pharmaco?economic*).ti.
66.	(price* or pricing*).ti,ab.
67.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
68.	(financ* or fee or fees).ti,ab.
69.	(value adj2 (money or monetary)).ti,ab.
70.	or/54-69
71.	23 and 43
72.	23 and 53
73.	23 and 70

Embase (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.
7.	case report/ or case study/
8.	(letter or comment*).ti.
9.	(conference abstract or conference paper).pt.
10.	or/4-9
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 or rodent*).ti.
20.	or/12-19
21.	3 not 20
22.	limit 21 to English language
23.	quality adjusted life year/
24.	"quality of life index"/
25.	short form 12/ or short form 20/ or short form 36/ or short form 8/
26.	sickness impact profile/

27.	(quality adj2 (wellbeing or well being)).ti,ab.
28.	sickness impact profile.ti,ab.
29.	disability adjusted life.ti,ab.
30.	(qal* or qtime* or qwb* or daly*).ti,ab.
31.	(euroqol* or eq5d* or eq 5*).ti,ab.
32.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
33.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
34.	(hui or hui1 or hui2 or hui3).ti,ab.
35.	(health* year* equivalent* or hye or hyes).ti,ab.
36.	discrete choice*.ti,ab.
37.	rosser.ti,ab.
38.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
39.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
40.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
41.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
42.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
43.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
44.	or/23-43
45.	statistical model/
46.	exp economic aspect/
47.	45 and 46
48.	*theoretical model/
49.	*nonbiological model/
50.	stochastic model/
51.	decision theory/
52.	decision tree/
53.	monte carlo method/
54.	(markov* or monte carlo).ti,ab.
55.	econom* model*.ti,ab.
56.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
57.	or/47-56
58.	health economics/
59.	exp economic evaluation/
60.	exp health care cost/
61.	exp fee/
62.	budget/
63.	funding/
64.	budget*.ti,ab.
65.	cost*.ti.

66.	(economic* or pharmaco?economic*).ti.
67.	(price* or pricing*).ti,ab.
68.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
69.	(financ* or fee or fees).ti,ab.
70.	(value adj2 (money or monetary)).ti,ab.
71.	or/58-70
72.	22 and 44
73.	22 and 57
74.	22 and 71

NHS EED and HTA (CRD) search terms

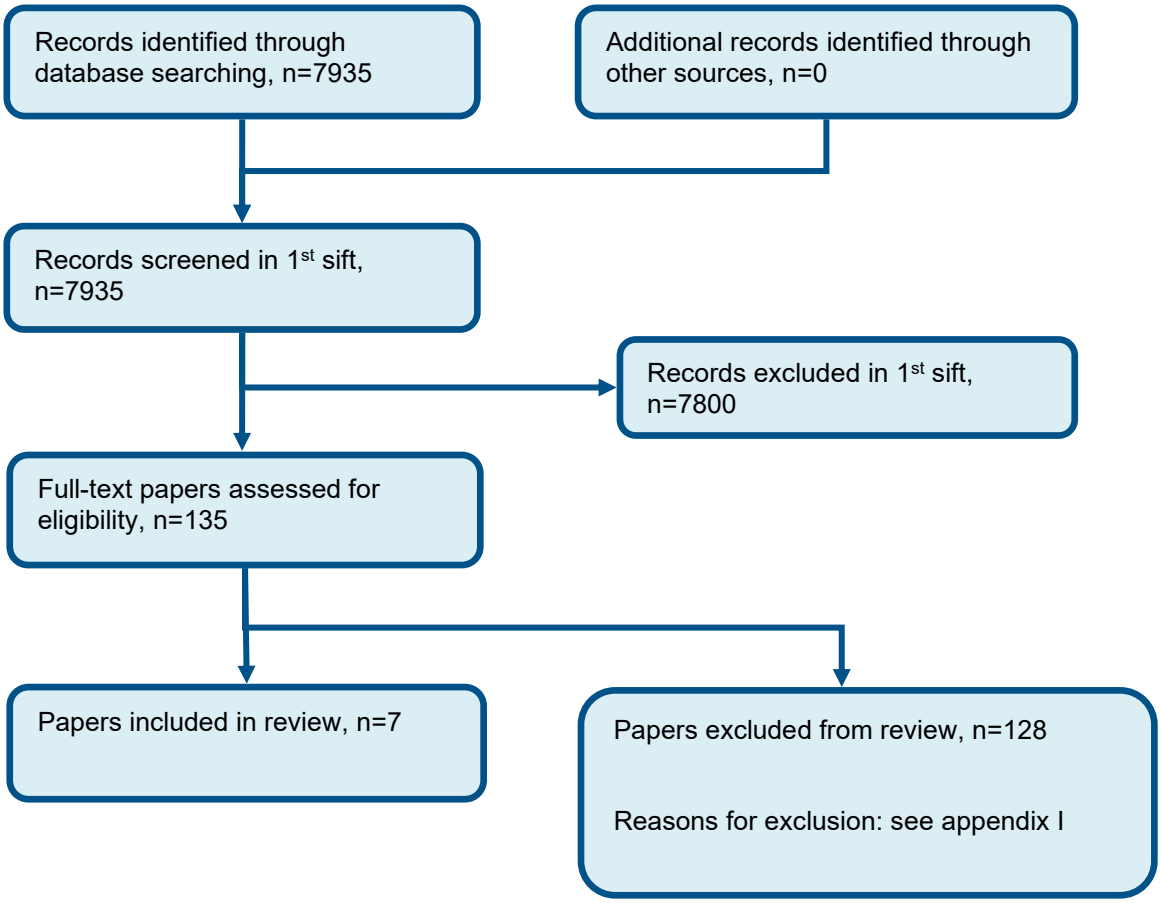
#1.	MeSH DESCRIPTOR Asthma EXPLODE ALL TREES
#2.	(asthma*)
#3.	#1 OR #2

INAHTA search terms

1.	(Asthma)[mh] OR (asthma*)[Title] OR (asthma*)[abs]

Appendix C –Diagnostic evidence study selection

Figure 1: Flow chart of clinical study selection for the review of diagnostic test accuracy of blood eosinophils for asthma



Appendix D –Diagnostic evidence

Reference	**Bao 2021 (Bao et al., 2021)**
Study type	Retrospective cross-sectional study
Study methodology	Data source: Retrospective data of adults with recurrent variable symptoms of dyspnoea, cough, wheeze, or chest tightness of at least 8 weeks' duration who were referred to the Pulmonary Outpatient Clinic of Shanghai General Hospital Recruitment: Not reported
Number of patients	n = 692
Patient characteristics	Age, mean (SD): Positive MCT: 43.90 (14.56), negative MCT: 43.80 (14.90) Gender (male to female ratio): Positive MCT; 53:117, negative MCT; 203:319 Smoking status: Non-smokers ICS use: None within a month Ethnicity: Not reported Setting: Pulmonary outpatient department (secondary care) Country: China Inclusion criteria: Aged 18-75 years, recurrent variable symptoms of dyspnoea, cough, wheeze, or chest tightness for >8 weeks, normal high-resolution CT and FEV_1 >80% of predicted Exclusion criteria: Respiratory tract infection within 8 weeks, abnormal haemoglobin, platelets or neutrophils, use of montelukast, LABAs, theophylline, anticholinergics or corticosteroids within 4 weeks, concomitant severe systemic diseases, smoking history >10 pack years, current smokers and those who had quit within 2 years
Target condition(s)	Bronchial hyperresponsiveness to methacholine

Reference	**Bao 2021 (Bao et al., 2021)**				
Index test(s) and reference standard	Index test Retrospective eosinophil data was use for this study. No information on protocol or standard used to conduct measurements. Cut-offs: 3.4% and 360 cells/µL (optimal threshold) Reference standard Methacholine challenge testing was used with a cut-off of ≤0.48 mg to indicate airway hyperresponsiveness. Time between measurement of index test and reference standard: Not reported				
2×2 table Eosinophils 3.4%		Reference standard +	Reference standard −	Total	Prevalence= 24.5%
	Index test +	95	176	271	
	Index test −	75	346	421	
	Total	170	522	692	
2×2 table Eosinophils 360 cells/µL		Reference standard +	Reference standard −	Total	
	Index test +	71	101	172	
	Index test −	99	421	520	
	Total	170	522	692	
Statistical measures	Index text: Eosinophils (3.4%) Sensitivity: 0.56 (95%CI 0.48-0.63) Specificity: 0.66 (95%CI 0.62-0.70) PPV: 35% NPV: 82% Index text: Eosinophils (360 cells/µL) Sensitivity: 0.42 (95%CI 0.34-0.50) Specificity: 0.81 (95%CI 0.77-0.84) PPV: 41% NPV: 81%				
Source of funding	Supported by the National Natural Science Foundation of China; Appropriate technique application Program of Shanghai Municipal Health system, Scientific and Technological Innovation program funded by Science and Technology Commission of Shanghai municipality and the Program of Shanghai Municipal Health System				
Limitations	Risk of bias: Downgraded by two increments due to concerns arising from the method of participant selection (not reported) and interpretation of the index test and reference standard (unclear if blinded)				

Reference	**Bao 2021 (Bao et al., 2021)**
	Indirectness: Downgraded by one increment due to reference standard (unclear clinician decision in diagnosis) indirectness
Comments	2x2 tables calculated using sensitivity, specificity and prevalence (24.5%) data reported in paper

Reference	**Koca Kalkan 2021 (Koca Kalkan et al., 2021)**
Study type	Retrospective cohort study
Study methodology	Data source: Adults presenting with respiratory symptoms suggestive of asthma (cough, wheezing, dyspnoea, chest tightness) but with normal spirometry values and negative bronchodilator reversibility test (400 mcg of salbutamol), who underwent FeNO and methacholine BPT. Recruitment: not specified
Number of patients	n = 51
Patient characteristics	Age, median (SD): 40.2 (12.3) years Gender (male to female ratio): 12/39 Smoking status: 5.9% current smokers, 23.5% ex-smokers, 70.6% never smoked Ethnicity: not specified ICS use: not reported Setting: outpatients Country: Turkey Inclusion criteria: people aged 18-65 years, with symptoms suggestive of asthma (cough, wheezing, dyspnoea, chest tightness), normal spirometry and no bronchodilator reversibility after 400 mcg of salbutamol inhalation, and in whom FeNO and methacholine provocation tests performed. Exclusion criteria: possible/definite diagnosis of other chronic pulmonary disease (COPD, bronchiectasis, sarcoidosis etc.), acute upper or lower respiratory tract infections within the previous 6 weeks, and significant problems causing an inability to comply with study tests
Target condition	Asthma

Reference	**Koca Kalkan 2021 (Koca Kalkan et al., 2021)**				
Index test(s) and reference standard	Index test: Absolute cell count of eosinophils in peripheral blood Method not specified Cut-off: 150/µl (optimal threshold) Reference standard: Bronchial hyperreactivity (defined by bronchial provocation test) Methacholine bronchial provocation tests were performed in accordance with the ERS guidelines. Participants inhaled a dose of isotonic saline, followed by 5 methacholine dilutions of 0.0625, 0.25, 1, 4 and 16 mg/ml, until the highest concentration of 16 mg/ml or a 20% decrease in FEV_1 was reached. A positive test result was defined by a decrease in FEV1 20% or more. The provocative concentration of methacholine required to induce a 20% fall in FEV_1 was calculated in each subject with a positive test. Time between measurement of index test and reference standard: not specified				
2×2 table		Reference standard +	Reference standard −	Total	Prevalence= 37.2%
	Index test +	15	11	26	
	Index test −	4	21	25	
	Total	19	32	51	
Statistical measures	Sensitivity: 0.79 (95%CI 0.54-0.94) Specificity: 0.66 (95%CI 0.47-0.81) PPV: 53% NPV: 85%				
Source of funding	None				
Limitations	Risk of bias: Downgraded by two increments due to concerns arising from the method of participant selection (method not reported) and the interpretation of the index test and reference standard (unclear if blinded) Indirectness: Downgraded by one increment due to population (ICS use not reported) indirectness				
Comments	2x2 data calculated from sensitivity, specificity and prevalence (37.2%) reported in paper				

Reference	**Livnat 2015 (Livnat et al., 2015)**
Study type	Prospective cohort study
Study methodology	Data source: Children aged 6-18 years referred for methacholine challenge test (MCT) during a 14-month period (July 2011- September 2012) Recruitment: Consecutive

Reference	Livnat 2015 (Livnat et al., 2015)
Number of patients	n = 131 (63 MCT positive, 68 MCT negative)
Patient characteristics	Age, mean (SD): negative MCT: 12.9 (3.9); positive MCT: 12.4 (3.6) Gender (male to female ratio): negative MCT: 41/27; positive MCT: 38/25 Exposure to passive smoking: negative MCT 28 (41.2%); positive MCT 28 (44.4%) Ethnicity: not specified ICS use: not specified Setting: Pulmonary Outpatient Clinic of a tertiary university-affiliated medical centre. Country: Israel Inclusion criteria: Children aged 6-18 years referred for methacholine challenge test (MCT) during a 14-month period (July 2011-September 2012) Exclusion criteria: baseline FEV_1 <65%, presence of other systemic or lung disease, anti-inflammatory drugs, or upper respiratory tract infection in the last month.
Target condition	Bronchial hyperresponsiveness
Index test(s) and reference standard	Index test: Blood eosinophil count Evaluations were performed in a single clinic visit and included medical history, assessment of BHR by MCT, blood tests and eosinophil count. Cut-off: 500/mL (optimal threshold) Reference standard: Methacholine Challenge Test (MCT) Nebulized methacholine was inhaled for 2 min, with 5-min intervals between doses, until the maximal concentration or the end point was reached. PC20– FEV_1 was determined by the provocative concentration that reduced FEV_1 by 20 % from baseline. On completing the MCT, 200 mg of albuterol inhaler was given to all patients by a spacer device to restore airway calibre. Patients with a positive MCT (PC20 >8 mg/ml) were considered as Group I, while patients with a negative MCT (PC20 <8 mg/ml) were considered as Group II.

Reference	**Livnat 2015 (Livnat et al., 2015)**				
	Time between measurement of index test and reference standard: not specified				
2×2 table		Reference standard +	Reference standard −	Total	Prevalence= 48%
	Index test +	23	6	29	
	Index test −	40	62	102	
	Total	63	68	131	
Statistical measures	Sensitivity: 0.37 (95%CI 0.25-0.50) Specificity: 0.91 (95%CI 0.82-0.97) PPV: 79% NPV: 61%				
Source of funding	Not specified				
Limitations	Risk of bias: Downgraded by one increment due to concerns arising from the interpretation of the index test and reference standard (unclear if blinded) Indirectness: Downgraded by one increment due to reference standard (unclear clinician decision in diagnosis) indirectness				
Comments	2x2 data calculated from sensitivity, specificity and prevalence (48%) reported in paper				

Reference	**Louis 2023 (Louis et al., 2023)**
Study type	Prospective cross-sectional study
Study methodology	Data source: Adult patients investigated at an asthma clinic of Liege University Recruitment: Not reported
Number of patients	n = 303 (split into a training (n=166) and validation (n=137) cohort. Only data from the training cohort is available for the optimal threshold analysis).
Patient characteristics	Age, mean (SD): 51 (16) years Gender (male:female ratio): 121:182 Smoking status: 62 smokers, 84 ex-smokers, 157 non-smokers Atopy: 136 atopic Ethnicity: Not reported

Reference	**Louis 2023 (Louis et al., 2023)**
	Setting: Secondary care Country: Belgium Inclusion criteria: Untreated patients aged ≥18 years who sought medical attention and in whom asthma was suspected Exclusion criteria: None specified
Target condition	Asthma
Index test(s) and reference standard	Index test: Blood eosinophil counts were determined by routine laboratory analysis Cut-off: >300 μL^{-1} (pre-specified) Reference standard As per GINA guidelines, asthma diagnosis was based on the presence of typical symptoms (wheezing, dyspnoea, cough, sputum production and chest tightness) combined with ⩾12% and ⩾200 mL FEV_1 reversibility after inhalation of 400 µg salbutamol and/or a PC20 methacholine causing a 20% fall in FEV_1 ⩽8 mg·mL−1 when FEV_1 is ⩾70% predicted Time between measurement of index test and reference standard: 1-2 weeks
2×2 table	

	Reference standard +	Reference standard −	Total	Prevalence= 61.1%
Index test +	41	18	59	
Index test −	144	100	244	
Total	185	118	303	

Statistical measures	Sensitivity: 0.22 (95%CI 0.16-0.29) Specificity: 0.85 (95%CI 0.77-0.91) PPV: 69% NPV: 41%
Source of funding	Funding from the European Union, FEDER APPS INTERREG
Limitations	Risk of bias: Downgraded by two increments due to concerns arising from the method of participant recruitment (method not reported) and the interpretation of the index test and reference standard (unclear if blinded). Indirectness: Downgraded by one increment due to population (mixed smoking status) indirectness
Comments	Sensitivity and specificity calculated from 2x2 data reported in paper and supplementary material

Reference	**Nekoee 2020 (Nekoee et al., 2020)**
Study type	Retrospective cross-sectional diagnostic accuracy study
Study methodology	Data source: Retrospective study of database data of untreated patients referred to an asthma clinic by two respiratory physicians for chronic or episodic respiratory symptoms suggestive of asthma Recruitment: Not reported
Number of patients	n = 702
Patient characteristics	Age, mean: 51 years Gender (% female): 58% Smoking status: 57% never smokers, 24% ex-smokers, 19% current smokers Atopy: Not reported Ethnicity: Not reported Setting: Asthma clinic (secondary care) Country: Not reported Inclusion criteria: Underwent investigations at an asthma clinic prior to receiving maintenance therapy Exclusion criteria: None reported
Target condition(s)	Asthma
Index test(s) and reference standard	Index test Eosinophils – method/protocol followed to obtain measurements not reported Cut-off: 4.4% (optimal threshold) Reference standard Asthma was diagnosed by either bronchodilator reversibility (⩾12% from baseline and 200 mL) and/or bronchial hyperresponsiveness to methacholine (provocative concentration causing a 20% fall in FEV_1 ⩽8 $mg \cdot mL^{-1}$). Patients who were negative tested negative to both tests

Reference	**Nekoee 2020 (Nekoee et al., 2020)**				
	Time between measurement of index test and reference standard: 1-2 weeks				
2×2 table		Reference standard +	Reference standard −	Total	Prevalence= 49.7%
	Index test +	80	32	112	
	Index test −	269	321	590	
	Total	349	353	702	
Statistical measures	Index text Sensitivity: 0.23 (95%CI 0.19-0.28) Specificity: 0.91 (95%CI 0.87-0.94) PPV: 72% NPV: 54%				
Source of funding	Supported by a Federal Belgian Government Excellence of Science grant				
Limitations	Risk of bias: Downgraded by two increments due to concerns arising from patient selection (method of selection not reported), unclear interpretation of the index test and reference standard (unclear if blinded) and the flow and timing of participants through the study (not all participants were diagnosed with the same reference standard) Indirectness: Downgraded by two increments due to population (mixed smoking status) and reference standard (unclear clinician involvement in diagnosis) indirectness				
Comments	2x2 data calculated from sensitivity, specificity and prevalence (49.7%) data reported in paper				

Reference	**Popovic 2002 (Popovic-Grle et al., 2002)**
Study type	Diagnostic cross-sectional study
Study methodology	Data source: Outpatients with dyspnoea treated for breathlessness; referred by GP due to suspected asthma Recruitment: not specified
Number of patients	n = 195
Patient characteristics	Age, mean (SD): 36.81 (6.22) Gender (male to female ratio): 84/75 (out of 159 for which characteristics were given: n=141 with asthma, n=18 control group) Smoking status: 20% current smokers

<table>
<tr><td>Reference</td><td colspan="5">Popovic 2002 (Popovic-Grle et al., 2002)</td></tr>
<tr><td></td><td colspan="5">Ethnicity: not specified

ICS use: not reported

Setting: Outpatients (secondary care)

Country: Croatia

Inclusion criteria: Outpatients treated for breathlessness

Exclusion criteria: none reported</td></tr>
<tr><td>Target condition</td><td colspan="5">Asthma</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5">Index test:
Method not specified.

Cut-off: not reported.

Reference standard: Physician diagnosis (experienced pulmonologist)
Based on questionnaire (medical history of occasional asthma attacks with wheezing and nocturnal wakening due to dyspnoea), and based on bronchodilation test (reversible obstruction) with salbutamol.

Time between measurement of index test and reference standard: not specified</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">Prevalence= 72.3%</td></tr>
<tr><td></td><td>Index test +</td><td>21</td><td>33</td><td>54</td></tr>
<tr><td></td><td>Index test −</td><td>120</td><td>21</td><td>141</td></tr>
<tr><td></td><td>Total</td><td>141</td><td>54</td><td>195</td></tr>
<tr><td>Statistical measures</td><td colspan="5">Sensitivity: 0.15 (95%CI 0.09-0.22)
Specificity: 0.39 (95%CI 0.26-0.53)
PPV: 39%
NPV: 15%</td></tr>
</table>

Reference	**Popovic 2002 (Popovic-Grle et al., 2002)**
Source of funding	Not specified
Limitations	Risk of bias: Downgraded by two increments due to concerns arising from the selection of participants (method not reported) and interpretation of the index test and reference standard (unclear if blinded) Indirectness: Downgraded by two increments due to population (ICS use not reported) and index test (cut-off not reported) indirectness
Comments	2x2 data calculated from sensitivity, specificity and prevalence (72.3%) reported in paper

Reference	**Tilemann 2011 (Tilemann et al., 2011)**
Study type	Prospective cross-sectional study
Study methodology	Data source: Adults presenting to their GP for the first time with complaints suggestive of obstructive airways disease. Patients had dyspnoea, coughing and/or expectoration persisting for at least 2 months. Patients were referred to the lung function laboratory of a university hospital for further examination. Recruitment: Consecutive patients, time frame not specified
Number of patients	n = 197 (study contained 210 participants, with 13 missing eosinophil measurements)
Patient characteristics	Age, mean (SD): Asthma: 38.0 (14.6), COPD: 56.8 (11.7), Partial reversibility: 57.9 (11.2), No OAD: 42.3 (14.4) Gender (male to female ratio): 86:124 Ethnicity: Not reported Smoking status: 63 (30%) current smokers, 36 (17%) past smokers, 111 (53%) never smokers ICS use: 11 patients (5.2%) had been started on inhaled corticosteroids by their GP. Setting: Secondary care Country: Germany Inclusion criteria: Patients presenting to their GP with respiratory symptoms for the first time Exclusion criteria: Patients with respiratory tract infections 6 weeks prior to investigation

Reference	**Tilemann 2011 (Tilemann et al., 2011)**
Target condition(s)	Asthma
Index test(s) and reference standard	Index test Samples of peripheral venous blood were collected. Eosinophil counts were performed with flow cytometry. Cut-off: 4.15% (optimal threshold) Reference standard All subjects with underwent whole body plethysmography in the lung function laboratory. Patients with an FEV_1 <80% of predicted received a bronchodilator test with additional whole-body plethysmography 20 minutes after inhaling 400µg salbutamol. An obstructive airway disease was diagnosed if FEV_1/VC was ≤0.7. The obstruction was classified as irreversible (indicating COPD) if the post-bronchodilator FEV1 was <12% compared with baseline and was <200mL. The obstruction was classified as fully reversible (indicating asthma) if the degree of reversibility in FEV1 was >12% and >200mL from baseline and lung volume returned to predicted normal range. An incomplete bronchodilator response (indicating partial reversibility) was deemed to be present if the bronchodilation response was >12% and >200mL compared with baseline but lung volumes remained below the predicted levels. If there was no obstruction in the first lung function test, a bronchial provocation test with methacholine was performed according to ATS guidelines to determine bronchial hyperresponsiveness.25 Asthma was diagnosed if there was a fall of >20% in FEV_1 after inhaling methacholine stepwise up to the maximum concentration (PC20 ≤16mg/mL). In some cases, asthma and COPD could hardly be differentiated. Repeated measurements after trials of medication were required, particularly to identify asthma with fixed obstruction Time between measurement of index test and reference standard: Within 2 weeks

2×2 table

	Reference standard +	Reference standard −	Total	Prevalence= 40.1%
Index test +	29	20	49	
Index test −	52	97	148	
Total	81	116	197	

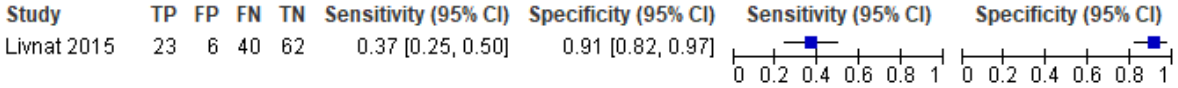
Statistical measures	Sensitivity: 0.36 (95%CI 0.25-0.47) Specificity: 0.83 (95%CI 0.75-0.89) PPV: 59% NPV: 65%
Source of funding	The trial was funded by the Federal Ministry of Education and Research, Germany

Reference	**Tilemann 2011 (Tilemann et al., 2011)**
Limitations	Risk of bias: Downgraded by two increments due to concerns arising from the interpretation of the index test and reference standard (unclear if blinded) and the flow and timing of participants through the study (not all participants received the same reference standard) Indirectness: Downgraded by two increments due to population indirectness (5.2% of patients on ICS and <4-week washout) and reference standard indirectness (no clinician judgement in diagnosis)
Comments	2x2 data calculated using sensitivity, specificity and prevalence (40.1% (based off complete study population, n=210)) reported in paper

Appendix E – Forest plots

Children/young people

Figure 2: Eosinophils (cut-off: 500/mL) vs methacholine bronchial challenge test



Adults (non-smokers)

Figure 3: Eosinophils (cut-off: 3.4%) vs methacholine bronchial challenge test

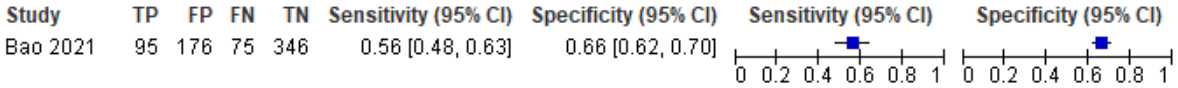
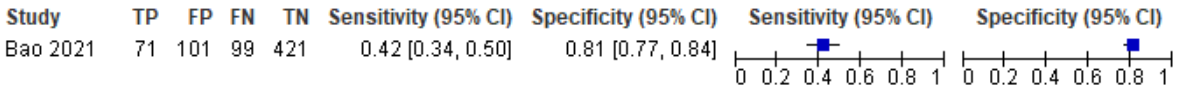


Figure 4: Eosinophils (cut-off: 360 cells/µL) vs methacholine bronchial challenge test



Adults (mixed smoking status)

Figure 5: Eosinophils (cut-off: 150/µL) vs methacholine bronchial challenge test

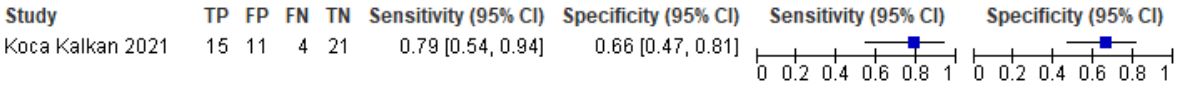


Figure 6: Eosinophils (cut-off: 4.4%) vs bronchodilator reversibility and/or methacholine bronchial challenge test

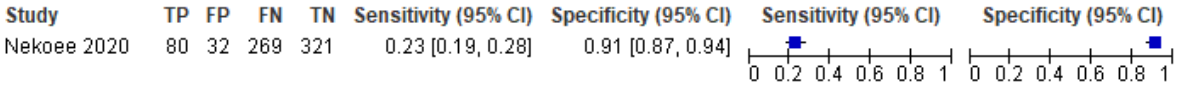


Figure 7: Sputum eosinophils (cut-off not reported) vs clinician diagnosis and bronchodilator reversibility

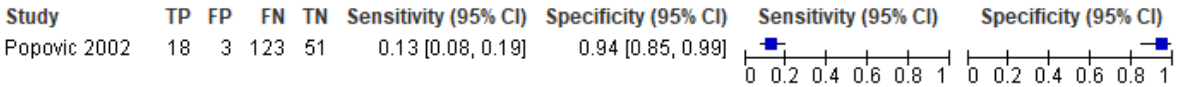


Figure 8: Eosinophilia (cut-off not reported) vs clinician diagnosis and bronchodilator reversibility

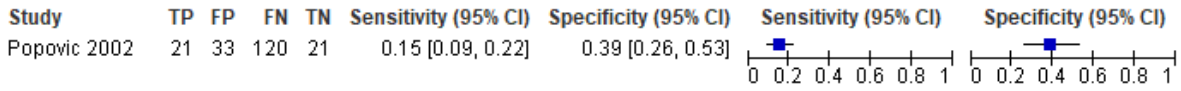


Figure 9: Eosinophils (cut-off: 4.15%) vs whole body plethysmography assessment of spirometry and bronchodilator reversibility or methacholine bronchial challenge test

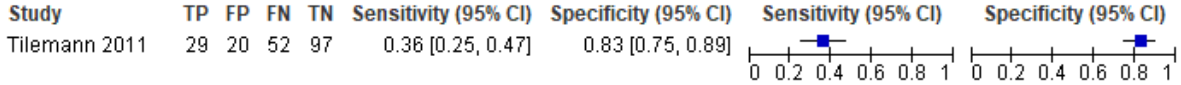
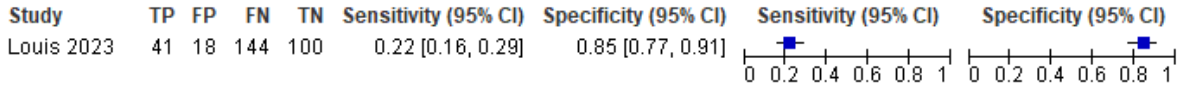
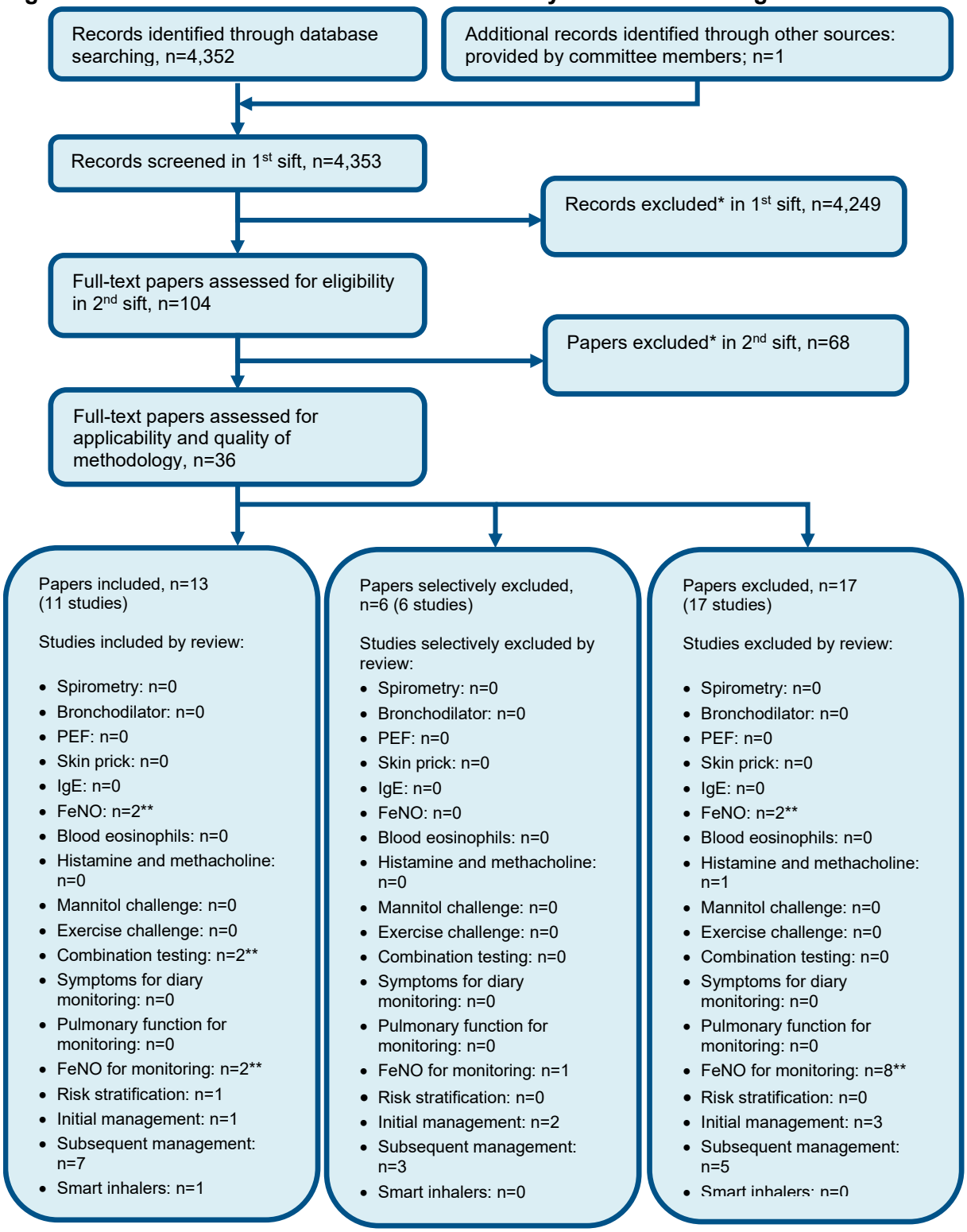


Figure 10: Eosinophils (cut-off: >300 µL^{-1}) vs clinician diagnosis with bronchodilator reversibility and/or methacholine bronchial challenge tests



Appendix F – Economic evidence study selection

Figure 11: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language
** Includes studies that are in multiple reviews

Appendix G – Economic evidence tables

None.

Appendix H – Excluded studies

Clinical studies

Table 10: Studies excluded from the clinical review

Study	Code [Reason]
Abbas, A.H., Rasheed, M.A., Al-Hindy, H.A.-A. et al. (2021) The role of serum IL-1beta in combination with fractional exhaled nitric oxide in the diagnosis of adult bronchial asthma. NeuroQuantology 19(8): 13-19	- Study does not contain an intervention relevant to this review protocol *no measurement of blood eosinophils*
Albers, FC, Lugogo, N, Gilson, MJ et al. (2016) Long-term safety and efficacy of mepolizumab in patients with severe eosinophilic asthma. Journal of allergy and clinical immunology 137(2suppl1): ab14	- Conference abstract
Albers, FC, Price, R, Ortega, H et al. (2016) Effect of mepolizumab in severe eosinophilic asthma patients in relation to their baseline ACQ-5 and SGRQ scores. Allergy 71: 257-258	- Conference abstract
Badar, Ahmed, Salem, Ayad Mohammed, Bamosa, Abdullah Omar et al. (2020) Association Between FeNO, Total Blood IgE, Peripheral Blood Eosinophil and Inflammatory Cytokines in Partly Controlled Asthma. Journal of asthma and allergy 13: 533-543	- Incorrect outcome *detecting eosinophilic airway inflammation in population of known asthmatics*
Baldo, Danielle Cristiane, Romaldini, Jose Gustavo, Pizzichini, Marcia Margaret Menezes et al. (2023) Periostin as an important biomarker of inflammatory phenotype T2 in Brazilian asthma patients. Jornal brasileiro de pneumologia : publicacao oficial da Sociedade Brasileira de Pneumologia e Tisilogia 49(1): e20220040	- Population not relevant to this review protocol *Population does not meet protocol. Non asthmatics are healthy matched controls*
Ban, Ga Young, Ye, Young Min, Kim, Sang Ha et al. (2017) Plasma LTE4/PGF2alpha Ratio and Blood Eosinophil Count Are Increased in Elderly Asthmatics With Previous Asthma Exacerbation. Allergy, asthma & immunology research 9(4): 378-382	- Population not relevant to this review protocol *Known asthmatics already being treated for asthma following the step 1 and 2 of GINA guidelines*
Barril, S., Sebastian, L., Cotta, G. et al. (2016) Utility of Induced Sputum in Routine Clinical	- Population not relevant to this review protocol

Study	Code [Reason]
Practice. Archivos de Bronconeumologia 52(5): 250-255	*People with known asthma (including with ICS treatment), chronic cough or gastroesophageal reflux; measurement of inflammatory cell count in sputum not in blood; no relevant data*
Bedolla-Barajas, Martin, Raul Ortiz-Peregrina, Jose, Daniel Hernandez-Colin, Dante et al. (2019) The characterization of asthma with blood eosinophilia in adults in Latin America. The Journal of asthma : official journal of the Association for the Care of Asthma 56(11): 1138-1146	- Population not relevant to this review protocol *known asthmatic with or without blood eosinophilia*
Benson, Victoria S, Hartl, Sylvia, Barnes, Neil et al. (2022) Blood eosinophil counts in the general population and airways disease: a comprehensive review and meta-analysis. The European respiratory journal 59(1)	- Systematic review used as source of primary studies
Bjornsson, E, Janson, C, Hakansson, L et al. (1996) Eosinophil peroxidase: a new serum marker of atopy and bronchial hyper-responsiveness. Respiratory medicine 90(1): 39-46	- Data not reported in an extractable format or a format that can be analysed
Boulet, Louis-Philippe, Robitaille, Catherine, Deschesnes, Francine et al. (2017) Comparative Clinical, Physiological, and Inflammatory Characteristics of Elderly Subjects With or Without Asthma and Young Subjects With Asthma. Chest 152(6): 1203-1213	- Population not relevant to this review protocol *comparison between elderly with known asthma and without asthma and young people with known asthma; no relevant data: correlational data between populations, no diagnostic accuracy data*
Brusselle, Guy, Germinaro, Matthew, Weiss, Sivan et al. (2017) Reslizumab in patients with inadequately controlled late-onset asthma and elevated blood eosinophils. Pulmonary pharmacology & therapeutics 43: 39-45	- Systematic review used as source of primary studies
Burte, E, Bousquet, J, Siroux, V et al. (2017) The sensitization pattern differs according to rhinitis and asthma multimorbidity in adults: the EGEA study. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 47(4): 520-529	- No relevant data *reports number of blood eosinophils between different groups but no diagnostic accuracy data*
Byeon, J.H., Ri, S., Amarsaikhan, O. et al. (2017) Association between sensitization to mold and impaired pulmonary function in	- Population not relevant to this review protocol *All people with known asthma; no diagnostic accuracy data*

Study	Code [Reason]
children with asthma. Allergy, Asthma and Immunology Research 9(6): 509-516	
Cao, Chao, Li, Wen, Hua, Wen et al. (2017) Proteomic analysis of sputum reveals novel biomarkers for various presentations of asthma. Journal of translational medicine 15(1): 171	- Study does not contain an intervention relevant to this review protocol *sputum not blood eosinophil samples; no diagnostic accuracy data*
Casale, Thomas B, Pacou, Maud, Mesana, Laura et al. (2019) Reslizumab Compared with Benralizumab in Patients with Eosinophilic Asthma: A Systematic Literature Review and Network Meta-Analysis. The journal of allergy and clinical immunology. In practice 7(1): 122-130e1	- Systematic review used as source of primary studies
Casciano, Julian, Krishnan, Jerry A, Small, Mary Buatti et al. (2016) Burden of asthma with elevated blood eosinophil levels. BMC pulmonary medicine 16(1): 100	- Population not relevant to this review protocol *all were people with known asthma; no relevant outcomes*
Casciano, Julian, Krishnan, Jerry, Small, Mary Buatti et al. (2017) Progression to Uncontrolled Severe Asthma: A Novel Risk Equation. Journal of managed care & specialty pharmacy 23(1): 44-50	- Population not relevant to this review protocol *people with known asthma and no relevant data reported*
Castro, Mario, Corren, Jonathan, Pavord, Ian D et al. (2018) Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. The New England journal of medicine 378(26): 2486-2496	- Study does not contain an intervention relevant to this review protocol *RCT but randomisation/diagnosis not done based on eosinophil counts; no relevant data*
Che Mat, Che Mohd Hilmi, Md Shukri, Norasnieda, Mohamad, Sakinah et al. (2023) Diagnostic value of serum and tissue eosinophil in diagnosis of asthma among patients with chronic rhinosinusitis. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 280(5): 2283-2291	- Study design not relevant to this review protocol *Case control study with N<50* - Population not relevant to this review protocol *Washout period only 2 weeeks*
Chen, Ming-Han, Kan, Hung-Tsai, Liu, Chun-Yu et al. (2017) Serum decoy receptor 3 is a biomarker for disease severity in nonatopic asthma patients. Journal of the Formosan	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
Medical Association = Taiwan yi zhi 116(1): 49-56	*correlational data; no diagnostic accuracy data; non-RCT study (so not eligible for clinical evidence review either)*
Chevrier, Stephanie; Abdulnour, Joseph; Saint-Pierre, Mathieu D (2022) Predictors of methacholine challenge testing results in subjects without airflow obstruction. The Journal of asthma : official journal of the Association for the Care of Asthma 59(10): 2060-2068	- Data not reported in an extractable format or a format that can be analysed *reports blood eosinophil counts but no sensitivity/specificity data*
Chou, Kun-Ta, Su, Kang-Cheng, Hsiao, Yi-Han et al. (2017) Post-bronchodilator Reversibility of FEV1 and Eosinophilic Airway Inflammation in COPD. Archivos de bronconeumologia 53(10): 547-553	- Population not relevant to this review protocol *COPD patients; no relevant data: correlation of sputum eosinophilia with FEV1 values in COPD population*
Cianchetti, S, Bacci, E, Ruocco, L et al. (2014) Are sputum eosinophil cationic protein and eosinophils differently associated with clinical and functional findings of asthma?. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 44(5): 673-80	- Population not relevant to this review protocol *population of known asthmatics; no relevant data*
Cosickic, Almira, Skokic, Fahrija, Selimovic, Amela et al. (2017) Development of Respiratory Allergies, Asthma and Allergic Rhinits in Children with Atopic Dermatitis. Acta clinica Croatica 56(2): 308-317	- No relevant data *Correlational data reported to examine risk factors including eosinophil count to developing asthma*
Cote, Andreanne, Russell, Richard J, Boulet, Louis-Philippe et al. (2020) Managing Chronic Cough Due to Asthma and NAEB in Adults and Adolescents: CHEST Guideline and Expert Panel Report. Chest 158(1): 68-96	- Systematic review used as source of primary studies
Coumou, Hanneke, Westerhof, Guus A, de Nijs, Selma B et al. (2018) Diagnosing persistent blood eosinophilia in asthma with single blood eosinophil or exhaled nitric oxide level. Respiratory medicine 141: 81-86	- Population not relevant to this review protocol *people being treated with ICS*
de Farias, Camyla F, Amorim, Maria M F, Dracoulakis, Michel et al. (2017) Nasal lavage, blood or sputum: Which is best for phenotyping asthma?. Respirology (Carlton, Vic.) 22(4): 671-677	- Population not relevant to this review protocol *People with known asthma being treated with ICS*

Study	Code [Reason]
Demarche, Sophie, Schleich, Florence, Henket, Monique et al. (2016) Detailed analysis of sputum and systemic inflammation in asthma phenotypes: are paucigranulocytic asthmatics really non-inflammatory?. BMC pulmonary medicine 16: 46	- Data not reported in an extractable format or a format that can be analysed
Dogru, M and Seren, L P (2017) Serum 25-hydroxyvitamin D levels in children with recurrent wheezing and relation to the phenotypes and frequency of wheezing. European annals of allergy and clinical immunology 49(6): 257-262	- No relevant data *reports eosinophils in people with and without wheezing but no diagnostic accuracy data*
Dong, Z., Myklebust, A., Johnsen, I.B. et al. (2023) Type 2 cytokine genes as allergic asthma risk factors after viral bronchiolitis in early childhood. Frontiers in Immunology 13: 1054119	- Incorrect outcome *No relevant outcomes from protocol*
Farne, H.A., Wilson, A., Powell, C. et al. (2017) Anti-IL5 therapies for asthma. Cochrane Database of Systematic Reviews 2017(9): cd010834	- No relevant data *Cochrane review with different aim to the current review, comparing different treatments for asthma with randomisation not done based on blood eosinophil counts*
Feng, M.; Yang, X.; He, Y. (2019) Effects of bronchial provocation test and bronchial dilation test for the diagnosis of lung diseases. Artificial Cells, Nanomedicine and Biotechnology 47(1): 1452-1457	- No relevant data
Feng-Jia, Chen, Xin-Yan, Huang, Geng-Peng, Lin et al. (2018) Validity of fractional exhaled nitric oxide and small airway function indices in diagnosis of cough-variant asthma. The Journal of asthma : official journal of the Association for the Care of Asthma 55(7): 750-755	- Study does not contain an intervention relevant to this review protocol *no blood eosinophil measures*
Fitzpatrick, Anne M, Grunwell, Jocelyn R, Cottrill, Kirsten A et al. (2023) Blood Eosinophils for Prediction of Exacerbation in Preschool Children With Recurrent Wheezing. The journal of allergy and clinical immunology. In practice 11(5): 1485-1493e8	- Incorrect outcome *No process for diagnosis of asthma reported (no reference standard etc)*
Fujimura, M, Songur, N, Kamio, Y et al. (1997) Detection of eosinophils in hypertonic saline-induced sputum in patients with chronic	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
nonproductive cough. The Journal of asthma : official journal of the Association for the Care of Asthma 34(2): 119-26	*sputum eosinophilia not blood eosinophils*
Gangwar, R.S., Minai-Fleminger, Y., Seaf, M. et al. (2017) CD48 on blood leukocytes and in serum of asthma patients varies with severity. Allergy: European Journal of Allergy and Clinical Immunology 72(6): 888-895	- Population not relevant to this review protocol *approximately 30% with previous ICS use*
Gao, Jie, Chen, Zhaocheng, Jie, Xiang et al. (2018) Both fractional exhaled nitric oxide and sputum eosinophil were associated with uncontrolled asthma. Journal of asthma and allergy 11: 73-79	- Population not relevant to this review protocol *known asthmatic patients with no comparison group; eosinophil sample obtained from sputum not blood*
Gao, Jie and Wu, Feng (2018) Association between fractional exhaled nitric oxide, sputum induction and peripheral blood eosinophil in uncontrolled asthma. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology 14: 21	- Population not relevant to this review protocol *case series of peple with known asthma; no comparison group*
Gao, Jie, Zhou, Wutie, Chen, Bida et al. (2017) Sputum cell count: biomarkers in the differentiation of asthma, COPD and asthma-COPD overlap. International journal of chronic obstructive pulmonary disease 12: 2703-2710	- No relevant data *results relevant to sputum eosinophilia not blood sampled*
Halvani, Abolhasan; Tahghighi, Fatemeh; Nadooshan, Hossein Hadi (2012) Evaluation of correlation between airway and serum inflammatory markers in asthmatic patients. Lung India : official organ of Indian Chest Society 29(2): 143-6	- Population not relevant to this review protocol *known asthmatic patients 50% of which had ICS use; no relevant data*
Hambleton, Kirsty, Connolly, Clare M, Borg, Catherine et al. (2017) Comparison of the peripheral blood eosinophil count using near-patient testing and standard automated laboratory measurement in healthy, asthmatic and COPD subjects. International journal of chronic obstructive pulmonary disease 12: 2771-2775	- Incorrect outcome *detecting asthma and COPD vs no asthma/COPD in a mixed population of known asthmatics, people with COPD and controls*
Hancox, Robert J; Pavord, Ian D; Sears, Malcolm R (2018) Associations between blood eosinophils and decline in lung function among	- No relevant data *correlational data; no diagnostic accuracy calculable*

Study	Code [Reason]
adults with and without asthma. The European respiratory journal 51(4)	
Hilvering, B, Vijverberg, S J H, Jansen, J et al. (2017) Diagnosing eosinophilic asthma using a multivariate prediction model based on blood granulocyte responsiveness. Allergy 72(8): 1202-1211	- Population not relevant to this review protocol *known asthmatics, no comparison group*
Holden, K.A., Roland, D., Welsh, K.G. et al. (2017) Comparison of Blood Eosinophil Numbers between Acute Asthma and Stable Disease in Children with Preschool Wheeze. Pediatric, Allergy, Immunology, and Pulmonology 30(4): 210-217	- Incorrect outcome *distinguishing between children with wheezing and no wheezing; unclear if diagnosis of asthma was made at any point*
Hou, Xiangqing, Luo, Wenting, Gan, Hui et al. (2022) Childhood blood eosinophils and symptoms of allergic disorders: a cross-sectional study in Southern China. Annals of medicine 54(1): 2929-2940	- Incorrect outcome *Only reports on associations between eosinophils and asthma; no outcomes as specified in protocol*
Hsiao, Yi-Han, Lin, Yu-Jung, Jeng, Tien-Hsin et al. (2022) Potentiality of impulse oscillometry to evaluate bronchodilator reversibility in untreated adult patients with newly diagnosed asthma. Journal of the Chinese Medical Association : JCMA 85(8): 859-865	- No relevant data *no diagnostic test accuracy data for blood eosinophil*
Huang, W.-C., Fox, G.J., Pham, N.Y. et al. (2021) A syndromic approach to assess diagnosis and management of patients presenting with respiratory symptoms to healthcare facilities in Vietnam. ERJ Open Research 7(1): 00572-2020	- No relevant data
Hunter, Cameron J, Brightling, Christopher E, Woltmann, Gerrit et al. (2002) A comparison of the validity of different diagnostic tests in adults with asthma. Chest 121(4): 1051-7	- Duplicate reference
Hur, Gyu-Young, Ye, Young-Min, Yang, Eunmi et al. (2020) Serum potential biomarkers according to sputum inflammatory cell profiles in adult asthmatics. The Korean journal of internal medicine 35(4): 988-997	- Population not relevant to this review protocol *all were known asthmatics; measuring sputum eosinophilia*
Inoue, Hideki, Ito, Isao, Niimi, Akio et al. (2017) Association of interleukin 1 receptor-like 1 gene polymorphisms with eosinophilic phenotype in	- Population not relevant to this review protocol

Study	Code [Reason]
Japanese adults with asthma. Respiratory investigation 55(6): 338-347	*retrospective study of known asthmatics; no relevant data: correlational data between tests including FeNO and blood eosinophil counts*
James, A, Janson, C, Malinovschi, A et al. (2017) Serum periostin relates to type-2 inflammation and lung function in asthma: Data from the large population-based cohort Swedish GA(2)LEN. Allergy 72(11): 1753-1760	- Data not reported in an extractable format or a format that can be analysed *no relevant data; incorrect reference standard: diagnosis of asthma was self-reposted*
Jiang, Yi, An, Ruoli, Cheng, Li et al. (2021) Classification of non-acute bronchial asthma according to allergy and eosinophil characteristics: a retrospective study. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology 17(1): 45	- Population not relevant to this review protocol *people with known asthma; no comparison group and no relevant data reported*
Karakoc, F, Remes, S T, Martinez, F D et al. (2002) The association between persistent eosinophilia and asthma in childhood is independent of atopic status. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 32(1): 51-6	- Population not relevant to this review protocol *1246 healthy infants, not suspected of asthma, recruited in a longitudinal prospective birth cohort study; no sensitivity/specificity data*
Kawamatawong, T.; Charoenniwassakul, S.; Rerkpattanapipat, T. (2017) The asthma and chronic obstructive pulmonary disease overlap syndrome in tertiary care setting Thailand. Asia Pacific Allergy 7(4): 227-233	- No relevant data *reports mean eosinophil count between asthma and COPD patients, no diagnostic accuracy data*
Ketelaar, M E, van de Kant, K D, Dijk, F N et al. (2017) Predictive value of serum sST2 in preschool wheezers for development of asthma with high FeNO. Allergy 72(11): 1811-1815	- No relevant data
Khadadah, M, Onadeko, B O, Ezeamuzie, C I et al. (2000) The association of skin test reactivity, total serum IgE levels, and peripheral blood eosinophilia with asthma in Kuwait. The Journal of asthma : official journal of the Association for the Care of Asthma 37(6): 481-8	- Data not reported in an extractable format or a format that can be analysed *no sensitivity/specificity data reported or calculable. Paper reports number of cases with blood eosinophil above a certain cut-off but it is unclear if 'cases' involved both people with asthma and controls; correlational data between blood eosinophil and other measures reported.*
Koller, D Y, Wojnarowski, C, Herkner, K R et al. (1997) High levels of eosinophil cationic protein in wheezing infants predict the development of	- Population not relevant to this review protocol *Infants aged 4-9 months*

Study	Code [Reason]
asthma. The Journal of allergy and clinical immunology 99(6pt1): 752-6	
Korevaar, D.A., Westerhof, G.A., Spijker, R. et al. (2014) Diagnostic accuracy of markers for detection of airway eosinophilia in asthma: A systematic review. European Respiratory Journal	- Full text paper not available *abstract only*
Korevaar, Daniel A, Westerhof, Guus A, Wang, Junfeng et al. (2015) Diagnostic accuracy of minimally invasive markers for detection of airway eosinophilia in asthma: a systematic review and meta-analysis. The Lancet. Respiratory medicine 3(4): 290-300	- Systematic review used as source of primary studies *Incorrect reference standard: sputum eosinophil; large number of studies in corticosteroid treated patients only*
Koshak, E A and Alamoudi, O S (1999) Do eosinophil counts correlate differently with asthma severity by symptoms versus peak flow rate?. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 83(6pt1): 567-71	- Population not relevant to this review protocol *Known asthmatics; no relevant data: only correlational data reported*
Kroegel, C, Schuler, M, Forster, M et al. (1998) Evidence for eosinophil activation in bronchiectasis unrelated to cystic fibrosis and bronchopulmonary aspergillosis: discrepancy between blood eosinophil counts and serum eosinophil cationic protein levels. Thorax 53(6): 498-500	- No relevant data *comparison of eosinophil levels in people with previously proven or newly diagnosed bronchiectasis seeking medical advice, people with COPD, healthy controls; no diagnostic accuracy data*
Kumar, Raj and Gupta, Nitesh (2017) Exhaled nitric oxide atopy, and spirometry in asthma and rhinitis patients in India. Advances in respiratory medicine 85(4): 186-192	- No relevant data *no diagnostic accuracy data available for blood eosinophils*
Kumar, Roshan M, Pajanivel, R, Koteeswaran, G et al. (2017) Correlation of total serum immunoglobulin E level, sputum, and peripheral eosinophil count in assessing the clinical severity in bronchial asthma. Lung India : official organ of Indian Chest Society 34(3): 256-261	- Population not relevant to this review protocol *all known asthmatics with no comparison group; no diagnostic accuarcy data*
Kuwasaki, T, Chihara, J, Kayaba, H et al. (1998) Whole-blood flow-cytometric analysis of eosinophil EG2 expression as a marker of the pathological conditions of asthma. International archives of allergy and immunology 117suppl1: 77-80	- No relevant data *comparison of EG2 positive eosinophil between asthmatics and controls; no relevant data*

Study	Code [Reason]
Li, Jiang-Hua, Han, Rui, Wang, Yu-Bo et al. (2021) Diagnostic possibility of the combination of exhaled nitric oxide and blood eosinophil count for eosinophilic asthma. BMC pulmonary medicine 21(1): 259	- No relevant data *no data for the test in isolation; to be included in the combination of tests review*
Li, Jinfeng, Wang, Fangfang, Lin, Cunzhi et al. (2017) The efficacy and safety of reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: A systematic review and meta-analysis. The Journal of asthma : official journal of the Association for the Care of Asthma 54(3): 300-307	- Systematic review used as source of primary studies
Li, Meng, Yang, Tian, He, Ruiqing et al. (2020) The Value of Inflammatory Biomarkers in Differentiating Asthma-COPD Overlap from COPD. International journal of chronic obstructive pulmonary disease 15: 3025-3037	- Population not relevant to this review protocol *mixed population of COPD and people with COPD-asthma overlap*
Li, Min, Wen Ma, Zi, Jun Deng, Su et al. (2022) Development and validation of a noninvasive prediction model for identifying eosinophilic asthma. Respiratory medicine 201: 106935	- Data not reported in an extractable format or a format that can be analysed *Multivariate model testing variables including FeNO and blood eosinophils to predict eosinophilic asthma; no sensitivity/specificity data*
Li, Y, Wang, H, Gao, Y et al. (2017) Change of serum periostin level in children with bronchial asthma and significance. Journal of jilin university medicine edition 43(1): 101-105	- Study not reported in English
Liu, Jiaxing, Xu, Rong, Zhan, Chen et al. (2019) Clinical utility of ultrahigh fractional exhaled nitric oxide in predicting bronchial hyperresponsiveness in patients with suspected asthma. Postgraduate medical journal 95(1128): 541-546	- No relevant data *reports numbers of sputum eosinophils; no diagnostic accuracy data*
Liu, Tian, Wu, Jinxiang, Zhao, Jiping et al. (2015) Type 2 innate lymphoid cells: A novel biomarker of eosinophilic airway inflammation in patients with mild to moderate asthma. Respiratory medicine 109(11): 1391-6	- Incorrect outcome *eosinophilic airway inflammation*
Lluncor, Marina, Barranco, Pilar, Amaya, Emerson-Daniel et al. (2019) Relationship between upper airway diseases, exhaled nitric oxide, and bronchial hyperresponsiveness to	- Study does not contain an intervention relevant to this review protocol *blood eosinophil not measures; no relevant data*

Study	Code [Reason]
methacholine. The Journal of asthma : official journal of the Association for the Care of Asthma 56(1): 53-60	
Majoor, CJ, Sneeboer, MS, De Kievit, A et al. (2016) Eosinophilic inflammation amplifies the prednisolone-induced prothrombotic state in asthma. European respiratory journal 48	- Full text paper not available *abstract only*
Malerba, Mario, Ragnoli, Beatrice, Azzolina, Danila et al. (2021) Predictive Markers of Bronchial Hyperreactivity in a Large Cohort of Young Adults With Cough Variant Asthma. Frontiers in pharmacology 12: 630334	- No relevant data *data related to eosinophil count in induced sputum not blood*
Maspero, J; Jacobs, J; Garin, M (2016) Improvements in asthma quality of life questionnaire (AQLQ) domains with reslizumab in patients with inadequately controlled asthma and elevated blood eosinophils. Journal of allergy and clinical immunology 137(2suppl1): ab15	- Conference abstract
Metso, T, Kilpio, K, Bjorksten, F et al. (1996) Can early asthma be confirmed by laboratory tests?. Allergy 51(4): 226-31	- Population not relevant to this review protocol *all but one participant were receiving anti-inflamatory medication (potentially steroids)*
Mikalsen, Ingvild Bruun; Halvorsen, Thomas; Oymar, Knut (2014) Blood eosinophil counts during bronchiolitis are related to bronchial hyper-responsiveness and lung function in early adolescence. Acta paediatrica (Oslo, Norway : 1992) 103(1): 86-92	- Population not relevant to this review protocol *children hospitalised for acute bronchiolitis in their first year of life; measurements taken at 20 months and then at 11 years; no diagnostic accuracy data*
Mogensen, Ida, Vonk, Judith M, Wijnant, Sara R A et al. (2020) Blood eosinophil level and lung function trajectories: cross-sectional and longitudinal studies in European cohorts. ERJ open research 6(4)	- No relevant data *correlational analysis between different tests; no diagnostic accuracy data calculable*
Murphy, V. and Gibson, P. (2016) The use of fractional exhaled nitric oxide-based management for non-eosinophilic asthma during pregnancy. Respirology 21(suppl2): 93	- Conference abstract
Murphy, V.E. and Gibson, P.G. (2016) The use of fractional exhaled nitric oxide (FENO)-based management for non-eosinophilic asthma during	- Conference abstract

Study	Code [Reason]
pregnancy. Journal of Paediatrics and Child Health 52(supplement2): 41-42	
Nair, Parameswaran, Wenzel, Sally, Rabe, Klaus F et al. (2017) Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. The New England journal of medicine 376(25): 2448-2458	- No relevant data *RCT with randomisation not based on eosinophil blood count; no diagnostic accuracy data*
Nakwan, Narongwit, Thidarat Ruklerd, Thidarat, Perkleang, Thitima et al. (2022) The levels and correlations of FeNO, blood eosinophils and lung function in well-controlled asthma. Advances in respiratory medicine	- Population not relevant to this review protocol *people with known well-controlled asthma*
Nordlund, B, Konradsen, J R, Kull, I et al. (2012) IgE antibodies to animal-derived lipocalin, kallikrein and secretoglobin are markers of bronchial inflammation in severe childhood asthma. Allergy 67(5): 661-9	- Population not relevant to this review protocol *all were participants with known asthma; no relevant data: comparison between severe and controlled asthmatics*
Park, H.-S., Lee, S.H., Werkstrom, V. et al. (2018) Benralizumab reduces exacerbations and improves lung function in patients from republic of Korea with severe, uncontrolled asthma: Subgroup analysis of the SIROCCO Trial. Journal of Allergy and Clinical Immunology 141(2supplement1): ab14	- Conference abstract
Park, J W, Whang, Y W, Kim, C W et al. (1998) Eosinophil count and eosinophil cationic protein concentration of induced sputum in the diagnosis and assessment of airway inflammation in bronchial asthma. Allergy and asthma proceedings 19(2): 61-7	- No relevant data *data concerning sputum eosinophilia not blood samples*
Pavord, Ian D, Holliday, Mark, Reddel, Helen K et al. (2020) Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: a prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial. The Lancet. Respiratory medicine 8(7): 671-680	- Population not relevant to this review protocol *people with a self-reported diagnosis of asthma; no relevant outcomes*
Perfetti, L., Galdi, E., Brame, B. et al. (1999) Serum eosinophil cationic protein (sECP)in subjects with a history of asthma symptoms with or without rhinitis. Allergy: European Journal of Allergy and Clinical Immunology 54(9): 962-967	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
Petsky, H.L.; Kew, K.M.; Chang, A.B. (2016) Exhaled nitric oxide levels to guide treatment for children with asthma. Cochrane Database of Systematic Reviews 2016(11): cd011439	- No relevant data *Review with different aim: evaluating the efficacy of tailoring asthma medications based on fractional exhaled nitric oxide (FeNO), in comparison to not using FeNO; no relevant data/outcomes, not looking at the test of interest*
Pizzichini, E, Pizzichini, M M, Efthimiadis, A et al. (1997) Measuring airway inflammation in asthma: eosinophils and eosinophilic cationic protein in induced sputum compared with peripheral blood. The Journal of allergy and clinical immunology 99(4): 539-44	- Data not reported in an extractable format or a format that can be analysed *correlation and AUC data for blood and sputum eosinophil measures between asthmatics and controls; no sensitivity/specificity data extractable*
Power, Sharon, Williams, Mathew, Semprini, Alex et al. (2017) RCT of the effect of berryfruit polyphenolic cultivar extract in mild steroid-naive asthma: a cross-over, placebo-controlled study. BMJ open 7(3): e013850	- No relevant data *RCT with randomisation and diagnosis not based on blood eosinophil counts.*
Prehn, A, Seger, R A, Faber, J et al. (1998) The relationship of serum-eosinophil cationic protein and eosinophil count to disease activity in children with bronchial asthma. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 9(4): 197-203	- Data not reported in an extractable format or a format that can be analysed *Correlational data, no diagnostic accuracy*
Qing, Miao, Wei, Xu, Zhen, Li et al. (2017) Influence of Sensitization Patterns on Fractional Exhaled Nitric Oxide in Asthmatic Children. Iranian journal of allergy, asthma, and immunology 16(1): 53-59	- Conference abstract
Racine, Genevieve, Castano, Roberto, Cartier, Andre et al. (2017) Diagnostic Accuracy of Inflammatory Markers for Diagnosing Occupational Asthma. The journal of allergy and clinical immunology. In practice 5(5): 1371-1377e1	- Incorrect outcome *occupational asthma*
Ramonell, Richard P and Iftikhar, Imran H (2020) Effect of Anti-IL5, Anti-IL5R, Anti-IL13 Therapy on Asthma Exacerbations: A Network Meta-analysis. Lung 198(1): 95-103	- Systematic review used as source of primary studies
Ramsahai, J.M., Simpson, J., Cook, A. et al. (2020) Managing T2-High Inflammation in	- Full text paper not available

Study	Code [Reason]
Severe Asthma - Are Biomarkers Better Than Clinician Judgement?. European Respiratory Journal 56(supplement64)	*abstract only*
Rio Ramirez, Maria Teresa, Juretschke Moragues, Maria Antonia, Fernandez Gonzalez, Rocio et al. (2018) Value of Exhaled Nitric Oxide (FeNO) And Eosinophilia During the Exacerbations of Chronic Obstructive Pulmonary Disease Requiring Hospital Admission. COPD 15(4): 369-376	- Population not relevant to this review protocol *people with acute exacerbation of COPD; study aiming to characterise the COPD phenotype*
Roquet, A, Hallden, G, Ihre, E et al. (1996) Eosinophil activity markers in peripheral blood have high predictive value for bronchial hyperreactivity in patients with suspected mild asthma. Allergy 51(7): 482-8	- No relevant data *diagnostic accuracy not given*
Roseti, S., Corren, J., Parnes, J. et al. (2017) Late Breaking Abstract-Efficacy and safety of tezepelumab in adults with severe asthma: A randomized phase 2 study. European Respiratory Journal 50(supplement61)	- Full text paper not available *abstract only*
Rydell, Niclas, Nagao, Mizuho, Moverare, Robert et al. (2022) Serum Eosinophilic Cationic Protein Is a Reliable Biomarker for Childhood Asthma. International archives of allergy and immunology 183(7): 744-752	- Population not relevant to this review protocol *Study recruited volunteers, not people with respiratory symptoms*
Sanz, M L, Parra, A, Prieto, I et al. (1997) Serum eosinophil peroxidase (EPO) levels in asthmatic patients. Allergy 52(4): 417-22	- Conference abstract
Satouchi, M, Maeda, H, Yu, Y et al. (1996) Clinical significance of the increased peak levels of exhaled nitric oxide in patients with bronchial asthma. Internal medicine (Tokyo, Japan) 35(4): 270-5	- No relevant data *Nitric oxide measurement; no eosinophilic blood count; no diagnostic accuracy data*
Shields, M D, Brown, V, Stevenson, E C et al. (1999) Serum eosinophilic cationic protein and blood eosinophil counts for the prediction of the presence of airways inflammation in children with wheezing. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 29(10): 1382-9	- Population not relevant to this review protocol *47% had steroid use*
Shin, Sheojung, Whitmore, George Alex, Boulet, Louis-Philippe et al. (2023) Anticipating	- Data not reported in an extractable format or a format that can be analysed

Study	Code [Reason]
undiagnosed asthma in symptomatic adults with normal pre- and post-bronchodilator spirometry: a decision tool for bronchial challenge testing. BMC pulmonary medicine 23(1): 496	*Paper doesn't give any useable cut-offs for any specific tests, and as a combination test it also includes 'female sex' as a parameter so not restricted to only the tests we are assessing.*
Silvestri, Michela, Sabatini, Federica, Sale, Rosa et al. (2003) Correlations between exhaled nitric oxide levels, blood eosinophilia, and airway obstruction reversibility in childhood asthma are detectable only in atopic individuals. Pediatric pulmonology 35(5): 358-63	- Population not relevant to this review protocol *Known asthmatic children with and without atopy; no relevant data: comparison of blood eosinophilia and FeNO levels in asthmatic children with and without atopy.*
Soma, Tomoyuki, Iemura, Hidetoshi, Naito, Erika et al. (2018) Implication of fraction of exhaled nitric oxide and blood eosinophil count in severe asthma. Allergology international : official journal of the Japanese Society of Allergology 67s: 3-s11	- Conference abstract
Tomasiak-Lozowska, Maria Magdalena, Zietkowski, Ziemowit, Przeslaw, Katarzyna et al. (2012) Inflammatory markers and acid-base equilibrium in exhaled breath condensate of stable and unstable asthma patients. International archives of allergy and immunology 159(2): 121-9	- Population not relevant to this review protocol *32% ICS use; no diagnostic accuracy data*
Tomita, Katsuyuki, Sano, Hiroyuki, Chiba, Yasutaka et al. (2013) A scoring algorithm for predicting the presence of adult asthma: a prospective derivation study. Primary care respiratory journal : journal of the General Practice Airways Group 22(1): 51-8	- Inadequate ICS washout period *24-hour washout applied prior to testing*
Tsilogianni, Zoi, Ntontsi, Polyxeni, Papaioannou, Andriana I et al. (2017) Biomarkers Guided Treatment Strategies in Adult Patients with Asthma: Ready for the Clinical Field?. Archivum immunologiae et therapiae experimentalis 65(1): 1-9	- Review article but not a systematic review
Tuchinda, M, Habananada, S, Vareenil, J et al. (1987) Asthma in Thai children: a study of 2000 cases. Annals of allergy 59(3): 207-11	- Duplicate reference
Turner, M O, Johnston, P R, Pizzichini, E et al. (1998) Anti-inflammatory effects of salmeterol compared with beclomethasone in eosinophilic mild exacerbations of asthma: a randomized,	- Population not relevant to this review protocol *people with known asthma on treatment in inhaled beta-agonists with or without Inhaled steroids*

Study	Code [Reason]
placebo controlled trial. Canadian respiratory journal 5(4): 261-8	
Ulrik, C S (1998) Eosinophils and pulmonary function: an epidemiologic study of adolescents and young adults. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 80(6): 487-93	- Population not relevant to this review protocol *Most likely large number or all participants were on steroid medication as study reports they were allowed to continue with their corticosteroid medication during the study; no diagnostic accuracy data*
Vanto, T and Koskinen, P (1998) Serum eosinophil cationic protein in the evaluation of asthma severity in children. Allergy 53(4): 415-9	- Population not relevant to this review protocol *>10% of participants were already receiving ICS and no washout period was applied*
Vatrella, A, Ponticiello, A, Parrella, R et al. (1996) Serum eosinophil cationic protein (ECP) as a marker of disease activity and treatment efficacy in seasonal asthma. Allergy 51(8): 547-55	- No relevant data *known asthmatics randomised to receive inhaled corticosteroids or placebo*
Vila-Indurain, B; Munoz-Lopez, F; Martin-Mateos, M (1999) Evaluation of blood eosinophilia and the eosinophil cationic protein (ECP) in the serum of asthmatic children with varying degree of severity. Allergologia et immunopathologia 27(6): 304-8	- Data not reported in an extractable format or a format that can be analysed *reports eosinophil counts in asthmatics vs controls but no diagnostic accuracy data*
Wang, Jingcai, Yang, Lixin, Sun, Peng et al. (2023) Expression patterns of serum miR-27a-3p and activating transcription factor 3 in children with bronchial asthma and their correlations with airway inflammation. The clinical respiratory journal	- Incorrect outcome *No relevant outcomes and cases and controls*
Wei, Xuan, Li, Xiaofeng, Wei, Zuyou et al. (2022) Clinical analysis of hypereosinophilic syndrome first presenting with asthma-like symptoms. Annals of medicine 54(1): 11-21	- No relevant data *correlational data*
Yancey, S.W., Mayer, B., Gunsoy, N. et al. (2016) Exacerbation reduction in severe eosinophilic asthma based on eosinophil thresholds. Journal of Allergy and Clinical Immunology 137(2suppl1): ab208	- Conference abstract
Yancey, Steven W; Bradford, Eric S; Keene, Oliver N (2019) Disease burden and efficacy of mepolizumab in patients with severe asthma	- Population not relevant to this review protocol

Study	Code [Reason]
and blood eosinophil counts of >=150-300cells/muL. Respiratory medicine 151: 139-141	*known asthmatic; comparison of outcomes in subgroups with different level of eosinophil counts but participants not diagnosed/randomised based on blood eosinophil levels; no diagnostic accuracy data*
Yune, Sehyo, Lee, Jin Young, Choi, Dong Chull et al. (2015) Fractional exhaled nitric oxide: comparison between portable devices and correlation with sputum eosinophils. Allergy, asthma & immunology research 7(4): 404-8	- No relevant data *no diagnostic accuracy data relevant to eosinophil counts*
Zeiger, R.S., Schatz, M., Li, Q. et al. (2015) The association of blood eosinophil counts to future asthma exacerbations in children with persistent asthma. Journal of Allergy and Clinical Immunology: In Practice 3(2): 283-287e4	- Incorrect outcome *asthma exacerbations in relation to blood eosinophil levels*
Zeiger, Robert S, Schatz, Michael, Li, Qiaowu et al. (2017) Burden of Chronic Oral Corticosteroid Use by Adults with Persistent Asthma. The journal of allergy and clinical immunology. In practice 5(4): 1050-1060e9	- Population not relevant to this review protocol *people with known persistent asthma at baseline; no relevant data*
Zhao, Bo, Zheng, Haiming, Li, Xiaopan et al. (2021) Evaluation of the peripheral blood eosinophil count as a predictor for fractional exhaled nitric oxide or bronchodilator reversibility test outcome. Allergy and asthma proceedings 42(3): 228-234	- Population not relevant to this review protocol *>10% of participants were current ICS users and no washout period was applied prior to testing*
Zhu, Haiyan, Hao, Chuangli, Yu, Xingmei et al. (2021) Fractional Exhaled Nitric Oxide (FeNO) Integrating Airway Hyperresponsiveness (AHR) Examination Promotes Etiologic Diagnosis and Treatment for Children with Chronic Cough. Medical science monitor : international medical journal of experimental and clinical research 27: e928502	- No relevant data *sputum eosinophils*
Zhu, Huiyuan, Yan, Shaochun, Wu, Jingshuo et al. (2021) Serum macrophage migration inhibitory factor as a potential biomarker to evaluate therapeutic response in patients with allergic asthma: an exploratory study. Journal of Zhejiang University. Science. B 22(6): 512-520	- No relevant data *AUC curves calculated to determine sensitivity/specificity of blood eosinophil count and FeNO to predict therapeutic response to treatment*
Zhu, Zheng, Xie, Yanqing, Guan, Weijie et al. (2016) FeNO for detecting lower airway	- No relevant data

Study	Code [Reason]
involvement in patients with allergic rhinitis. Experimental and therapeutic medicine 12(4): 2336-2340	*no diagnostic accuracy data for blood eosinophils*
Zietkowski, Z, Bodzenta-Lukaszyk, A, Tomasiak, M M et al. (2006) Comparison of exhaled nitric oxide measurement with conventional tests in steroid-naive asthma patients. Journal of investigational allergology & clinical immunology 16(4): 239-46	- Duplicate reference
Zorampari, C., Prakash, A., Rehan, H.S. et al. (2022) Serum dipeptidyl peptidase-4 and eosinophil cationic protein levels in patients of bronchial asthma. Pulmonary Pharmacology and Therapeutics 72: 102109	- Population not relevant to this review protocol *asthma patients on corticosteroids; no relevant data*

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 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.