British Thoracic Society

NICE National Institute for Health and Care Excellence

Healthcare Improvement Scotland | SIGN

Final

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

## [K] Evidence reviews for diagnostic accuracy of combination of tests

*BTS/NICE/SIGN collaborative guideline NG245*

*Evidence reviews underpinning recommendations 1.2.1, 1.2.2, 1.2.3, 1.2.4, 1.2.5, 1.2.6, 1.2.7, 1.3.1 and 1.3.2. in the guideline*

*November 2024*

*Final*

*Developed by BTS, NICE and SIGN*

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# Contents

# 1. Combination of tests

## 1.1 Review question

In people under investigation for asthma, what is the diagnostic test accuracy and clinical and cost effectiveness of a combination of tests?

### 1.1.1 Introduction

While it is important to look at the individual accuracy of tests which might help in the diagnosis of asthma, conventional wisdom is that no single test is sufficient to confirm the diagnosis. The various available tests are associated with different aspects of the pathophysiology of asthma (for example, some such as the eosinophil level are markers of allergic inflammation while others such as bronchodilator reversibility measure the variability of airflow obstruction). It is therefore likely that a suitable combination of tests will be more useful in the diagnostic process than any single test. The purpose of this review is to look at evidence on the effectiveness of any combination of the tests covered in other sections within this guideline in the diagnosis of asthma.

### 1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

No test-and-treat evidence was found so only the diagnostic accuracy evidence was reported.

**Table 1: PICO characteristics of diagnostic accuracy review question**

| | |
|---|---|
| **Population** | People with suspected asthma (presenting with respiratory symptoms).<br>Ages stratified into the following 2 groups:<br>• Children and young people (5-16 years old)<br>• Adults (≥17 years old)<br><br>Exclusion:<br>• Children under 5 years old<br>• People on steroid medication (washout period minimum of 4 weeks for inclusion) |
| **Target condition** | Asthma |
| **Index test** | Combinations of the following:<br>• Spirometry measures (report separately)<br>o FEV1/FVC ratio (<70%)<br>o Flow volume loop (graph)<br>o FEV1 (<80%) – if limited evidence from the above two measures<br>- FEV1 and FVC should be performed using the following criteria:<br>- Forced expiratory volume (FEV1) - patients perform manoeuvre until 3 readings are within 5% of each other (maximum 8 attempts) the measured value being the best of these 3 readings.<br>- Forced vital capacity (FVC) - patients perform manoeuvre until 3 readings are within 5% of each other (maximum 8 attempts) the measured value being the best of these 3 readings. |

| | |
|---|---|
| | • Bronchodilator response, measured using the following<br>  ○ PEF<br>  ○ FEV1<br>  - change in FEV1 % initial and change in FEV1 litres<br><br>• PEF variability (diurnal variability usually expressed as amplitude (highest – lowest reading) as a percentage of the mean or the highest reading). PEFv values should be recorded as the mean over a period of at least 3 days)<br><br>Skin prick tests for the most common allergens in children (1 - <5 years old, 5 - 16 years old) (reported separately)<br>• House dust mites<br>• Cat<br>• Dog<br>• Grass pollen* (native UK grasses)<br>• Tree pollen* (native UK trees)<br>• Mixed pollens* (native UK species)<br>• Aspergillus<br>• Alternaria<br>• Cladosporium<br>  ○ Cut off values: 3mm WHEAL (skin reaction) greater than the negative control in the presence of a positive control<br><br>• Serum IgE<br>• Total IgE<br>• Specific IgE* (including RAST test)<br>  ○ *Reported separately for the most common aero-allergens (dust mites, grass pollen, tree pollen, dog, cat, *Aspergillus, Alternaria, Cladosporium*).<br><br>• Fractional exhaled nitric oxide (FeNO) with a cut-off threshold between 20-50ppb and a flow rate of 50ml/s or equivalent.<br>• Peripheral blood eosinophil count (may be part of FBC)<br>• Bronchial challenge with:<br>  ○ Histamine PC20 and PD20<br>  ○ Methacholine PC20 and PD20<br>  ○ Cut-off threshold of 8mg/ml or a cut-off threshold identified from a ROC curve<br>• Mannitol<br>  ○ Cut-off threshold of 8mg/ml or a cut-off threshold identified from a ROC curve<br>• Exercise challenge test (>10% FEV1 bronchoconstriction in response to exercise – within 15 mins<br>  ○ Change in FEV1 ≥10% post-exercise |
| **Reference standard** | Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following (as appropriate based on the tests used in the study): |

| | |
|---|---|
| | • peak flow variability (cut-off value of more than 20% variability as indication of a positive test);<br>• 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);<br>• 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)<br>• FeNO<br><br>Maximum time period between the index test and reference standard: 12 months<br><br>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.<br>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. |
| **Statistical measures** | • Sensitivity - thresholds: upper 90%, lower 10%<br>• Specificity - thresholds: upper 80%, lower 50%<br>• Raw data to calculate 2x2 tables to calculate sensitivity and specificity<br>• Negative predictive value (NPV), Positive predictive value (PPV) |
| **Study design** | • Cross sectional studies<br>• 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

Six cross sectional studies were included in the review; (Bao, et al., 2021, Eom, et al., 2020, Koca Kalkan, et al., 2021, Parameswaran, et al., 1999, Porpodis, et al., 2017, Simpson, et al., 2024) these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below in Table 3 and 1.3 References. 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.

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

See the excluded studies list in Appendix H.

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

**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<br><br>N= 692<br><br>Mean age (SD): positive MCT; 43.90 (12.56), negative MCT: 43.80 (14.90)<br><br>China | Airway hyperresponsiveness to methacholine | FeNO and $FEV_1$/FVC<br><br>Eosinophils and $FEV_1$/FVC | Airway hyperresponsiveness was diagnosed using methacholine challenge testing | Retrospective cross-sectional study<br><br>Strata: Adults<br><br>ICS use: None within a month<br><br>Smoking status: Non-smokers<br><br>Indirectness: FeNO + $FEV_1$/FVC Downgraded by two increments due to index test (FeNO measurement standards not reported) and reference standard (unclear clinician decision in diagnosis) indirectness. Eosinophils + $FEV_1$/FVC downgraded by one increment due to reference standard indirectness |
| Eom 2020 (Eom et al., 2020) | N=275 children referred to an | Asthma | FeNO & spirometry combined | Asthma was assessed by a paediatric pulmonologist | Prospective cross-sectional study |

| Study | Population | Target condition | Index test | Reference standard | Comments |
|---|---|---|---|---|---|
| | outpatient clinic for diagnosis of asthma.<br><br>Age, mean (95%CI): Non-asthma diagnosis: 11.5 (10.7-12.3), asthma diagnosis: 11.6 (11.1-12.1)<br><br>South Korea | | | after at least 6 months of follow-up. The diagnosis of asthma was determined according to the Global Initiative for Asthma guidelines | Strata: Children/young people<br><br>ICS use: Four-week washout<br><br>Smoking status: No smokers, 40.6 and 45.2% of non-asthma and asthma diagnoses exposed to smoking |
| 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.<br><br>N=51 (n=19 eventually diagnosed with asthma)<br><br>Median age (SD): 40.2 (12.3) years<br><br>Turkey | Asthma | Absolute eosinophil count in peripheral blood and FeNO combined<br><br>Cut-off: Eosinophils >150/µl and FeNO >14 ppb | Bronchial hyperactivity defined by the methacholine bronchial provocation tests | Retrospective cohort study<br><br>Atopy presence: 12 (27.6%)<br><br>ICS use: Not reported<br><br>Smoking history n (%): never 36 (70.6%); ex-smoker 12 (23.5%), current smoker 3 (5.9%), pack years 4(1-60)<br><br>Indirectness: Downgraded by two increments due to population (ICS use not reported) and reference standard (clinician decision not |

| Study | Population | Target condition | Index test | Reference standard | Comments |
|---|---|---|---|---|---|
| | | | | | involved) indirectness |
| Parameswaran 1999 (Parameswaran et al., 1999) | N=132 medical records of people referred for evaluation of respiratory symptoms suggestive of asthma<br><br>Age, mean (SD): 38.9 (17.9) years<br><br>Canada | Asthma | Clinician diagnosis of asthma with access to methacholine challenge test and peak expiratory flow monitoring results | The diagnosis of the physician at his first assessment of the patient, without any tests, was coded as: definitely asthma; possibly asthma or definitely not asthma | Retrospective cross-sectional study<br><br>Strata: Adults<br><br>ICS use: Not reported<br><br>Smoking status: Not reported<br><br>Indirectness: Downgraded by one increment due to population (ICS use not reported) indirectness |
| Porpodis 2017 (Porpodis et al., 2017) | N=88 people with asthma related symptoms in the past month visiting an asthma clinic for asthma diagnosis<br><br>Age, mean (SD): 38.56 (16.73) years<br><br>Greece | Asthma | Bronchial challenge with methacholine (cut-off: PC20 FEV1 ≤16 mg/mL) + bronchial challenge with mannitol (cut-off: PD15 FEV1 or 10% between doses <625 mg) | Asthma diagnosis according to GINA guidelines: combination of at least a ≥12% (and ≥200 mL) increase in baseline FEV1 after albuterol, along with new symptoms of coughing, wheezing, or shortness of breath over the past month | Prospective cross-sectional study<br><br>Strata: Adults<br><br>ICS use: Treatment naïve<br><br>Smoking status: 15% current smokers |
| Simpson 2024 (Simpson et al., 2024) | Patients referred by general practitioners with symptoms suggestive of asthma<br><br>N=118; mean age | Asthma | ERS-defined asthma<br><br>NICE-defined asthma (pathways 1-6) | Diagnosis by an expert panel, including at least three asthma clinicians with access to history, physical examination, ACQ, and all test results before and after ICS | Prospective cross-sectional study<br><br>Strata: Adults |

| Study | Population | Target condition | Index test | Reference standard | Comments |
|---|---|---|---|---|---|
| | (SD): 26 (12) years<br><br>UK | | NICE-defined asthma/suspect asthma (pathways 1-9)<br><br>GINA-defined asthma | | ICS use: 4-week washout<br><br>Smoking status: Mixed (40 (35%) current or ex-smokers) |

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 combinations of diagnostic tests in children and young people**

| Studies | N | Risk of bias | Inconsistency | Indirectness | Imprecision | Effect size (95%CI) | Quality |
|---|---|---|---|---|---|---|---|
| Probability of asthma using logistical regression models including combinations as predictors (cut-off: 0.6) FeNO (individual cut-off: 19.6 ppb) + $FEV_1$ (individual cut-off 88.4%) vs clinician diagnosis with bronchodilator reversibility or PEF variability tests | | | | | | | |
| 1 cross-sectional study | 275 | Not serious | Not serious | Not serious | Not serious | Sensitivity= 0.82 (0.76-0.87) | HIGH |
| | | Not serious | Not serious | Not serious | Serious[1] | Specificity= 0.80 (0.70-0.88) | MODERATE |
| Probability of asthma using logistical regression models including combinations as predictors (cut-off: 0.6) FeNO (individual cut-off: 19.6 ppb) + $FEV_1$/FVC (individual cut-off 85.3%) vs clinician diagnosis with bronchodilator reversibility or PEF variability tests | | | | | | | |
| 1 cross-sectional study | 275 | Not serious | Not serious | Not serious | Not serious | Sensitivity= 0.85 (0.79-0.90) | HIGH |
| | | Not serious | Not serious | Not serious | Serious[1] | Specificity= 0.75 (0.64-0.84) | MODERATE |

1. *Downgraded by one increment due to the 95%CI overlapping the threshold corresponding to 'high specificity' (80%)*

**Clinical evidence summary: diagnostic test accuracy for combinations of diagnostic tests in adults**

| Studies | N | Risk of bias | Inconsistency | Indirectness | Imprecision | Effect size (95%CI) | Quality |
|---|---|---|---|---|---|---|---|
| Bronchial challenge test with methacholine (cut-off: PC20 $FEV_1$ <8 mg/mL) + peak expiratory flow variability (cut-off: 20%) vs clinician diagnosis without objective tests | | | | | | | |
| | 132 | Very serious[1] | Not serious | Serious[2] | Not serious | Sensitivity= 0.75 (0.60-0.86) | VERY LOW |

| Studies | N | Risk of bias | Inconsistency | Indirectness | Imprecision | Effect size (95%CI) | Quality |
|---|---|---|---|---|---|---|---|
| 1 cross-sectional study | | Very serious[1] | Not serious | Serious[2] | Serious[3] | Specificity= 0.78 (0.67-0.86) | VERY LOW |
| Bronchial challenge with methacholine (cut-off: PC20 $FEV_1$ ≤16 mg/mL) + bronchial challenge with mannitol (cut-off: PD15 $FEV_1$ or 10% between doses <625 mg) vs clinician diagnosis with bronchodilator reversibility test | | | | | | | |
| 1 cross-sectional study | 88 | Very serious[1] | Not serious | Not serious | Not serious | Sensitivity= 0.65 (0.52-0.76) | LOW |
| | | Very serious[1] | Not serious | Not serious | Serious[3] | Specificity= 0.94 (0.76-1.00) | VERY LOW |
| Peripheral blood eosinophil count (cut-off: >150/µl) + FeNO (cut-off: >14 ppb) vs diagnosis with methacholine bronchial challenge test | | | | | | | |
| 1 cross-sectional study | 51 | Very serious[1] | Not serious | Very serious[4] | Serious[5] | Sensitivity= 1.00 (0.82-1.00) | VERY LOW |
| | | Very serious[1] | Not serious | Very serious[4] | Serious[6] | Specificity= 0.47 (0.29-0.65) | VERY LOW |
| FeNO (cut-off: 41 ppb) + $FEV_1$/FVC (cut-off: 84.67%) vs diagnosis with methacholine bronchial challenge test | | | | | | | |
| 1 cross-sectional study | 692 | Very serious[1] | Not serious | Very serious[7] | Serious[8] | Sensitivity= 0.86 (0.80-0.91) | VERY LOW |
| | | Very serious[1] | Not serious | Very serious[7] | Not serious | Specificity= 0.62 (0.57-0.66) | VERY LOW |
| Eosinophils (cut-off: 3.4% or 360 cells/µl) + $FEV_1$/FVC (cut-off: 84.67%) vs diagnosis with methacholine bronchial challenge test | | | | | | | |
| 1 cross-sectional study | 692 | Very serious[1] | Not serious | Serious[8] | Not serious | Sensitivity= 0.56 (0.49-0.64) | VERY LOW |
| | | Very serious[1] | Not serious | Serious[8] | Serious[3] | Specificity= 0.81 (0.77-0.84) | VERY LOW |
| ERS-defined asthma vs expert panel diagnosis with multiple diagnostic tests | | | | | | | |
| 1 cross-sectional study | 118 | Very serious[1] | Not serious | Not serious | Not serious | Sensitivity= 0.81 (0.70-0.90) | LOW |
| | | Very serious[1] | Not serious | Not serious | Serious[3] | Specificity= 0.85 (0.72-0.94) | VERY LOW |
| NICE-defined (pathways 1-6) asthma vs expert panel diagnosis with multiple diagnostic tests | | | | | | | |
| 1 cross-sectional study | 118 | Very serious[1] | Not serious | Not serious | Not serious | Sensitivity= 0.41 (0.30-0.54) | LOW |
| | | Very serious[1] | Not serious | Not serious | Not serious | Specificity= 1.00 (0.93-1.00) | LOW |
| NICE-defined (pathways 1-9) asthma or suspected asthma vs expert panel diagnosis with multiple diagnostic tests | | | | | | | |
| 1 cross-sectional study | 118 | Very serious[1] | Not serious | Not serious | Not serious | Sensitivity= 0.49 (0.36-0.61) | LOW |
| | | Very serious[1] | Not serious | Not serious | Not serious | Specificity= 1.00 (0.93-1.00) | LOW |
| GINA-defined asthma vs expert panel diagnosis with multiple diagnostic tests | | | | | | | |
| 1 cross-sectional study | 118 | Very serious[1] | Not serious | Not serious | Not serious | Sensitivity= 0.47 (0.35-0.59) | LOW |
| | | Very serious[1] | Not serious | Not serious | Not serious | Specificity= 1.00 (0.93-1.00) | LOW |

1. *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)*

2. *Downgraded by one increment due to population (ICS use not reported) indirectness*
3. *Downgraded by one increment due to the 95%CI overlapping the threshold corresponding to 'high specificity' (80%)*
4. *Downgraded by two increments due to population (ICS use not reported) and reference standard (clinician decision not involved in diagnosis) indirectness*
5. *Downgraded by one increment due to the 95%CI overlapping the threshold corresponding to 'high sensitivity' (90%)*
6. *Downgraded by one increment due to the 95%CI overlapping the threshold corresponding to 'low specificity' (50%)*
7. *Downgraded by two increments due to index test (no information on standards FeNO was conducted to) and reference standard (unclear clinician decision in diagnosis) indirectness*
8. *Downgraded by one increment due to reference standard (unclear clinician decision in diagnosis) indirectness*

## 1.1.7 Economic evidence

### 1.1.7.1 Included studies

Two health economic studies with the relevant comparison were included in this review. (Harnan, et al., 2015, National Institute for, et al., 2017) These are summarised in the health economic evidence profile below (Table 4) and the health economic evidence tables in Appendix G.

### 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

**Table 4: Health economic evidence profile: Sequence/combination of tests**

<table>
<tr><th>Study</th><th>Applicability</th><th>Limitations</th><th>Other comments</th><th>Incremental cost</th><th>Incremental effects</th><th>Cost effectiveness</th><th>Uncertainty</th></tr>
<tr>
<td>NICE 2017(National Institute for et al., 2017) (UK)</td>
<td>Directly applicable</td>
<td>Potentially serious limitations[a]</td>
<td>
<ul>
<li>Probabilistic model (decision tree and Markov model) based on NICE CG80 clinical review. Assumptions were used for conditional dependence and false negative, false positive clinical pathways.</li>
<li>Cost-utility analysis (QALYs)</li>
<li>Population: Adults who present symptoms of asthma to their GP</li>
<li>Comparators:
<ul>
<li>Current practice CP: Diagnosis without objective test</li>
<li>Strategy 1: Spirometry, BDR(+)/FeNO(-)</li>
<li>Strategy 2: Spirometry, BDR(+)/FeNO(-) and PEF(-)</li>
</ul></li>
</ul>
</td>
<td colspan="3">
<table>
<tr><th>Int</th><th>Cost[b]:</th><th>QALY</th><th>Inc cost</th><th>Inc QALY</th><th>ICER</th></tr>
<tr><td>S1</td><td>£3,753</td><td>16.7760</td><td colspan="3">Dominated by S3</td></tr>
<tr><td>CP</td><td>£3,730</td><td>16.7766</td><td colspan="3">Dominated by S3</td></tr>
<tr><td>S2</td><td>£3,686</td><td>16.7776</td><td colspan="3">Dominated by S3</td></tr>
<tr><td>S3</td><td>£3,683</td><td>16.7783</td><td colspan="3">Baseline</td></tr>
<tr><td>S5</td><td>£3,686</td><td>16.7784</td><td>£3</td><td>0.0001</td><td>£20,276</td></tr>
<tr><td>S4</td><td>£3,691</td><td>16.7785</td><td colspan="3">Extended dominated by S6</td></tr>
<tr><td>S6</td><td>£3,695</td><td>16.7787</td><td>£9</td><td>0.0003</td><td>£32,565</td></tr>
</table>
Strategy 3 which uses spirometry, bronchodilator reversibility, FeNO, PEF variability and methacholine challenge test (CT) was the most cost-effective at a £20,000 threshold
</td>
<td>
Probability S3 cost effective (£20 threshold): 44%<br><br>
A series of sensitivity analyses were conducted. Only the following results in a change in conclusion of the model:<br>
Increasing sensitivity and specificity of BDR or FeNO made intervention 6 the most cost-effective as it reduces people receiving a methacholine test at the end of the sequence;<br>
If the cost of a methacholine challenge is reduced to £77, intervention 7 (maximum use of methacholine) becomes the most cost-effective,<br>
If FeNO device is used less than 28 times in 5 years (thus increasing the marginal per-test cost), intervention 1 (diagnosis without objective test)
</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Applicability</th><th>Limitations</th><th>Other comments</th><th>Incremental cost</th><th>Incremental effects</th><th>Cost effectiveness</th><th>Uncertainty</th></tr>
<tr><td></td><td></td><td></td><td>○ Strategy 3: Spirometry, BDR(+)/FeNO(-), PEF(-) and methacholine test<br>○ Strategy 4: Spirometry, BDR(+)/FeNO(-), PEF(-) and expanded use of methacholine test (1)<br>○ Strategy 5: Spirometry, BDR(+)/FeNO(-), PEF(-) and expanded use of methacholine test (2)<br>○ Strategy 6: Spirometry, BDR(+)/FeNO(-), PEF(-) and expanded use of methacholine test (maximum use)<br><br>Time horizon: lifetime</td><td></td><td></td><td></td><td>becomes the most cost-effective</td></tr>
<tr><td>Harnan 2015(Harnan et al., 2015) (UK)</td><td>Directly applicable</td><td>Potentially serious limitations[c]</td><td>• Probabilistic decision tree model based on a systematic review of the diagnostic accuracy of FeNO</td><td colspan="3"><table><tr><th>Int</th><th>Cost[f]:</th><th>QALY</th><th>Inc cost</th><th>Inc QALY</th><th>ICER</th></tr><tr><td>7</td><td>£907.71</td><td>4.2686</td><td colspan="3">Dominated by 2</td></tr></table></td><td>Deterministic analyses conducted. The results were robust in most cases. The model was sensitive to assumptions about the length of time needed to resolve misdiagnoses;</td></tr>
</table>

<table>
<tr><th>Study</th><th>Applicability</th><th>Limitations</th><th>Other comments</th><th colspan="6">Incremental cost / Incremental effects / Cost effectiveness</th><th>Uncertainty</th></tr>
<tr><td></td><td></td><td></td><td>• Cost-utility analysis (QALYs)<br>• Population: People with suspected asthma<br>• Comparators[d]:<br>1.Bronchial challenge test with methacholine (MCT)<br>2.FeNO[e] + Bronchodilator reversibility<br>3.FeNO[e]<br>4.FeNO[e] + FEV1<br>5.PEF<br>6.Bronchodilator reversibility<br>7.FEV1/FVC<br>• Time horizon: 5 years</td><td colspan="6"><table><tr><td>6</td><td>£886.27</td><td>4.2710</td><td colspan="3">Dominated by 2</td></tr><tr><td>5</td><td>£877.91</td><td>4.2719</td><td colspan="3">Dominated by 2</td></tr><tr><td>3</td><td>£821.20</td><td>4.2771</td><td colspan="3">Dominated by 2</td></tr><tr><td>4</td><td>£811.4</td><td>4.2783</td><td colspan="3">Dominated by 2</td></tr><tr><td>2</td><td>£687.34</td><td>4.2829</td><td colspan="3">Baseline</td></tr><tr><td>1</td><td>£1226</td><td>4.2834</td><td>£538.66</td><td>0.0005</td><td>£1,077,320</td></tr></table><br>FeNO + bronchodilator reversibility was the most cost-effective intervention at £20,000 per QALY.</td><td>assumptions about health losses incurred by patients who have false-negative results; the costs of asthma management; and the use of rule-in and rule-out diagnostic decision rules. The only sensitivity analysis where FeNO + bronchodilator reversibility (NObreath) was no longer the most cost-effective intervention was when it was assumed all tests were conducted in secondary care (including FeNO). In this instance, MCT was dominant.<br><br>Results based on the point estimates of parameters reflect the results of PSA.</td></tr>
<tr><td>NICE 2024</td><td>Directly applicable</td><td>Minor limitations</td><td>• Probabilistic model using observed or simulated IPD to estimate the joint accuracy of numerous diagnostic strategies. Correlation between tests was incorporated using observed correlation in RADicA study. Two different models</td><td colspan="6"><table><tr><th colspan="6">Adult model</th></tr><tr><td>Strategy</td><td>Cost per patient (£)</td><td>QALY per patient</td><td>Net Health Benefits</td><td>Rank</td><td>% CE at 20k per QALY</td></tr><tr><td>1</td><td>1409 (1317 - 1501)</td><td>19.03 (16.98 - 21.08)</td><td>18.955 (18.78 - 19.13)</td><td>1</td><td>88%</td></tr><tr><td>2</td><td>1432 (1338</td><td>18.98 (16.93</td><td>18.91 (18.732</td><td>5</td><td>0%</td></tr></table></td><td>Comprehensive probabilistic scenarios analyses were conducted in both adults and children.<br><br>In adults, strategy 1 was the most cost-effective in al scenarios except when it was assumed that untreated asthma caused no quality of life reduction. In this scenario, strategy 6, which is considerably less</td></tr>
</table>

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost effectiveness | | Uncertainty |
|---|---|---|---|---|---|---|---|---|
| | | | were developed for children and adults with the appropriate assumptions and data inputs<br>• Cost-utility analysis (QALYs)<br>• Population: adults (30) or children (16) with respiratory symptoms suggestive of asthma<br>• Comparators[g] – adults:<br>1.Blood eosinophils, BDR and methacholine<br>2.FeNO, BDR and methacholine<br>3.PEFv, BDR and methacholine<br>4.Blood eosinophils + FeNO, BDR and methacholine<br>5.Blood eosinophils, FeNO, BDR and methacholine<br>6.Blood eosinophils, FeNO + BDR, PEFv and methacholine<br>7.Blood eosinophils, BDR + FeNO and methacholine | - 1526) | - 21.03) | - 19.088) | | | sensitive, became the most cost-effective.<br><br>In children, strategy 1 was the most cost-effective in all scenarios except when the prevalence of asthma was increased to 80%. In this scenario, strategy 8, which is less specific, became the most cost-effective. |
| | | | | 3 | 1451 (1359 - 1543) | 19.02 (16.97 - 21.07) | 18.946 (18.772 - 19.12) | 3 | 3% | |
| | | | | 4 | 1429 (1332 - 1526) | 18.98 (16.93 - 21.03) | 18.909 (18.726 - 19.092) | 6 | 0% | |
| | | | | 5 | 1425 (1327 - 1523) | 18.98 (16.93 - 21.03) | 18.909 (18.727 - 19.091) | 6 | 0% | |
| | | | | 6 | 1355 (1264 - 1446) | 19.02 (16.97 - 21.07) | 18.948 (18.774 - 19.122) | 2 | 8% | |
| | | | | 7 | 1425 (1327 - 1523) | 18.98 (16.93 - 21.03) | 18.91 (18.727 - 19.093) | 5 | 0% | |
| | | | | 8 | 1462 (1366 - 1558) | 18.97 (16.92 - 21.02) | 18.896 (18.715 - 19.077) | 7 | 0% | |
| | | | | 9 | 1430 (1333 - 1527) | 18.98 (16.93 - 21.03) | 18.91 (18.727 - 19.093) | 5 | 0% | |
| | | | | 10 | 1444 (1351 - 1537) | 19.01 (16.96 - 21.06) | 18.939 (18.763 - 19.115) | 4 | 1% | |
| | | | | **Children model** | | | | | | |

<table>
<tr><th>Study</th><th>Applicability</th><th>Limitations</th><th>Other comments</th><th>Incremental cost</th><th>Incremental effects</th><th>Cost effectiveness</th><th>Uncertainty</th></tr>
<tr><td></td><td></td><td></td><td>8.PEFv, BDR + FeNO and methacholine<br>9.BDR + FeNO, blood eosinophils and methacholine<br>10. Blood eosinophils + PEFv, BDR and methacholine<br>• Comparators[g] – children:<br>1.FeNO, SPT/IgE and methacholine<br>2.Blood eosinophils + BDR, SPT/IgE and methacholine<br>3.PEFv + FeNO, SPT/IgE and methacholine<br>4.Blood eosinophils, SPT/IgE and methacholine<br>5.SPT/IgE, FeNO, BDR and methacholine<br>6.FeNO, BDR, SPT/IgE and blood eosinophils<br>7.FeNO, BDR, SPT/IgE, methacholine<br>8.Blood eosinophils, FeNO, BDR and methcholine<br>9.PEFv, SPT/IgE and methacholine</td><td colspan="3"><table>
<tr><th>Strategy</th><th>Cost per patient (£)</th><th>QALY per patient</th><th>Net Health Benefits</th><th>Rank</th><th>% CE at 20k</th></tr>
<tr><td>1</td><td>1092 (971 - 1213)</td><td>23.14 (21.09 - 25.19)</td><td>23.085 (22.913 - 23.257)</td><td>1</td><td>80%</td></tr>
<tr><td>2</td><td>1129 (1008 - 1250)</td><td>23.12 (21.07 - 25.17)</td><td>23.064 (22.886 - 23.242)</td><td>6</td><td>0%</td></tr>
<tr><td>3</td><td>1141 (1020 - 1262)</td><td>23.1 (21.05 - 25.15)</td><td>23.044 (22.861 - 23.227)</td><td>8</td><td>0%</td></tr>
<tr><td>4</td><td>1090 (969 - 1211)</td><td>23.13 (21.08 - 25.18)</td><td>23.076 (22.901 - 23.251)</td><td>3</td><td>7%</td></tr>
<tr><td>5</td><td>1102 (981 - 1223)</td><td>23.13 (21.08 - 25.18)</td><td>23.079 (22.907 - 23.251)</td><td>2</td><td>11%</td></tr>
<tr><td>6</td><td>1081 (959 - 1203)</td><td>23.1 (21.06 - 25.14)</td><td>23.041 (22.871 - 23.211)</td><td>9</td><td>0%</td></tr>
<tr><td>7</td><td>1127 (1006 - 1248)</td><td>23.13 (21.08 - 25.18)</td><td>23.072 (22.898 - 23.246)</td><td>5</td><td>1%</td></tr>
<tr><td>8</td><td>1175 (1053 - 1297)</td><td>23.12 (21.07 - 25.17)</td><td>23.058 (22.875 - 23.241)</td><td>7</td><td>1%</td></tr>
</table></td><td></td></tr>
</table>

| Study | Applicability | Limitations | Other comments | Incremental cost | | Incremental effects | | Cost effectiveness | | Uncertainty |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 10. FeNO & BDR, SPT/IgE and methacholine | 9 | 1130 (1008 - 1252) | 23.1 (21.05 - 25.15) | 23.044 (22.861 - 23.227) | 8 | 0% | |
| | | | | 10 | 1123 (1002 - 1244) | 23.13 (21.08 - 25.18) | 23.073 (22.899 - 23.247) | 4 | 1% | |

*Abbreviations: 95% CI= 95% confidence interval; BDR= bronchodilator reversibility test; COPD= Chronic obstructive pulmonary disease; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); FeNO= fractional exhaled nitric oxide; FEV1= forced expiratory volume ; FN= false negative; FP= false positive; FVC=forced vital capacity; HRQoL= health related quality of life; ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; PEF= Peak Flow Measurement; PSSRU= Personal and Social Services Research Unit; QALYs= quality-adjusted life years; SPT = skin prick test*

*(a) Prevalence of asthma taken from the studies that informed diagnostic accuracy, which may not reflect UK specific asthma prevalence rates. No information was available on people who receive a false negative or false positive diagnosis and a number of assumptions had to be made regarding maximum length of misdiagnosis. The evidence used for diagnostic accuracy was not conducted in the appropriate subgroups of patients but based instead on a review on all patients who present asthma symptoms. Conditional dependence was incorporated into the model using GC expert opinion but without supporting data. The clinical review suggests that there is a moderate conditional dependence between spirometry and BDR and between methacholine challenge and FeNO, which were both considered conditionally independent in the model. This implies that the model might have overestimated the usefulness of offering BDR after spirometry and methacholine challenge after FeNO. Strategy reflecting current practice (diagnosis without objective test) assumed a sensitivity of 100% and that 1/3 of people will be misdiagnosed. These assumptions are based on a Canadian study on an obese and non-obese population and might not be applicable to the UK NHS settings as practices vary significantly across countries.*

*(b) 2014 UK pounds. Cost components incorporated: exacerbation (hospitalised and non-hospitalised), diagnostic test, respiratory outpatient visit, GP appointment, asthma management, COPD management, heart failure.*

*(c) EQ-5D data was not identified via systematic review of literature and it is unclear if all are from UK representative population. Diagnostic accuracy of non-FeNO comparators were not identified through systematic review of the evidence. The study used to estimate sensitivity and specificity of FeNO + BDR (Cordeiro 2011) was excluded in the clinical review as it also used BDR as reference standard. Prevalence of asthma taken from the studies that informed diagnostic accuracy, which may not reflect UK specific asthma prevalence rates. Due to the limited evidence base the model necessarily makes a number of unadjusted (naive) indirect comparisons between the included studies. The model structure doesn't reflect a sequential testing pathway however author states due to evidence limitations they were not able to undertake this. Uncertainty surrounding health losses associated with misdiagnosis: model elicited estimates of the duration required to resolve a FN/FP diagnosis and these estimates were very uncertain. There was also uncertainty surrounding the magnitude of the HRQoL loss as well as the duration over which this loss is incurred. Authors noted that it is possible that health losses associated with FP diagnoses in patients with more serious underlying pathology are underestimated, although they are not clear how this uncertainty could have been resolved empirically.*

*(d) Strategies including sputum induction were excluded as out of scope.*

*(e) All three FeNO devices (NIOX MINO, NIOX VERO and NObreath) were included in a single comparator using their average cost. Accuracy was assumed to be the same.*

*(f) 2012/2013 UK pounds. Cost components incorporated: Test costs, maintenance costs of devices, primary care costs (measuring FeNO, spirometry and reversibility testing requires 2 GP visit and 1 nurse visit), secondary care costs (sputum induction and the methacholine challenge test), cost of asthma management (in line with BTS/SIGN asthma guidelines), cost of resolving misdiagnosis (1 additional primary care appointment, 2 additional secondary care and 1 laboratory visit), costs associated with loss of control for FN patients (1 exacerbation per year).*

*(g) See section 1.1.9 and the economic report for more a more detailed description of the comparators.*

### 1.1.9 Economic model

A health economic model was developed to assess the cost-effectiveness of numerous potential sequences or combination of tests to diagnose asthma in people with respiratory symptoms as seen in primary care in the UK. More details are available in the full economic report published alongside the guideline.

#### Population and strategies

The analysis focused on adults and children with respiratory symptoms suggestive of asthma as seen in primary care. Two different analyses were conducted on children and adults with population-specific inputs and assumptions. The strategies that were included in the report are the following:

**Table 5: Diagnostic strategies in adults**

| S | 1st step | 2nd step | 3rd step | 4th step |
|---|---|---|---|---|
| 1 | Blood Eosinophils | +: Diagnose asthma<br>-: BDR | +: Diagnose asthma<br>-: Methacholine | – |
| 2 | FeNO | +: Diagnose asthma<br>-: BDR | +: Diagnose asthma<br>-: Methacholine | – |
| 3 | PEFv | +: Diagnose asthma<br>-: BDR, | +: Diagnose asthma-:<br>Methacholine, | – |
| 4 | Blood Eosinophils &<br>FeNO | +: Diagnose asthma<br>-: BDR, | +: Diagnose asthma<br>-: Methacholine | – |
| 5 | Blood Eosinophils | +: Diagnose asthma<br>-: FeNO | +: Diagnose asthma<br>-: BDR, | +: Diagnose asthma<br>-: Methacholine |
| 6 | Blood Eosinophils | +: Diagnose asthma<br>-: BDR & FeNO | +: Diagnose asthma,<br>-: Exclude asthma,<br>?: PEFv | +: Diagnose asthma<br>-: Methacholine |
| 7 | Blood Eosinophils | +: Diagnose asthma<br>-: BDR & FeNO, | +: Diagnose asthma,<br>-: Methacholine<br>?: Diagnose asthma | – |
| 8 | PEFv | +: Diagnose asthma,<br>-: BDR & FeNO | +: Diagnose asthma,<br>-: Methacholine<br>?: Diagnose asthma | – |
| 9 | BDR & FeNO | +: Diagnose asthma<br>-: Blood Eosinophils<br>?: Diagnose asthma | +: Diagnose asthma<br>-: Methacholine | – |
| 10 | Blood Eosinophils &<br>PEFv | +: Diagnose asthma<br>-: BDR<br>?: Diagnose asthma | +: Diagnose asthma<br>-: Methacholine<br>?: Diagnose asthma | – |

*Abbreviations: BDR: bronchodilator reversibility; FeNO: Fractional exhaled nitric oxide; PEFv: Peak expiratory flow variability*
*Legend: +: positive result at previous step; -: negative result at previous step; ?: indeterminate result at previous step*

**Table 6: Diagnostic strategies in children**

| S | 1st step | 2nd step | 3rd step | 4th step |
|---|---|---|---|---|
| 1 | FeNO | +: Dismiss<br>-: SPT/IgE | +: Methacholine<br>-: Dismiss | — |
| 2 | BDR | +: Dismiss<br>-: SPT/IgE | +: Methacholine<br>-: Dismiss | — |
| 3 | PEFv | +: Dismiss<br>-: SPT/IgE | +: Methacholine<br>-: Dismiss | — |
| 4 | Blood Eosinophils | +: Dismiss<br>-: SPT/IgE | +: Methacholine<br>-: Dismiss | — |
| 5 | FeNO | +: Dismiss<br>-: BDR | +: Dismiss<br>-: SPT/IgE | +: Methacholine<br>-: Dismiss |
| 6 | FeNO | +: Dismiss<br>-: SPT | +: Blood eosinophils<br>-: Dismiss | +: Dismiss<br>-: Methacholine |
| 7 | FeNO & PEFv | +: Dismiss<br>-: SPT | +: Methacholine<br>-: Dismiss | — |
| 8 | FeNO & Blood Eosinophils | +: Dismiss<br>-: SPT | +: Methacholine<br>-: Dismiss | — |
| 9 | FeNO & BDR | +: Dismiss<br>-: SPT/IgE | +: Methacholine<br>-: Dismiss | — |
| 10 | PEFv | +: Dismiss<br>-: BDR | +: Dismiss<br>-: Methacholine | — |

*Abbreviations: BDR: bronchodilator reversibility; FeNO: Fractional exhaled nitric oxide; PEFv: Peak expiratory flow variability; STP = skin prick test*
*Legend: +: positive result at previous step; -: negative result at previous step; ?: indeterminate result at previous step*

### Model structure

- Individual patient data (IPD) from RADicA study(Simpson et al., 2024) were used to calculate joint sensitivity and specificity in adults.
- In children, IPD from RADicA and accuracy data derived from the clinical review were combined to generate IPD test results.
- A decision tree model was developed to estimate the number of people with a true positive (TP), true negative (TN), false positive (FP), false negative (FN) diagnosis and associated resource use.
- Two Markov models were used to simulate short-term and long-term natural history of those with diagnosed and undiagnosed asthma.
- People with undiagnosed asthma exhibit a lower quality of life and move to the diagnosed state as soon as they experience an asthma exacerbation. If no

exacerbation occurs, they move to the diagnosed state as soon as they reach the end of the short-term model (2 years in the base case).
- A partition survival model was used to simulate the lifetime of those without asthma.
- People without asthma who are treated for the condition exhibit a lower quality of life and can transit to the untreated state using probabilities derived by a longitudinal study.
- Remission from asthma was included only in the children model and was assumed not occur beyond 20 years from the diagnosis.

**Data sources**

- The costs of all diagnostic tests conducted in primary care were calculated using a micro-costing approach. Bronchial challenge tests, that are administer in secondary care and blood eosinophil count were costed using HRG codes from the NHS National Collection Costs.
- The accuracy of diagnostic tests was derived from RADicA study(Simpson et al., 2024) for adults, and from the clinical review for children. RADicA was used to incorporate conditional dependencies between test results in adults and children alike.
- Time-to-first exacerbation and annualised exacerbation rate was estimated from the Novel START trial(Beasley, et al., 2019).
- Time spent with a false positive diagnosis was estimated using a longitudinal Canadian study(Pakhale, et al., 2011).
- The quality of life associated with controlled or uncontrolled asthma was calculated through a bespoke analysis of the Health Survey for England (HSE)(NHS Digital, 2019).
- Costs of asthma management and monitoring were estimated using BNF(Joint Formulary Committee, 2024), NHS National Collection Costs(NHS England, 2022) and PSSRU(Jones, et al.).

**Results**

The model was run separately for adults and children using appropriate assumptions and data inputs. The base case analyses below are from an English NHS perspective. Analyses were also conducted from a Scottish NHS perspective, the results were similar to the English NHS perspective and are can be found in the full report. Results for adults and children are shown in Table 7 and Table 8, respectively.

**Table 7: Probabilistic cost-effectiveness results in adults – base case**

| Strategy | Cost per patient | QALY per patient | Net Health Benefits | Rank | % cost-effective at 20k |
|---|---|---|---|---|---|
| 1 | 1409 (1317 - 1501) | 19.03 (16.98 - 21.08) | 18.955 (18.78 - 19.13) | 1 | 88.02% |
| 2 | 1432 (1338 - 1526) | 18.98 (16.93 - 21.03) | 18.91 (18.732 - 19.088) | 5 | 0% |
| 3 | 1451 (1359 - 1543) | 19.02 (16.97 - 21.07) | 18.946 (18.772 - 19.12) | 3 | 3.33% |
| 4 | 1429 (1332 - 1526) | 18.98 (16.93 - 21.03) | 18.909 (18.726 - 19.092) | 6 | 0% |
| 5 | 1425 (1327 - 1523) | 18.98 (16.93 - 21.03) | 18.909 (18.727 - 19.091) | 6 | 0.01% |
| 6 | 1355 (1264 - 1446) | 19.02 (16.97 - 21.07) | 18.948 (18.774 - 19.122) | 2 | 7.99% |
| 7 | 1425 (1327 - 1523) | 18.98 (16.93 - 21.03) | 18.91 (18.727 - 19.093) | 5 | 0% |
| 8 | 1462 (1366 - 1558) | 18.97 (16.92 - 21.02) | 18.896 (18.715 - 19.077) | 7 | 0% |
| 9 | 1430 (1333 - 1527) | 18.98 (16.93 - 21.03) | 18.91 (18.727 - 19.093) | 5 | 0.01% |
| 10 | 1444 (1351 - 1537) | 19.01 (16.96 - 21.06) | 18.939 (18.763 - 19.115) | 4 | 0.64% |

**Table 8: Probabilistic cost-effectiveness results in children – base case**

| Strategy | Cost per patient | QALY per patient | Net Health Benefits | Rank | % cost-effective at 20k |
|---|---|---|---|---|---|
| 1 | 1076 (958 - 1194) | 23.14 (21.09 - 25.19) | 23.085 (22.913 - 23.257) | 1 | 46.38% |
| 2 | 1125 (1007 - 1243) | 23.13 (21.08 - 25.18) | 23.069 (22.895 - 23.243) | 5 | 0% |
| 3 | 1114 (995 - 1233) | 23.1 (21.05 - 25.15) | 23.043 (22.86 - 23.226) | 6 | 0% |
| 4 | 1074 (956 - 1192) | 23.13 (21.08 - 25.18) | 23.075 (22.899 - 23.251) | 3 | 2.66% |
| 5 | 1111 (993 - 1229) | 23.13 (21.08 - 25.18) | 23.072 (22.898 - 23.246) | 4 | 0.15% |
| 6 | 1067 (949 - 1185) | 23.14 (21.09 - 25.19) | 23.084 (22.911 - 23.257) | 1 | 46.88% |
| 7 | 1125 (1006 - 1244) | 23.1 (21.05 - 25.15) | 23.042 (22.858 - 23.226) | 7 | 0% |
| 8 | 1081 (963 - 1199) | 23.13 (21.08 - 25.18) | 23.076 (22.9 - 23.252) | 2 | 3.75% |
| 9 | 1107 (989 - 1225) | 23.13 (21.08 - 25.18) | 23.072 (22.898 - 23.246) | 4 | 0.18% |
| 10 | 1178 (1057 - 1299) | 23.09 (21.03 - 25.15) | 23.027 (22.837 - 23.217) | 8 | 0% |

All the cost-effective strategies in adults reflected a “gradual rule-in” approach, where two uncorrelated but highly specific tests are given in sequence, to rule-in as many people as possible. The last step is reached by those who tested negative in the two previous steps and requires an “all-round” test, a test with high sensitivity and specificity, such as bronchial challenge test with methacholine. The most cost-effective strategy involved testing all adults with blood eosinophils, followed by a BDR for those who tested negative at the first test, followed by a bronchial challenge test with methacholine for those who tested negative in both steps. A threshold analysis revealed that FeNO could potentially be a cost-effective initial test at cut-off values where its specificity aligns with that of blood eosinophils.

The model showed that all the cost-effective strategies in children reflected a “rule-in-rule-out” approach, where highly specific tests and highly sensitive tests are alternated in a sequence, followed by a final “all-round” bronchial challenge test with methacholine. Two most cost-effective strategies were identified in children. The first involved testing all children with FeNO, re-test those who are negative with either skin prick test or IgE, and finally refer to a bronchial challenge test those who were negative in the first step and positive in the second. The second is a variation of the first including an additional blood eosinophils test to rule in asthma before reaching the step requiring methacholine.

Table 9 illustrates the most cost-effective strategies in adults and children.

**Table 9: Most cost-effective strategies in children and adults**

| Population | Approach | 1st step | 2nd step | 3rd step | 4th step |
|---|---|---|---|---|---|
| **Adults** | **Gradual rule-in** | Blood Eosinophils | +: Dismiss<br>-: BDR | +: Dismiss<br>-: Methacholine | – |
| **Children** | **Rule-in-rule-out** | FeNO | +: Dismiss<br>-: SPT/IgE | +: Methacholine<br>-: Dismiss | – |
| | | FeNO | +: Dismiss<br>-: SPT/IgE | +: Blood eosinophils<br>-: Dismiss | +: Dismiss<br>-: Methacholine |

*Abbreviations: BDR: bronchodilator reversibility; FeNO: Fractional exhaled nitric oxide; SPT: skin prick test*

### 1.1.10 Unit costs

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

| Test | Cost of consumables | Staff time required | Total cost |
|---|---|---|---|
| Spirometry | £1.80 | 20 minutes | £22.93 |
| BDR | £7.47 | 30 minutes | £39.16 |
| PEFv | £4.65 | 20 minutes | £25.78 |
| FeNO | £6.37 | 15 minutes | £22.21 |
| Skin prick test[(a)] | £2.75 | 40 minutes | £45 |
| Total IgE blood test[(a)] | NA | NA | £16.03 |
| Blood eosinophils | NA | NA | Adults: £7.66<br>Children: £8.07 |
| Bronchial challenge test with mannitol or methacholine | NA | NA | £179.49 |

*(a) Only in children*

For more detailed information, the methodology used to calculate the cost of each test is described in the economic report and the evidence reviews of each test.

### 1.1.11 Evidence statements

**Economic**

- One cost utility analysis comparing multiple diagnostic strategies found that a strategy which uses spirometry, bronchodilator reversibility, FeNO, PEF variability and methacholine challenge test was the most cost-effective at a £20,000 threshold for diagnosing asthma in adults. This analysis was assessed as directly applicable with potentially serious limitations.
- One cost utility analysis comparing multiple diagnostic strategies found that a strategy which uses FeNO and bronchodilator reversibility was the most cost-effective at a £20,000 threshold for diagnosing asthma in adults. This analysis was assessed as directly applicable with potentially serious limitations.
- An original cost utility analysis comparing multiple diagnostic strategy in children and adults found that:

- A gradual rule-in approach is cost effective in adults at a £20,000 threshold, which involves an initial blood eosinophils test, followed by BDR for those who tested negative and a final bronchial challenge test with methacholine for those who tested negative for both previous tests
- A rule-in-rule-out approach is cost-effective in children at a £20,000 threshold, which involves an initial FeNO (≥ 35 ppb), followed by a skin prick test or IgE for those who tested negative and a final bronchial challenge test with methacholine for those who tested negative for FeNO and positive for skin prick test/IgE. A slight variation was also find to be cost-effective which includes a blood eosinophil test before the bronchial challenge test.

The analysis was assessed as directly applicable with minor limitations.

# 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 test combinations for diagnosing asthma 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 combination of tests would be recommended and 0.1 and 0.5 below which the combination is of no clinical use. The committee viewed sensitivity and specificity with equal importance. The consequences of an insensitive test, increasing the likelihood of incorrectly ruling out an asthma diagnosis and thus not appropriately treating symptoms, were deemed to be equal to those of an unspecific test that increases the likelihood of incorrectly ruling in an asthma diagnosis, resulting in unnecessary exposure to pharmacological treatments.

### 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 combinations of tests in terms of the clinical outcomes set in the protocol.

Diagnostic accuracy

Six cross sectional studies examining the diagnostic accuracy of a combination of tests for asthma were identified, five in adults and one in children and young people. The quality of the evidence in adults was all low to very low-quality, with very serious risk of bias present in all evidence due to unclear methods of participant recruitment and unclear blinding of index test and reference standard results. Indirectness was present in the majority of the evidence, most frequently due to ICS status of participants not being reported, and less frequently due to an unclear involvement of a clinician decision in the final asthma diagnosis. There was also a large amount of imprecision noted across the evidence base, with all but one specificity estimates being downgraded by one increment due to the 95%CI overlapping a threshold for decision-making.

### 1.2.3 Benefits and harms

Children and young people

Moderate-high-quality evidence from one study reported the diagnostic accuracy of spirometry and FeNO using a cut-off of 0.6 on a logistical regression model for diagnosing asthma. This evidence showed both a high sensitivity of 0.82 and specificity of 0.80, with the latter meeting the threshold for decision-making, when using $FEV_1$ as a percentage of predicted values (cut-off 88.4%) in combination with FeNO (cut-off 19.6 ppb). The same study reported the accuracy of $FEV_1$/FVC ratio (cut-off 85.3%) combined with FeNO (cut-off 19.6 ppb), showing a high sensitivity of 0.85 and a moderate specificity of 0.75, neither of which met the decision-making threshold. Both specificity estimates were downgraded for imprecision as a result of the 95%CI overlapping the upper threshold for decision-making. The committee acknowledged the relatively high sensitivity and specificity values reported but noted that the cut-offs used were derived to give the best possible test discrimination in the study cohort and were not tested prospectively.

Adults

Very low-quality evidence from one study reported the accuracy of combining methacholine bronchial challenge testing, using a cut-off of PC20 $FEV_1$ <8 mg/mL, with peak flow variability, using a cut-off of 20%. This evidence showed a moderate sensitivity and specificity of 0.75 and 0.78,

respectively, with neither meeting the decision-making threshold. This evidence was downgraded due to risk of bias arising from an unclear method of participant recruitment and unclear blinding of test results, as well as due to indirectness resulting from an unclear pre-study ICS status. The specificity estimate was further downgraded due to the 95%CI overlapping the upper threshold for decision-making.

Low-very low-quality evidence from one study reported the accuracy of combining methacholine bronchial challenge testing, using a cut-off of PC20 $FEV_1$ ≤16 mg/mL, with mannitol bronchial challenge testing, using a cut-off of PD15 $FEV_1$ <625 mg. This evidence showed a moderate sensitivity of 0.65 and a high specificity of 0.94, with the latter meeting the decision-making threshold, although this estimate was downgraded for imprecision due to the 95%CI crossing the threshold. Furthermore, this evidence was downgraded due to risk of bias resulting from an unclear method of participant recruitment and unclear blinding of test results. The committee acknowledged the high specificity reported but highlighted that conducting two bronchial challenge tests is impractical for both patients and clinicians and that there is likely to be a strong correlation between the two tests.

Very low-quality evidence from one study reported the accuracy of combining eosinophils, using a cut-off of >150/µl, with FeNO, using a cut-off of 14 ppb. This evidence reported a high sensitivity of 1.00, and a moderate specificity of 0.47, with the former meeting the decision-making threshold, although this estimate was downgraded for imprecision. The evidence was further downgraded due to risk of bias resulting from an unclear method of participant recruitment and unclear blinding of test results. The committee acknowledged the high sensitivity reported but highlighted that both eosinophils and FeNO are makers of inflammation, and there is likely to be a strong correlation between the two tests. This was confirmed from the correlation analysis of RADicA conducted for the health economic model, which found FeNO and blood eosinophils highly correlated in both people with and without asthma (polychoric correlation between 0.40 – 0.60).

Very low-quality evidence from one study reported the accuracy of combining spirometry, using $FEV_1$/FVC ratio with a cut-off of 84.67%, with FeNO using a cut-off of 41ppb or with eosinophils using a cut-off of 3.4% or 360 cells/µl. When combined with FeNO, this evidence showed a high sensitivity of 0.86 and a moderate specificity of 0.62. When combined with eosinophils, this evidence showed a moderate sensitivity of 0.56 and a high specificity of 0.81, with the latter meeting the decision-making threshold. This evidence was downgraded due to risk of bias arising from an unclear method of participant recruitment and unclear blinding of test results. Furthermore, indirectness was present due to using a reference standard that did not include a clinician decision in the final diagnosis, with the FeNO-including combination being further downgraded due to not reporting the standard FeNO measurements were conducted to.

Low-very low-quality evidence from one study reported the accuracy of four previously developed diagnostic algorithms, combining multiple diagnostic tests with different pathways depending upon the result of each individual test. This study showed a high sensitivity and specificity of the ERS pathway (0.81 and 0.85, respectively), meeting the threshold for decision making for specificity, but not for sensitivity. The NICE pathways 1-6, which indicate confirmed asthma, showed a moderate sensitivity of 0.41 and a high specificity of 1.00. Alternatively, NICE pathways 1-9, which includes an additional three pathways that indicate a trial of treatment, showed a moderate sensitivity of 0.49 and a high specificity of 1.00. Finally, the GINA pathway showed a moderate sensitivity of 0.47 and a high specificity or 1.00. The latter three pathways

showed sensitivities that did not meet the decision-making threshold, whilst all showing perfect specificity. This evidence was downgraded due to very serious risk of bias resulting from an unclear method of participant selection and the interpretation of the index test and reference standard due to the index test results being involved as part of the reference standard diagnosis. Furthermore, the specificity estimate for the ERS pathway was downgraded by an additional increment due to imprecision resulting from the 95%CI overlapping the threshold corresponding to high specificity.

### 1.2.4 Cost effectiveness and resource use

Two studies looking at the most cost-effective combinations or sequences of tests were included in the economic review.

In 2015 the External Assessment Group (EAG) published a systematic review and cost-effectiveness analysis on the role of FeNO to diagnose asthma on both children and adults (Harnan 2015). The authors did not attempt to define a diagnostic pathway but looked at studies estimating the accuracy of FeNO together with other tests. They found that FeNO plus BDR was cost-effective compared to other tests alone or to FeNO plus spirometry. The analysis was considered directly applicable but with potentially serious limitations due to the inclusion of studies that were excluded in the clinical review and the use of unadjusted direct comparisons to estimate clinical effectiveness. Furthermore, the model structure does not resemble a sequential diagnostic pathway as the authors recognised they were unable to conduct such an analysis with the available evidence. Therefore, the committee deemed the study of limited usefulness.

A health economic model was developed to inform the diagnostic recommendations of NICE guideline NG80. The model compared 6 strategies including spirometry, BDR, FeNO, PEF variability and a methacholine test in adults. Although the analysis was directly applicable, it had a number of potentially serious limitations, including the reliance on assumptions rather than data to estimate conditional dependency and consequences of false negative and false positive diagnoses. Conditional dependency is particularly important to consider in similar analyses, as the rate of agreements between two or more tests could change the structure of a strategy: for instance, tests that are perfectly dependent would always give the same results, and therefore would not be helpful when included alongside. Moreover, the strategies included were similar and the algorithm produced was criticised for its complexity and lack of flexibility.

The committee acknowledged the significant heterogeneity in clinical practice in the UK, where physicians prefer different approaches to diagnose asthma. “Trial of treatment” is sometimes used when the diagnosis is uncertain by treating people with ICS and observing their response to the treatment. The committee agreed that this was not appropriate in most cases as symptoms such as wheeze or cough can have other causes, such as viral respiratory infections, which may improve naturally with this improvement being incorrectly attributed to the ICS treatment.  As there is no clear gold standard test to diagnose asthma, the committee recognised that it was important to identify a pragmatic and cost-effective diagnostic sequence or algorithm to reach an objective diagnosis in adults and children. The committee were aware that the

diagnostic algorithm produced by the previous NICE guideline proved hard to be implemented and lacked flexibility. Therefore, the committee highlighted the importance of developing a flexible model that could explore numerous strategies and help the committee reach a pragmatic recommendation.

An original economic model was developed for this purpose. The model explored different combinations and sequences of diagnostic tests and simulated lifetime consequences of accurate and inaccurate diagnoses to identify the most-cost effective diagnostic strategies in children and adults (see the Economic Report for more details).

Adults

While a variety of relatively inexpensive and highly specific tests were available, there were fewer tests with satisfactory sensitivity for adults. Bronchial challenge tests with either methacholine or mannitol were found to be all-round tests, showing satisfactory sensitivity and specificity. However, these tests tend to be conducted in secondary care, and therefore, are not widely available and considerably expensive. Numerous diagnostic strategies in adults were assessed through the model, which found that the most cost-effective approach involved adopting a gradual rule-in methodology:

- A cheap and highly specific initial test to rule in people with asthma
- A subsequent but uncorrelated highly specific test to those identified as negative
- A final all-round test (bronchial challenge test with methacholine or mannitol) to diagnose asthma in those who have not yet been ruled in

This approach proved to be the most cost-effective as it allowed to rule in asthma in a broad population using relatively inexpensive tests and confine the more expensive bronchial challenge tests to the end of the sequence as a final recourse. The model showed that in the majority of the simulations (80%), the most cost-effective 3 steps sequence was the following (strategy 1):

1. Test people with suspected asthma for blood eosinophils and diagnose asthma if the results are positive

2. If negative in the first step, test with BDR and diagnose asthma if the results are positive

3. If negative in the first and second step, conduct a bronchial challenge test using methacholine. Diagnose asthma if positive and discharge if negative.

Blood eosinophils was found to be the best initial test to offer at the beginning of the sequence due to its high specificity, low cost and low correlation with BDR and methacholine tests. The committee agreed that FeNO at high thresholds could achieve high specificity and

represents a potential cost-effective alternative to blood eosinophil. A threshold of 50ppb was used in the model and the committee recognised that the test would be highly specific at that cut-off. Following a discussion of the evidence, the committee made a recommendation reflecting strategy 1 and including either blood eosinophils or FeNO, BDR and bronchial challenge test. The committee acknowledged that, although appropriate in the majority of cases, blood eosinophils and FeNO may perform poorly in elderly people with asthma, who have a lower prevalence of atopy. However, the committee recognised that re-testing with BDR those who had a negative result in the first step ensures that non-atopic asthma is ultimately detected by the algorithm. Although PEF was found to be a potentially cost-effective alternative as first-line test, the committee were concerned that poor patient compliance, particularly over a longer period, could make this test less reliable than other tests. However, the committee agreed that PEF is, in general, widely available and could be used in situations where the local unavailability of spirometry or long waiting list might delay an asthma diagnosis. Therefore, a recommendation to use PEF in such cases was included.

This recommendation reflects an important change in current practice, as practitioners across the country currently employ a variety of tests including “trials of treatment”. Therefore, there will be an immediate resource impact as more people will receive objective tests, however this extra cost is likely to be partially offset by savings occurring downstream. The recommended strategy is associated with a high sensitivity and very high specificity and, therefore, when implemented, will significantly reduce misdiagnoses in people with suspected asthma. This will ensure that people with asthma receive an accurate and prompt diagnosis, facilitating timely initiation of appropriate treatments. Moreover, this recommendation is anticipated to reduce NHS resource wastage as fewer people without asthma will be misdiagnosed avoiding unnecessary treatments. As the annual cost of asthma in the UK reached approximately £1.3 billion in 2023(Asthma and Lung UK, 2023), reducing wastage could free a significant amount of healthcare resources that could be reinvested into the NHS. The committee recognised that bronchial challenge test is not widely available across the country, which could hamper the implementation of the recommendation nationwide. Nevertheless, due to the lack of highly sensitive tests, the model determined the necessity and cost-effectiveness of including a bronchial challenge test at the end of the diagnostic algorithm for those who could not be definitively diagnosed in the preceding steps.

Children

A separate model was developed for children using children-specific diagnostic accuracy data and inputs. Unlike adults, children have access to two highly sensitive tests: skin prick test and IgE. This allows to define a different diagnostic strategy, the rule-in-rule-out approach:

- A cheap and highly specific initial test to rule in people with asthma
- A subsequent highly sensitive test to rule out people with asthma

- A final all-round test (bronchial challenge with methacholine or mannitol) to diagnose asthma in those who have not yet been ruled out or ruled in.

This approach proved to be the most cost-effective in children as it considerably reduced the proportion of children reaching the last stage and requiring an expensive bronchial challenge test. Strategy 1 and 6 were found to be the most cost-effective strategy in 93% with strategy 6 being more cost-effective when the IgE was used instead of a skin prick test at step 2. The strategies involve:

1. Test children with suspected asthma with FeNO and diagnose asthma if positive (>35ppb)

2. If negative in the first step, test with skin prick test or IgE and discharge those who are negative

3. Only strategy 3 – If positive at previous step, test for blood eosinophils. Diagnose asthma if this is also positive.

4. If still unsure, conduct a bronchial challenge test using methacholine. Diagnose asthma if positive and discharge if negative

FeNO with a high threshold (35 ppb) was found to be a cost-effective first-line test in children due to its high specificity and relatively low per test cost. Skin prick test or IgE were both found to be an excellent option in the second step due to their high sensitivity in children. The committee acknowledged that, while most children have atopic or allergic asthma, approximately 10% exhibit non-atopic or non-allergic asthma. Children with non-atopic asthma could be erroneously discharged following a negative FeNO and a negative skin prick test or IgE, as these tests perform poorly in children with non-allergic asthma. BDR, albeit not as cheap as FeNO measures lung airway's function, so it can identify children with atopic or non-atopic asthma alike. A strategy in children beginning with BDR was found to have satisfactory sensitivity and specificity (0.77 and 0.87, respectively) but was more costly, and became only the fifth most cost-effective strategy. The committee also acknowledged that FeNO devices may not be uniformly available across the country. Therefore, the committee recommended FeNO as first test for children, but included a BDR as an alternative if FeNO is unavailable, or if FeNO is negative. They agreed that this was justified on clinical and pragmatic grounds, as the model could not differentiate between atopic and non-atopic asthma and there was concern that the second group could be underdiagnosed. Although PEF was found to be, on average, less specific than in adults, the committee agree that is widely available and could be used in situations where the local unavailability of spirometry or long waiting list might delay an asthma diagnosis. Therefore, a recommendation to use PEF in such cases was included. The committee acknowledged that skin prick test availability is limited in some areas due to the lack of centres and training across the country and agreed that the inclusion of IgE as an alternative to skin prick test would significantly enhance the feasibility of implementing the recommendation.

This recommendation represents an important change in current practice, as asthma in children have been historically diagnosed with a variety of tests, including "trials of treatment". The recommended strategy is associated with a high sensitivity and specificity and, if implemented, could

significantly reduce false positive diagnoses leading to a lower wastage on asthma treatment cost, which is estimated to be around £1.5 billion in the UK(Asthma and Lung UK, 2023). Compared to adults, the rule-in-rule-out approach in children significantly reduces the proportion of children reaching the last step of the diagnostic pathway and requiring a bronchial challenge test. Still, around 30% of children with suspected asthma would be required to access secondary care for a bronchial challenge test, which could pose a challenge due to the limited availability of this service. However, the model clearly determined the necessity and cost-effectiveness of including a bronchial challenge test at the end of the pathway for children who could not be diagnosed or discharged in the preceding steps.

### 1.2.5 Recommendations supported by this evidence review

This evidence review supports recommendations 1.2.1, 1.2.2, 1.2.3, 1.2.4, 1.2.5, 1.2.6, 1.2.7, 1.3.1 and 1.3.2.Other evidence supporting these recommendations can be found in the evidence reviews on Spirometry (A), Bronchodilator response (B), PEF (C), Skin prick tests (D), IgE (E), FeNO (F), Blood eosinophils measures (G), Histamine and Methacholine (H), Mannitol challenge (I) and Exercise challenge (J).

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# Appendices

## Appendix A – Review protocols

**Review protocol for diagnostic accuracy and clinical and cost-effectiveness of a combination of tests for diagnosis of people with suspected asthma**

| ID | Field | Content |
|---|---|---|
| 0. | PROSPERO registration number | CRD42023442328 |
| 1. | Review title | Accuracy and clinical and cost-effectiveness of combination tests for diagnosis in people with suspected asthma |
| 2. | Review question | In people under investigation for asthma, what is the diagnostic test accuracy and clinical and cost-effectiveness of a combination of tests (as specified in 1.1-1.10)? |
| 3. | Objective | To evaluate the diagnostic test value of combination testing in diagnosing asthma.<br>This evidence review will have two stages:<br>(1) Identify the clinical and cost effectiveness of diagnosis with the test (test plus treatment)<br>(2) If evidence on clinical effectiveness is limited, the diagnostic accuracy will instead be determined |
| 4. | Searches | The following databases (from inception) will be searched:<br>• Cochrane Central Register of Controlled Trials (CENTRAL)<br>• Cochrane Database of Systematic Reviews (CDSR)<br>• Embase<br>• MEDLINE |

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| | | • Epistemonikos<br><br>Searches will be restricted by:<br>• English language studies<br>• Human studies<br><br>Other searches:<br>• Inclusion lists of systematic reviews<br><br>The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant.<br><br>The full search strategies will be published in the final review.<br><br>Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details). |
| 5. | Condition or domain being studied | Asthma |
| 6. | Population | Inclusion:<br>People with suspected asthma (presenting with respiratory symptoms).<br><br>Ages stratified into the following 2 groups:<br>• Children/young people (5-16 years old) |

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| | | • Adolescents/ Adults (≥17 years old)<br><br>NOTE: ensure inclusion of people who have already received a test previously (negative outcome) and are undergoing a second test in the present paper<br><br>Exclusion:<br><br>Children under 5 years old<br><br>• People on steroid medication (washout period minimum of 4 weeks for inclusion) |
| 7. | Test | Combinations of the following:<br><br>Spirometry measures (report separately)<br>• FEV1/FVC ratio (<70%)<br>• Flow volume loop (graph)<br>• FEV1 (<80%) – if limited evidence from the above two measures<br><br>• Pre bronchodilator values (applies for all above measures)<br>• FEV1 and FVC should be performed using the following criteria:<br>• Forced expiratory volume (FEV1) - patients perform manoeuvre until 3 readings are within 5% of each other (maximum 8 attempts) the measured value being the best of these 3 readings.<br>• Forced vital capacity (FVC) - patients perform manoeuvre until 3 readings are within 5% of each other (maximum 8 attempts) the measured value being the best of these 3 readings. |

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| | | Bronchodilator response, measured using the following<br>• PEF<br>• FEV1<br>  ○ change in FEV1 % initial and change in FEV1 litres<br><br>PEF variability (diurnal variability usually expressed as amplitude (highest – lowest reading) as a percentage of the mean or the highest reading). PEFv values should be recorded as the mean over a period of at least 3 days)<br><br>Skin prick tests for the most common allergens in children (1 - <5 years old, 5 - 16 years old) (reported separately)<br>• House dust mites<br>• Cat<br>• Dog<br>• Grass pollen* (native UK grasses)<br>• Tree pollen* (native UK trees)<br>• Mixed pollens* (native UK species)<br>• Aspergillus<br>• Alternaria<br>• Cladosporium<br>Cut off values: 3mm WHEAL (skin reaction) greater than the negative control in the presence of a positive control<br><br>Serum IgE<br>• Total IgE<br>• Specific IgE* (including RAST test) |

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| | | *Reported separately for the most common aero-allergens (dust mites, grass pollen, tree pollen, dog, cat, *Aspergillus, Alternaria, Cladosporium*).<br>NOTE: serum IgE must have been assessed using ELISA (apart from RAST) as other techniques are not current/no longer used.<br><br>Fractional exhaled nitric oxide (FeNO) with a cut-off threshold between 20-50ppb and a flow rate of 50ml/s or equivalent.<br><br>Peripheral blood eosinophil count (may be part of FBC)<br><br>Bronchial challenge with:<br>• Histamine PC20 and PD20<br>• Methacholine PC20 and PD20<br>[Cut-off threshold of 8mg/ml or a cut-off threshold identified from a ROC curve]<br>• Mannitol<br>Cut-off threshold of 8mg/ml or a cut-off threshold identified from a ROC curve<br><br>Exercise challenge test (>10% FEV1 bronchoconstriction in response to exercise – within 15 mins)<br>1. Change in FEV1 ≥10% post-exercise<br>NOTE: usually this is a 6 minute exercise challenge test. |
| 8. | Reference standard | Effectiveness (test-and-treat)<br>• Compare to each other<br><br>Diagnostic accuracy |

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| | | Reference standard: Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following (as appropriate based on the tests used in the study):<br>• peak flow variability (cut-off value of more than 20% variability as indication of a positive test);<br>• 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);<br>• 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)<br>• FeNO<br>Maximum time period between the index test and reference standard: 12 months<br>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.<br>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. |
| 9. | Types of study to be included | Clinical effectiveness (test and treat):<br>• Systematic reviews of RCTs<br>• Parallel RCTs<br>Published NMAs and IPDs will be considered for inclusion.<br>Diagnostic test accuracy: |

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| | | • Cross sectional studies<br>• Cohort studies will be included |
| 10. | Other exclusion criteria | • Non-English language studies.<br>• Non comparative cohort studies<br>• Before and after studies<br>• Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.<br>• Not looking at occupational asthma /allergens<br>• Not looking at validation studies, or studies comparing different spirometry or flow volume loop measures<br>• Not looking at factors which influence measurements |
| 11. | Context | Primary, secondary and community care settings |
| 12. | Primary outcomes (critical outcomes) | All outcomes are considered equally important for decision making a therefore have all been rated as critical:<br><br>Clinical effectiveness (test and treat) outcomes:<br>• Severe asthma exacerbations (defined as asthma exacerbations requiring oral corticosteroid use (dichotomous outcome at ≥6 months)<br>• Mortality (dichotomous outcome at ≥6 months)<br>• Quality of life (QOL; validated scale, including asthma specific questionnaires AQLQ; health-related) (continuous outcome at ≥3 months)<br>• Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months) |

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| | | • Hospital admissions (dichotomous outcome at ≥6 months)<br>• Reliever/rescue medication use (continuous outcome at ≥3 months)<br>• 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.*<br>• Adverse events<br>  ○ Linear growth (continuous outcome at ≥1 year),<br>  ○ Pneumonia frequency (dichotomous outcome at ≥3 months)<br>  ○ Adrenal insufficiency as defined by study, including short synacthen test and morning cortisol (dichotomous outcome at ≥3 months)<br>  ○ Bone mineral density (continuous outcome at ≥6 months)<br>  ○ Acute symptoms (any symptom e.g. flushing, coughing, may be referred to as tolerability/acceptability – time frame immediately post test (10 mins)<br>• Inflammatory markers; exhaled nitric oxide (continuous outcome at ≥8 weeks)<br><br>Diagnostic accuracy outcomes:<br>• Sensitivity<br>• thresholds: upper 90, lower 10<br>• Specificity<br>• thresholds: upper 80, lower 50 |

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| | | • Raw data to calculate 2x2 tables to calculate sensitivity and specificity<br>• Negative predictive value (NPV), Positive predictive value (PPV) |
| 13. | Data extraction (selection and coding) | All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated.<br><br>10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.<br><br>The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.<br><br>A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).<br><br>10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:<br>• papers were included /excluded appropriately<br>• a sample of the data extractions<br>• correct methods are used to synthesise data<br>• a sample of the risk of bias assessments<br><br>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.<br><br>Study investigators may be contacted for missing data where time and resources allow. |

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| 14. | Risk of bias (quality) assessment | Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.<br>• Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)<br>• Randomised Controlled Trial: Cochrane RoB (2.0)<br>• QUADAS-2 checklist |
| 15. | Strategy for data synthesis | <u>Diagnostic intervention (test and treat):</u><br>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.<br>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.<br>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.<br>The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, |

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| | | Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/<br><br>Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.<br><br>WinBUGS will be used for network meta-analysis, if possible given the data identified.<br><br>Diagnostic accuracy:<br><br>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.<br><br>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. | |
| 16. | Analysis of sub-groups | Stratification<br>• Different reference standards<br>• Different thresholds<br>• Combination tests (and sequence used)* | |
| 17. | Type and method of review | ☒ | Intervention |
| | | ☒ | Diagnostic |
| | | ☐ | Prognostic |
| | | ☐ | Qualitative |

| | | | |
|---|---|---|---|
| | | ☐ | Epidemiologic |
| | | ☐ | Service Delivery |
| | | ☐ | Other (please specify) |
| 18. | Language | English | |
| 19. | Country | England | |
| 20. | Anticipated or actual start date | | |
| 21. | Anticipated completion date | 31 July 2024 | |
| 22. | 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 | ☐ / ☐ |
| 23. | Named contact | 5a. Named contact<br>National Guideline Centre<br><br>5b Named contact e-mail<br>asthmachronicmanagement@nice.org.uk | |

| | | |
|---|---|---|
| | | 5e Organisational affiliation of the review<br>National Institute for Health and Care Excellence (NICE) and National Guideline Centre |
| 24. | Review team members | From the National Guideline Centre:<br>Bernard Higgins (Guideline lead)<br>Sharon Swain (Guideline lead)<br>Qudsia Malik (Senior systematic reviewer)<br>Clare Jones (Senior systematic reviewer)<br>Toby Sands (Systematic reviewer)<br>Alfredo Mariani (Senior health economist)<br>Lina Gulhane (Head of information specialists)<br>Stephen Deed (Information specialist)<br>Amy Crisp (Senior project manager) |
| 25. | Funding sources/sponsor | This systematic review is being completed by the National Guideline Centre which receives funding from NICE. |
| 26. | 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 |

| | | | |
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| | | will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline. | |
| 27. | 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 | |
| 28. | Other registration details | N/A | |
| 29. | Reference/URL for published protocol | N/A | |
| 30. | Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:<br>• notifying registered stakeholders of publication<br>• publicising the guideline through NICE's newsletter and alerts<br>• 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. | |
| 31. | Keywords | N/A | |
| 32. | Details of existing review of same topic by same authors | N/A | |
| 33. | Current review status | ☒ | Ongoing |
| | | ☐ | Completed but not published |
| | | ☐ | Completed and published |
| | | ☐ | Completed, published and being updated |
| | | ☐ | Discontinued |
| 34. | Additional information | N/A | |

| | | |
|---|---|---|
| 35. | Details of final publication | www.nice.org.uk |

## Health economic review protocol

**Table 10: 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.<br>• 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).<br>• 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.)<br>• Unpublished reports will not be considered unless submitted as part of a call for evidence.<br>• 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.<br>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)<br><br>**Inclusion and exclusion criteria**<br>• 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.<br>• 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.

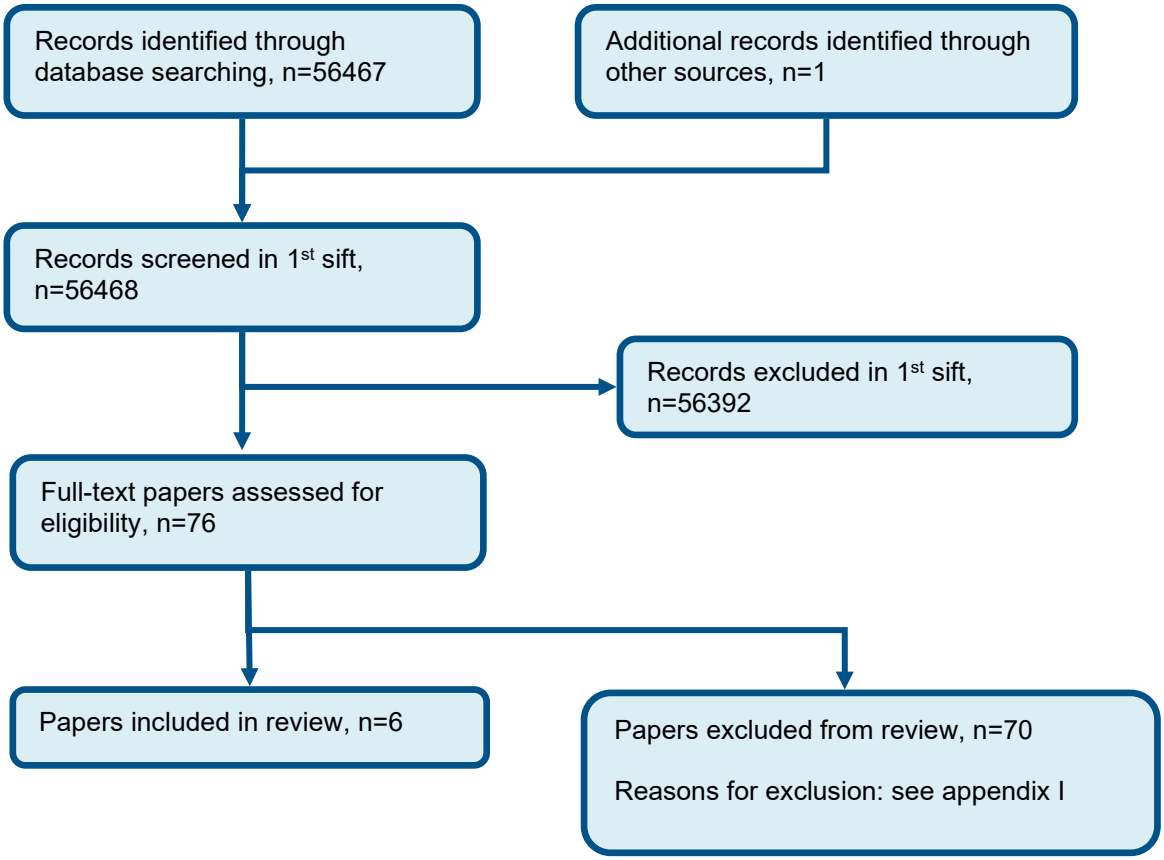
| | |
|---|---|
| | *Quality and relevance of effectiveness data used in the health economic analysis:*<br>• The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline. |

# Appendix B – Literature search strategies

There was no specific search strategy for this review. All studies were identified during the searches for review questions 1.1-1.10. For details of the search strategies for each individual test, refer to the Appendices of the corresponding reviews.

# Appendix C –Diagnostic evidence study selection

**Figure 1: Flow chart of clinical study selection for the review of combination of diagnostic tests**



# 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<br><br>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)<br><br>Gender (male to female ratio): Positive MCT; 53:117, negative MCT; 203:319<br><br>Smoking status: Non-smokers<br><br>ICS use: None within a month<br><br>Ethnicity: Not reported<br><br>Setting: Pulmonary outpatient department (secondary care)<br><br>Country: China<br><br>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<br><br>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 tests<br>**FeNO, eosinophils and spirometry**<br>Retrospective FeNO, eosinophil and spirometry data was used for this study. No information on protocol or standards measurements were performed to.<br><br>Cut-off: Individual cut-offs; 41 ppb, 3.4% or 360 cells/µL and $FEV_1$/FVC 84.67%. Combination cut-offs not reported<br><br>Reference standard<br>Methacholine challenge testing was used with a cut-off of ≤0.48 mg to indicate airway hyperresponsiveness.<br><br>Time between measurement of index test and reference standard: Not reported | | | | |
| **2×2 table FeNO + $FEV_1$/FVC** | | Reference standard + | Reference standard − | Total | Prevalence= 24.5% |
| | Index test + | 146 | 200 | 346 | |
| | Index test − | 24 | 322 | 346 | |
| | Total | 170 | 522 | 692 | |
| **2×2 table Eosinophils + $FEV_1$/FVC** | | Reference standard + | Reference standard − | Total | |
| | Index test + | 96 | 100 | 196 | |
| | Index test − | 74 | 422 | 496 | |
| | Total | 170 | 522 | 692 | |
| **Statistical measures** | Index text: FeNO + $FEV_1$/FVC<br>Sensitivity: 0.86 (95%CI 0.80-0.91)<br>Specificity: 0.62 (95%CI 0.57-0.66)<br>PPV: 42%<br>NPV: 93%<br><br>Index text: Eosinophils + $FEV_1$/FVC<br>Sensitivity: 0.56 (95%CI 0.49-0.64)<br>Specificity: 0.81 (95%CI 0.77-0.84)<br>PPV: 49%<br>NPV: 85% | | | | |
| **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 (method not reported) and the interpretation of the index test and reference standard (unclear if blinded) | | | | |

| | |
|---|---|
| **Reference** | **Bao 2021 (Bao et al., 2021)** |
| | Indirectness: Downgraded by two increments due to index test (no information on standards FeNO measurements were conducted to and no flow rate reported) and reference standard (unclear clinician decision in diagnosis) indirectness |
| **Comments** | 2x2 tables calculated using sensitivity, specificity and prevalence (24.5%) data reported in paper |

| | |
|---|---|
| **Reference** | **Eom 2020 (Eom et al., 2020)** |
| **Study type** | Prospective cross-sectional study |
| **Study methodology** | Data source: Patients referred to an outpatient clinic for diagnosis of asthma<br><br>Recruitment: Consecutive |
| **Number of patients** | n = 275 |
| **Patient characteristics** | Age, mean (95%CI): Non-asthma diagnosis: 11.5 (10.7-12.3), asthma diagnosis: 11.6 (11.1-12.1)<br><br>Gender (male to female ratio): Non-asthma diagnosis 30:54, asthma diagnosis: 65:126<br><br>Exposure to cigarette smoke: Non-asthma diagnosis: 45.2%, asthma diagnosis: 40.6%<br><br>Ethnicity: Not reported<br><br>ICS use: Four-week washout<br><br>Setting: Secondary care<br><br>Country: South Korea<br><br>Inclusion criteria: 8-16 years of age presenting with respiratory symptoms including cough, wheezing, or breathlessness for at least 1 month duration.<br><br>Exclusion criteria: Symptoms of respiratory tract infection or those with other systemic or inflammatory disease, receiving inhaled short-acting β2-agonists within 8 hours and receiving a regular treatment with controller medications for 1 month or more before evaluation. |
| **Target condition(s)** | Asthma |
| **Index test(s) and reference standard** | Index test<br>1) **FeNO measurement**: FeNO was measured using a NO analyser with electrochemical sensors, according to ATS/ERS guidelines. Participants were instructed to avoid eating, drinking and exercise 2 hours before FeNO measurements. Participants exhaled at a |

<table>
<tr><td>Reference</td><td colspan="5">Eom 2020 (Eom et al., 2020)</td></tr>
<tr><td></td><td colspan="5">constant flow rate of 50 mL/s after inhalation of ambient air through a nitric oxide scrubber to total lung capacity. Exhalation times were more than 8 seconds with a 2-minute analysis period. FeNO was measured twice and a third measurement was done if there is a more than 10% difference between the first two measurements.<br>2) Spirometry: Lung function was measured by a spirometer according to the ATS/ERS recommendations. FVC, FEV1, FEF25-75 and FEV1/FVC were obtained from the best of three reproducible forced expiratory manoeuvres. Percent predicted values were calculated based on the Third National Health and Nutrition Examination Survey.<br>3) Bronchodilator response: Measured 15 minutes after administration of four puffs (400 µg) of salbutamol using metered dose inhaler with a spacer according to ATS/ERS guideline.<br>4) IgE: Serum samples were assayed for total IgE and specific IgE to common aeroallergens including Dermatophagoides pteronyssinus, Dermatophagoides farinae, Alternaria, dog, cat, mugwort, Japanese hop, ragweed, birch, alder, Hazel and oak. IgE levels were considered positive at levels of 0.35 IU/mL or more.<br><br><u>Reference standard</u><br>Asthma was assessed by a paediatric pulmonologist after at least 6 months of follow-up. The diagnosis of asthma was determined according to the Global Initiative for Asthma guidelines and was based on the patient’s history of two or more clinical exacerbations of respiratory symptoms such as wheezing, shortness of breath and chest tightness or cough. Furthermore, spirometry was used to determine presence of variable expiratory airflow limitation, which was confirmed by increase in $FEV_1$ of more than 12% in response to a rapid-acting bronchodilator at any time during the follow-up period, increase in $FEV_1$ of more than 12% from baseline after 4 weeks of anti-inflammatory treatment, and/or variation in $FEV_1$ of more than 12% between visits. Children who did not have these characteristics and had never used asthma medication in the previous year were not considered to have asthma.<br><br>Time between measurement of index test and reference standard: 6 months</td></tr>
<tr><td rowspan="4">2×2 table<br>FeNO + $FEV_1$<br>(% predicted)</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">Prevalence= 69.5%</td></tr>
<tr><td>Index test +</td><td>157</td><td>17</td><td>174</td></tr>
<tr><td>Index test −</td><td>34</td><td>67</td><td>101</td></tr>
<tr><td>Total</td><td>191</td><td>84</td><td>275</td></tr>
<tr><td rowspan="4">2×2 table<br>FeNO +<br>$FEV_1$/FVC</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4"></td></tr>
<tr><td>Index test +</td><td>162</td><td>21</td><td>183</td></tr>
<tr><td>Index test −</td><td>29</td><td>63</td><td>92</td></tr>
<tr><td>Total</td><td>191</td><td>84</td><td>275</td></tr>
</table>

| | |
|---|---|
| **Reference** | **Eom 2020 (Eom et al., 2020)** |
| **Statistical measures** | Index text FeNO + $FEV_1$ (% predicted)<br>Sensitivity: 0.82 (95%CI 0.76-0.87)<br>Specificity: 0.80 (95%CI 0.70-0.88)<br>PPV: 90%<br>NPV: 66%<br><br>Index text FeNO + $FEV_1$/FVC<br>Sensitivity: 0.85 (95%CI 0.79-0.90)<br>Specificity: 0.75 (95%CI 0.64-0.84)<br>PPV: 89%<br>NPV: 68% |
| **Source of funding** | None declared |
| **Limitations** | Risk of bias: Not serious<br>Indirectness: Not serious |
| **Comments** | 2x2 tables calculated using sensitivity, specificity and prevalence (69.5%) 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.<br><br>Recruitment: Not specified |
| **Number of patients** | n = 51 (n=19 eventually diagnosed with asthma) |
| **Patient characteristics** | Age, median (SD): 40.2 (12.3) years<br><br>Gender (male to female ratio): 12/39<br><br>Ethnicity: Not specified<br><br>ICS use: Not reported |

| Reference | Koca Kalkan 2021 (Koca Kalkan et al., 2021) |
|---|---|
| | Setting: Outpatients<br><br>Country: Turkey<br><br>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 were performed.<br><br>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 a significant problems causing an inability to comply with the study tests.<br><br>Atopy: 12 (27.6%)<br><br>Smoking history n (%): never 36 (70.6%); ex-smoker 12 (23.5%), current smoker 3 (5.9%), pack years 4(1-60)<br><br>Median (range) duration of symptoms, months: cough: 12 (0-300); wheezing: 5.5 (0-120); dyspnoea: 30 (0-180); chest tightness 3 (0-120) |
| **Target condition** | Asthma |
| **Index test(s) and reference standard** | Index tests<br>**Absolute cell count of eosinophils in peripheral blood**<br>Method not specified<br><br>Cut-off: >150/µl<br><br>**FeNO**<br>FeNO was measured using an exhaled nitric oxide analyser at a standard flow rate of 50 mL/s, as per ATS/ERS recommendations. FeNO measurements were conducted prior to spirometry and methacholine challenge tests.<br><br>Cut-off: >14 ppb<br><br>Reference standard: Bronchial hyperreactivity (defined by methacholine challenge test)<br>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 FEV1 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 FEV1 (PC20) was calculated in each subject with a positive test. |

| | | | | | |
|---|---|---|---|---|---|
| **Reference** | **Koca Kalkan 2021 (Koca Kalkan et al., 2021)** | | | | |
| | Time between measurement of index test and reference standard: not specified | | | | |
| **2×2 table** | | Reference standard + | Reference standard − | Total | Prevalence= 37.2% |
| | Index test + | 19 | 17 | 36 | |
| | Index test − | 0 | 15 | 15 | |
| | Total | 19 | 32 | 51 | |
| **Statistical measures** | Index text: eosinophils >150/µL and FeNO >14 ppb<br>Sensitivity: 1.00 (95%CI 0.82-1.00)<br>Specificity: 0.47 (95%CI 0.29-0.65)<br>PPV: 53%<br>NPV: 100% | | | | |
| **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)<br>Indirectness: Downgraded by two increments due to population (ICS use not reported) and reference standard (clinician decision not involved in diagnosis) indirectness | | | | |
| **Comments** | 2x2 data calculated from sensitivity, specificity and prevalence (37.2%) reported in paper | | | | |

| | |
|---|---|
| **Reference** | **Parameswaran 1999 (Parameswaran et al., 1999)** |
| **Study type** | Retrospective diagnostic cross-sectional study |
| **Study methodology** | Data source: Medical records of patients referred to one physician at a university respiratory clinic between 1991-1997 for evaluation of respiratory symptoms considered suggestive of asthma<br><br>Recruitment: Not reported |
| **Number of patients** | n = 132 |
| **Patient characteristics** | Age, mean (SD): 38.9 (17.9) years<br><br>Gender (male to female ratio): 53:79<br><br>Smoking status: Not reported<br><br>Ethnicity: Not reported |

<table>
<tr><td>Reference</td><td colspan="6">Parameswaran 1999 (Parameswaran et al., 1999)</td></tr>
<tr><td></td><td colspan="6">ICS use: Not reported<br><br>Setting: Secondary care<br><br>Country: Canada<br><br>Inclusion criteria: None reported<br><br>Exclusion criteria: None reported</td></tr>
<tr><td>Target condition(s)</td><td colspan="6">Asthma</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="6"><u>Index tests</u><br>1) Methacholine challenge test - Methacholine tests were performed by the tidal breathing method and results expressed as provocative dose of methacholine causing a 20% fall in FEV1 (PC20) mg.mL-1 in noncumulative units. PC20 >16 mg.mL-1 (20% fall not achieved on final concentration) was recorded as 32 mg.mL-1. PC20 <8 mg/mL was considered indicative of airway hyperresponsiveness.<br>2) Peak expiratory flow monitoring - Home peak flow recordings were performed using the procedure recommended by the European Respiratory Society with a PEF monitor, usually for the 2 weeks preceding measurement of PC20. PEF was measured between 07:00-09:00 h and between 17:00-19:00 h, before inhaling b2-agonist if required. On each occasion, the best of three attempts was recorded. PEF variability was calculated as the difference between the lowest and highest PEF as a percentage of the highest PEF recorded during a 14-day period. PEFV >20% was considered indicative of variable airflow obstruction.<br><br><u>Reference standard</u><br>The diagnosis of the physician at his first assessment of the patient, as recorded in the consultation letter dictated when they did not have the results of either index test investigation, was coded as: a) definitely asthma; b) possibly asthma (uncertain); and c) definitely not asthma<br><br>Time between measurement of index test and reference standard: Not reported</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Reference standard indeterminate</td><td>Total</td><td>Prevalence= 38.6%</td></tr>
<tr><td></td><td>Index test +</td><td>38</td><td>3</td><td>15</td><td>56</td><td></td></tr>
<tr><td></td><td>Index test -</td><td>4</td><td>11</td><td>45</td><td>60</td><td></td></tr>
<tr><td></td><td>Index test indeterminate</td><td>9</td><td>0</td><td>7</td><td>16</td><td></td></tr>
</table>

| | | | | | | |
|---|---|---|---|---|---|---|
| **Reference** | **Parameswaran 1999 (Parameswaran et al., 1999)** | | | | | |
| | Total | 51 | 14 | 67 | 132 | |
| **Statistical measures** | Index text<br>Sensitivity: 0.75 (95%CI 0.60-0.86)<br>Specificity: 0.78 (95%CI 0.67-0.86)<br>PPV: 68%<br>NPV: 83% | | | | | |
| **Source of funding** | None reported | | | | | |
| **Limitations** | Risk of bias: Downgraded by two increments due to concerns arising from the method of patient selection (method not reported) and interpretation of the index test (not blinded to reference standard)<br>Indirectness: Downgraded by one increment due to population (ICS use not reported) indirectness | | | | | |
| **Comments** | Sensitivity and specificity calculated by analyst based on 2x2 data reported in paper. Indeterminate tests were deemed as negative in calculations. | | | | | |

| | |
|---|---|
| **Reference** | **Porpodis 2017 (Porpodis et al., 2017)** |
| **Study type** | Prospective cross-sectional study |
| **Study methodology** | Data source: Conducted in the Outpatient Clinic for Asthma, Pulmonary Department, within the Aristotle University of Thessaloniki<br><br>Recruitment: Subjects were recruited in the study when they visited the Asthma Clinic either for a formal examination of asthma diagnosis or after the referral of another specialist for work-up of respiratory symptoms |
| **Number of patients** | n = 88 |
| **Patient characteristics (per protocol)** | Age, mean (SD): 38.56 (16.73) years<br><br>Gender (male to female ratio): 41:47<br><br>Smoking status: Mixed, 17 current smokers (15%), 16 ex-smokers (14%)<br><br>Ethnicity: Not reported<br><br>ICS use: Therapy naïve<br><br>Setting: Secondary care<br><br>Country: Greece |

<table>
<tr><td>Reference</td><td colspan="5">Porpodis 2017 (Porpodis et al., 2017)</td></tr>
<tr><td></td><td colspan="5">Inclusion criteria: Asthma related symptoms in the previous month but without previous diagnosis of asthma and without initiation of treatment.<br><br>Exclusion criteria: Any other known cardiopulmonary or systematic disease</td></tr>
<tr><td>Target condition(s)</td><td colspan="5">Asthma</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5">Index test<br>1) Spirometry - Initially baseline $FEV_1$ was measured, using a portable spirometer, and the challenge tests were performed if $FEV_1$ was >60% of predicted.<br>2) Mannitol challenge test - The mannitol test was conducted using a standardized test kit that contained pre-filled mannitol capsules and a handheld powder device, where the patient inhaled escalating doses of powdered mannitol until either a drop of 15% of the $FEV_1$ baseline was achieved (PD15), or a more than 10% drop of $FEV_1$ between two consecutive measurements was observed. The maximum cumulative dose of mannitol was 635 mg.<br>3) Methacholine challenge test - The Methacholine challenge test was performed using inhaled incremental doses of methacholine in wet aerosol form, until a drop of 20% of the $FEV_1$ baseline was obtained (PC20), where the test was considered positive and the patient was assigned as having BHR. The exact methacholine provocative concentration causing a 20% decrease in FEV1 (PC20) was estimated from a dose-response curve and was considered as a threshold value. The test was terminated when either the threshold value had been reached or the highest concentration of methacholine had been given. Patients were considered hyperresponsive if they reacted by bronchoconstriction to PC20 ≤16 mg/ml. Positivity at 32 mg/ml was considered as negative for asthma.<br><br>Reference standard<br>According to GINA guidelines, the clinician diagnosis of asthma was established by the combination of at least a ≥12% (and at least 200 mL) increase in baseline FEV1 after albuterol, along with new symptoms of coughing, wheezing, or shortness of breath over the past month, and no previous diagnosis of asthma<br><br>Time between measurement of index test and reference standard: Unclear</td></tr>
<tr><td rowspan="4">2x2 table Positive to both Meth and Mann</td><td></td><td>Reference standard +</td><td>Reference standard -</td><td>Total</td><td rowspan="4">Prevalence= 76.1%</td></tr>
<tr><td>Index test +</td><td>52</td><td>3</td><td>55</td></tr>
<tr><td>Index test -</td><td>15</td><td>18</td><td>33</td></tr>
<tr><td>Total</td><td>67</td><td>21</td><td>88</td></tr>
</table>

| Reference | Porpodis 2017 (Porpodis et al., 2017) |
|---|---|
| Statistical measures | Index text<br>Sensitivity: 0.78 (95%CI 0.66-0.87)<br>Specificity: 0.86 (95%CI 0.64-0.97)<br>PPV: 97%<br>NPV: 45% |
| Source of funding | None reported |
| Limitations | Risk of bias: Downgraded by two increments due to the method of patient selection (recruitment method not reported) and interpretation of the index test and reference standard (unclear if clinician diagnosing asthma was blinded to bronchial challenge results)<br>Indirectness: None |

| Reference | Simpson 2024 (Simpson et al., 2024) |
|---|---|
| Study type | Prospective cross-sectional diagnostic accuracy study |
| Study methodology | Data source: People referred by general practitioners in Greater Manchester having presented with symptoms suggestive of asthma<br><br>Recruitment: Not reported |
| Number of patients | n = 118 |
| Patient characteristics | Age, mean (SD): 36 (12)<br><br>Gender (male to female ratio): 43:75<br><br>Smoking status: 40 (35%) current or ex-smokers<br><br>Atopy: 75/115 (65%) with ≥1 positive skin prick test result<br><br>Ethnicity: Not reported<br><br>Setting: Asthma clinic<br><br>Country: UK<br><br>Inclusion criteria: Presenting with symptoms of wheeze, chest tightness, cough and/or breathlessness |

| Reference | Simpson 2024 (Simpson et al., 2024) |
|---|---|
| | Exclusion criteria: Aged >70 years, inhaled or oral corticosteroid use within 4 weeks, antibiotic use within 2 weeks, smoking history >10 pack years, other significant lung disease, suspected alternative lung disease upon inspection of clinical history and initial physical examination |
| **Target condition(s)** | Asthma |
| **Index test(s) and reference standard** | Index test<br>ERS-defined asthma<br>Progressive diagnostic pathways whereby if an individual tested positive, they received no further testing. If negative participants proceed to the next pathway. If negative on all pathways, then the individual is deemed to not have asthma:<br>• Spirometry, $FEV_1$/FVC <75% and bronchodilator reversibility ≥12% and 200 mL<br>• FeNO >50 ppb<br>• PEF variability (PEFv), >20% over a minimum of 5 days<br>• Bronchial challenge test (BCT), with methacholine PD20 <0.20 mg<br><br>The pathways were as follows (brackets indicate the number of participants diagnosed per step):<br>• Positive spirometry, positive BDR (23 participants)<br>• Positive or negative spirometry, negative or not measured BDR, positive FeNO (27 participants)<br>• Positive or negative spirometry, negative or not measured BDR, negative FeNO, positive PEFv (3 participants)<br>• Positive or negative spirometry, negative or not measured BDR, negative FeNO, negative PEFv, positive BCT (11 participants)<br><br>NICE-defined asthma (pathways 1-6)<br>The current NICE diagnostic pathway comprises 15 possible pathways. Data from each participant was entered into each of the algorithms using the following cut-offs:<br>• Spirometry, $FEV_1$ <70% of predicted or LLN<br>• Bronchodilator reversibility (BDR), ≥12% and 200 mL<br>• FeNO, ≥40 ppb, or between 39 and 25 ppb<br>• PEF variability (PEFv), >20%<br>• Bronchial challenge test (BCT), with methacholine PD20 <0.20 mg<br><br>Missing test data was entered as negative so that all pathways could be completed. Positivity on any algorithm from 1-6 categorised a participant as having asthma (brackets indicate the number of participants diagnosed per algorithm):<br><br>• Negative spirometry, negative FeNO (≥40 ppb), positive PEFv, positive BCT (0 participants)<br>• Negative spirometry, positive FeNO (≥40 ppb), negative PEFv, positive BCT (13 participants)<br>• Negative spirometry, positive FeNO (≥40 ppb), positive PEFv (3 participants) |

| Reference | Simpson 2024 (Simpson et al., 2024) |
|---|---|

- Positive spirometry, negative BDR, negative FeNO (≥40 ppb), positive FeNO (39-25 ppb), negative PEFv, positive BCT (1 participant)
- Positive spirometry, positive BDR, negative FeNO (≥40 ppb), positive PEFv (0 participants)
- Positive spirometry, positive BDR, positive FeNO (≥40 ppb) (12 participants)

NICE-defined asthma/suspected asthma (pathways 1-9)
The same approach as that outlined above was applied, but also included pathways 7-9 which indicate a suspicion of asthma / inconclusive, which should be followed up by a trial of treatment. This data included individuals positive on any pathway from 1-9:

- Positive spirometry, negative BDR, negative FeNO (≥40 ppb), positive FeNO (39-25 ppb), positive PEFv (0 participants)
- Positive spirometry, negative BDR, positive FeNO (≥40 ppb) (4 participants)
- Positive spirometry, positive BDR, negative FeNO (≥40 ppb), positive FeNO (39-25 ppb), negative PEFv (1 participant)

The remaining 6 pathways indicated an alternative diagnosis other than asthma and were treated as negative in this index test.

GINA-defined asthma
Progressive diagnostic pathways whereby if an individual tested positive, they received no further testing. If negative participants proceed to the next pathway. If negative on all pathways, then the individual is deemed to not have asthma. The cut-offs used were as follows:

- Spirometry, $FEV_1$/FVC <LLN
- Bronchodilator reversibility (BDR), ≥12% and 200 mL
- PEF variability (PEFv), ≥10%
- Bronchial challenge test (BCT) with methacholine (PD20 <200 µg and/or mannitol (PD15 <635 mg)
- $FEV_1$ variability >12%
- $FEV_1$ response to ICS >12% and 200 mL (does not meet clinical protocol for this review. Only used in pathway 5, which no participants reached)

The diagnostic pathways were as follows (brackets indicate the number of participant diagnosed per pathway):

1. Positive spirometry, positive BDR (22 participants)
2. Positive spirometry, negative BDR, positive PEFv (7 participants)
3. Positive spirometry, negative BDR, negative PEFv, positive BCT (3 participants)
4. Positive spirometry, negative BDR, negative PEFv, negative BCT, positive $FEV_1$ variability (0 participants)
5. Positive spirometry, negative BDR, negative PEFv, negative BCT, negative $FEV_1$ variability, positive $FEV_1$ response to ICS (0 participants)

Reference standard
Expert panel objective evidence review was used as the reference standard. All evidence, including history, physical examination, Asthma Control Questionnaire, and all test results before and after ICS, was reviewed by at least three physicians (a minimum of two senior asthma physicians) with a diagnosis reached by consensus. Index test data were available to the assessors of the reference standard. Not

| Reference | Simpson 2024 (Simpson et al., 2024) | | | | |
|---|---|---|---|---|---|
| | all participants completed all aspects of the study, but all evaluable data were assessed including raw data (such as flow volume loops, dose-response curves, peak flow diaries), to take account of uncertainty and inherent biological variability. Participants were assigned a diagnosis of “asthma” or “not asthma” or were excluded from further analyses if a clear diagnosis was not possible.<br><br>Time between measurement of index test and reference standard: 8-12 weeks | | | | |
| **2×2 table ERS-defined asthma** | | Reference standard + | Reference standard − | Total | Prevalence= 59.3% |
| | Index test + | 57 | 7 | 64 | |
| | Index test − | 13 | 41 | 54 | |
| | Total | 70 | 48 | 118 | |
| **2×2 table NICE-defined asthma (pathways 1-6)** | | Reference standard + | Reference standard − | Total | |
| | Index test + | 29 | 0 | 29 | |
| | Index test − | 41 | 48 | 89 | |
| | Total | 70 | 48 | 118 | |
| **2×2 table NICE-defined asthma or suspected asthma (pathways 1-9)** | | Reference standard + | Reference standard − | Total | |
| | Index test + | 34 | 0 | 34 | |
| | Index test − | 36 | 48 | 84 | |
| | Total | 70 | 48 | 118 | |
| **2×2 table GINA-defined asthma** | | Reference standard + | Reference standard − | Total | |
| | Index test + | 33 | 0 | 33 | |
| | Index test − | 37 | 48 | 85 | |
| | Total | 70 | 48 | 118 | |
| **Statistical measures** | <u>Index text ERS-defined asthma</u><br>Sensitivity: 0.81 (0.70-0.90)<br>Specificity: 0.85 (0.72-0.94)<br>PPV: 89% (80-94)<br>NPV: 76% (66-84)<br><br><u>Index text NICE-defined asthma (pathways 1-6)</u><br>Sensitivity: 0.41 (0.30-0.59)<br>Specificity: 1.00 (0.93-1.00)<br>PPV: 100% (88-100) | | | | |

| Reference | Simpson 2024 (Simpson et al., 2024) |
|---|---|
| | NPV: 54% (49-59)<br><br>Index text NICE-defined or suspected asthma (pathways 1-9)<br>Sensitivity: 0.49 (0.36-0.61)<br>Specificity: 1.00 (0.93-1.00)<br>PPV: 100% (90-100)<br>NPV: 57% (52-63)<br><br>Index text GINA-defined asthma<br>Sensitivity: 0.47 (0.35-0.59)<br>Specificity: 1.00 (0.93-1.00)<br>PPV: 100% (89-100)<br>NPV: 56% (51-62) |
| **Source of funding** | Supported by the Manchester NIHR Biomedical Research Centre, Asthma UK/Innovate and Northwest Lung Centre Charity |
| **Limitations** | Risk of bias: Downgraded by two increments due to concerns arising from the method of participant selection (recruitment method not reported) and the interpretation of the index test and reference standard (clinicians had access to index test results whilst making the reference standard diagnosis)<br>Indirectness: None |

# Appendix E – Forest plots

## Coupled sensitivity and specificity forest plots

### Children/Young People

**Figure 2: Logistic regression model (cut-off: 0.6) incorporating FeNO (cut-off: 19.6) + % predicted $FEV_1$ (cut-off: 88.4%) vs clinician diagnosis**

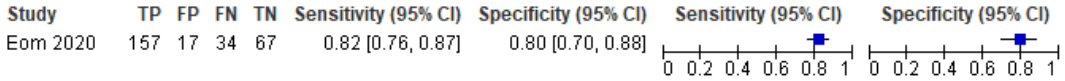
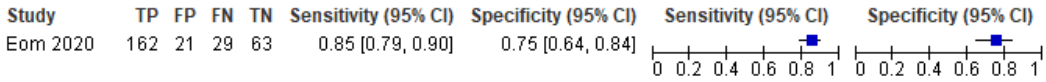



**Figure 3: Logistic regression model (cut-off: 0.6) incorporating FeNO (cut-off: 19.6) + $FEV_1$/FVC (cut-off: 85.3%) vs clinician diagnosis**




### Adults

**Figure 4: Bronchial challenge test with methacholine (cut-off: PC20 $FEV_1$ <8 mg/mL) + peak expiratory flow variability (cut-off: 20%) vs clinician diagnosis without objective tests**

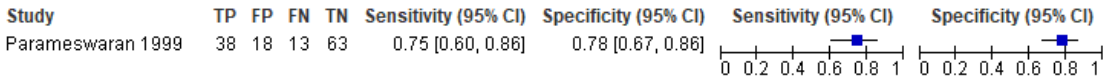



**Figure 5: Bronchial challenge with methacholine (cut-off: PC20 $FEV_1$ ≤16 mg/mL) + bronchial challenge with mannitol (cut-off: PD15 $FEV_1$ or 10% between doses <625 mg) vs clinician diagnosis with bronchodilator reversibility test**

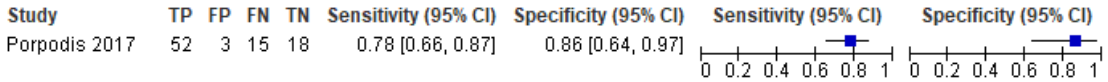



**Figure 6: Peripheral blood eosinophil count (cut-off: >150/µl) + FeNO (cut-off: >14 ppb) vs diagnosis with methacholine bronchial challenge test**

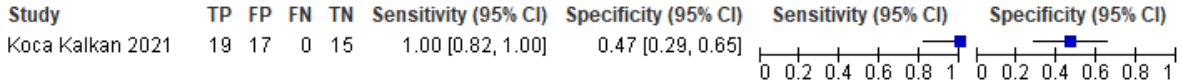


**Figure 7: FeNO (cut-off: 41 ppb) + $FEV_1$/FVC (cut-off: 84.67%) vs diagnosis with methacholine bronchial challenge test**

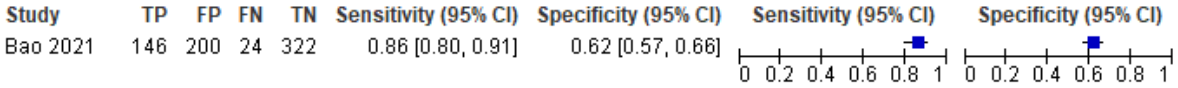



**Figure 8: Eosinophils (cut-off: 3.4% or 360 cells/µl) + $FEV_1$/FVC (cut-off: 84.67%) vs diagnosis with methacholine bronchial challenge test**

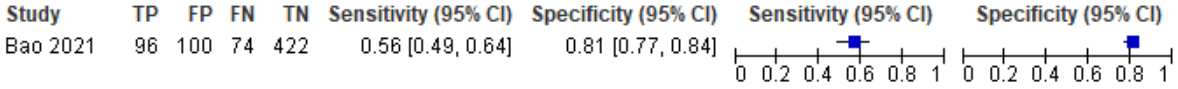



**Figure 9: ERS-defined asthma vs expert panel diagnosis with multiple diagnostic tests**

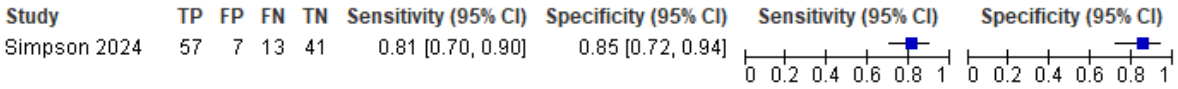



**Figure 10: NICE-defined (pathways 1-6) asthma vs expert panel diagnosis with multiple diagnostic tests**


**Figure 11: NICE-defined (pathways 1-9) asthma/suspected asthma vs expert panel diagnosis with multiple diagnostic tests**

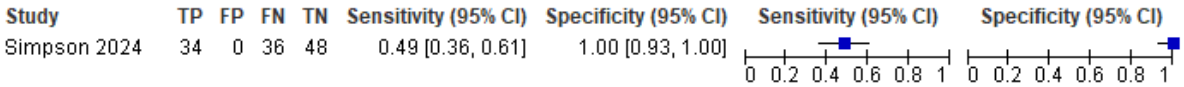
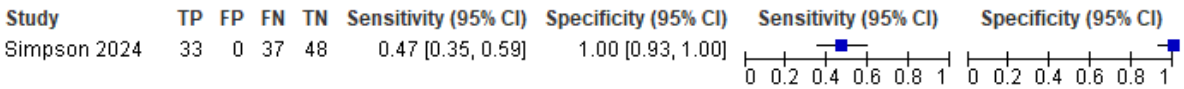
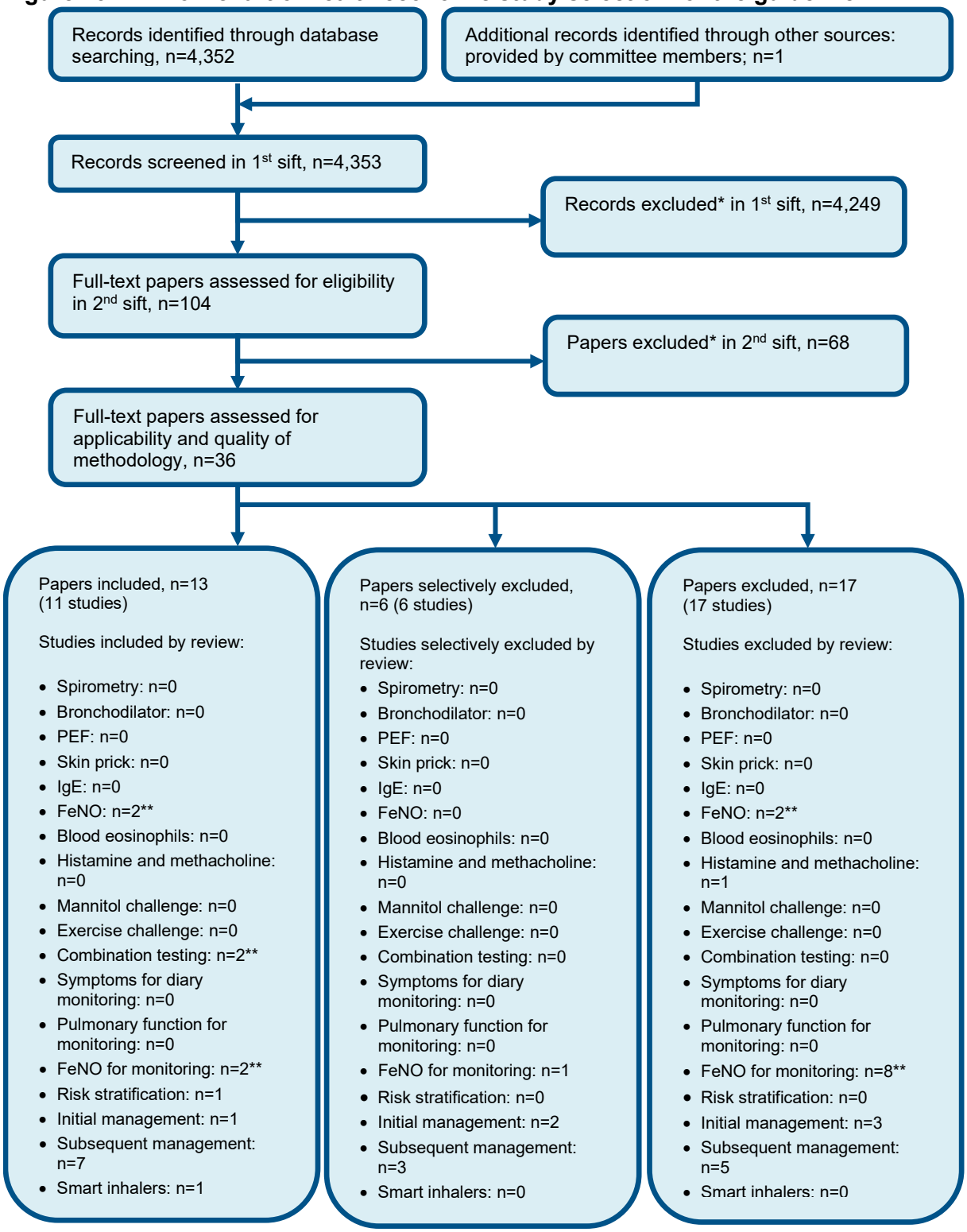



**Figure 12: GINA-defined asthma vs expert panel diagnosis with multiple diagnostic tests**



# Appendix F – Economic evidence study selection

**Figure 13: 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

<table>
<tr><th>Study</th><th colspan="4">NICE (2017)(National Institute for et al., 2017)</th></tr>
<tr><th>Study details</th><th>Population & interventions</th><th>Costs</th><th>Health outcomes</th><th>Cost effectiveness</th></tr>
<tr>
<td>Economic analysis: CUA (health outcome: QALYs)<br><br>Study design: Health economic model based on NICE clinical review on sensitivity and specificity of a variety of tests for asthma and prevalence information extracted from published trials.<br>Approach to analysis:<br>The model is based on two parts. A decision tree using the sensitivity and specificity estimated in the clinical review and combined with data on prevalence and a number of assumptions on conditional dependence was developed to estimate the proportion of true positive, true negative, false positive and false negative diagnosis. A</td>
<td>Population:<br>Adults who present symptoms of asthma to their GP<br><br>Cohort settings:<br>Start age: 43<br>Male: 40%<br><br>Intervention 1:<br>CP: Diagnosis without objective test<br><br>Intervention 2:<br>S1: Spirometry, BDR(+)/FeNO(-)<br><br>Intervention 3:<br>S2: Spirometry, BDR(+)/FeNO(-) and PEF(-)<br><br>Intervention 4:<br>S3: Spirometry, BDR(+)/FeNO(-), PEF(-) and methacholine test</td>
<td>Total costs (mean per patient):<br>Intervention 1: £3,730<br>Intervention 2: £3,753<br>Intervention 3: £3,686<br>Intervention 4: £3,683<br>Intervention 5: £3,691<br>Intervention 6: £3,686<br>Intervention 7: £3,695<br><br>Currency & cost year:<br>2014 UK Pounds<br>Cost components incorporated:<br>Exacerbation (hospitalised and non-hospitalised), diagnostic test, respiratory outpatient visit, GP appointment, asthma management, COPD management, heart failure</td>
<td>QALYs (mean per patient):<br>Intervention 1: 16.7766<br>Intervention 2: 16.7760<br>Intervention 3: 16.7776<br>Intervention 4: 16.7783<br>Intervention 5: 16.7785<br>Intervention 6: 16.7784<br>Intervention 7: 16.7787</td>
<td>
<table>
<tr><th>Int</th><th>Cost[(b)]:</th><th>QALY</th><th>Inc cost</th><th>Inc QALY</th><th>ICER</th></tr>
<tr><td>S1</td><td>£3,753</td><td>16.7760</td><td colspan="3">Dominated by S3</td></tr>
<tr><td>CP</td><td>£3,730</td><td>16.7766</td><td colspan="3">Dominated by S3</td></tr>
<tr><td>S2</td><td>£3,686</td><td>16.7776</td><td colspan="3">Dominated by S3</td></tr>
<tr><td>S3</td><td>£3,683</td><td>16.7783</td><td colspan="3">Baseline</td></tr>
<tr><td>S5</td><td>£3,686</td><td>16.7784</td><td>£3</td><td>0.0001</td><td>£20,276</td></tr>
<tr><td>S4</td><td>£3,691</td><td>16.7785</td><td colspan="3">Extended dominated by S6</td></tr>
<tr><td>S6</td><td>£3,695</td><td>16.7787</td><td>£9</td><td>0.0003</td><td>£32,565</td></tr>
</table>
Probability Intervention cost effective (£20K):<br>Intervention 1 (CP): 6%<br>Intervention 2 (S1): 0%<br>Intervention 3 (S2): 19%<br>Intervention 4 (S3): 44%<br>Intervention 5 (S4): 0%<br>Intervention 6 (S5): 23%<br>Intervention 7 (S6): 8%
</td>
</tr>
</table>

| | | | | |
|---|---|---|---|---|
| Markov model was then utilised to estimated patient's health and cost outcomes in the long-term.<br><br>**Perspective:** UK NHS<br>**Time horizon:** lifetime<br>**Discounting:** Costs: 3.5%; Outcomes: 3.5% | **Intervention 5:**<br>S4: Spirometry, BDR(+)/FeNO(-), PEF(-) and expanded use of methacholine test (1)<br><br>**Intervention 6:**<br>S5: Spirometry, BDR(+)/FeNO(-), PEF(-) and expanded use of methacholine test (2)<br><br>**Intervention 7:**<br>S6: Spirometry, BDR(+)/FeNO(-), PEF(-) and expanded use of methacholine test (maximum use) | | | **Analysis of uncertainty:** A series of sensitivity analyses were conducted. Only the following results in a change in conclusion of the model:<br>Increasing sensitivity and specificity of BDR or FeNO made intervention 6 the most cost-effective as it reduces people receiving a methacholine test at the end of the sequence.<br>If the cost of a methacholine challenge is reduced to £77, intervention 7 (maximum use of methacholine) becomes the most cost-effective,<br>If FeNO device is used less than 28 times in 5 years (thus increasing the marginal per-test cost), intervention 1 (diagnosis without objective test) becomes the most cost-effective |

**Data sources**

**Health outcomes:** Diagnostic accuracy data of tests was estimated from the studies included in the literature review. Prevalence of asthma was taken from a meta-analysis of diagnostic studies identified in the clinical review. The conditional dependence across all the diagnostic tests was estimated using GC expert opinion. **Quality-of-life weights:** EQ-5D utility scores were derived from a systematic search of the literature. One study using EQ-5D UK tariff weight was ultimately used in the analysis (McTaggart 2008). **Cost sources:** PSSRU, NHS Supply catalogue, NHS drug tariff and NHS Reference costs were used to estimate the cost of tests and of exacerbation episodes. Price 2007 was used to estimate the cost of annual asthma management. NICE guidelines on COPD and Acute heart failure were used to estimate the costs of diseases with similar symptoms of asthma (false positive).

**Comments**

**Source of funding:** NICE guideline NG80 **Limitations:** Prevalence of asthma taken from the studies that informed diagnostic accuracy, which may not reflect UK specific asthma prevalence rates. No information was available on people who receive a false negative or false positive diagnosis and a number of assumptions had to be made regarding maximum length of misdiagnosis. The evidence used for diagnostic accuracy was not conducted in the appropriate subgroups of patients but based instead on a review on all patients who present asthma symptoms. Conditional dependence was incorporated into the model using GC expert opinion but without supporting data. The clinical review suggests that there is a moderate conditional

dependence between spirometry and BDR and between methacholine challenge and FeNO, which were both considered conditionally independent in the model. This implies that the model might have overestimated the usefulness of offering BDR after spirometry and methacholine challenge after FeNO. Strategy reflecting current practice (diagnosis without objective test) assumed a sensitivity of 100% and that 1/3 of people will be misdiagnosed. These assumptions are based on a Canadian study on an obese and non-obese population and might not be applicable to the UK NHS settings as practices vary significantly across countries. **Other:** The diagnostic algorithm produced by this economic analysis has been criticised for being unnecessarily rigid and for not considering individual variability (for instance, severity of asthma symptoms) that could be as important as an objective test for reaching a diagnosis.

**Overall applicability:**[b] Directly applicable **Overall quality:**[c] Potentially serious limitations

*Abbreviations: 95% CI= 95% confidence interval; BDR= bronchodilator reversibility test; COPD= Chronic obstructive pulmonary disease; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); FeNO= fractional exhaled nitric oxide; FEV1= forced expiratory volume ; FN= false negative; FP= false positive; FVC=forced vital capacity; HRQoL= health related quality of life; ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; PEF= Peak Flow Measurement; PSSRU= Personal and Social Services Research Unit; QALYs= quality-adjusted life years;*

*(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.*

*(b) Directly applicable / Partially applicable / Not applicable*

*(c) Minor limitations / Potentially serious limitations / Very serious limitations*

<table>
<tr><th>Study</th><th colspan="4">Harnan 2015(Harnan et al., 2015), also reported in NICE Diagnostics Guidance 12(National Institute for Health and Care Excellence, 2014)</th></tr>
<tr><th>Study details</th><th>Population & interventions</th><th>Costs</th><th>Health outcomes</th><th>Cost effectiveness</th></tr>
<tr>
<td>Economic analysis: CUA (health outcome: QALYs)<br><br>Study design: Decision tree<br><br>Approach to analysis:<br><br>Diagnostic decision tree comparing FeNO to current standard tests in a population with suspected asthma. Model estimated proportion correctly or incorrectly diagnosed with/without asthma using published estimates of sensitivity and specificity. The model made the simplifying assumption that incorrect diagnoses (FNs and FPs) were resolved by subsequent tests after 8 months (95%CI: 4-12 months) and 18 months (95%CI: 12-24 months) respectively.</td>
<td>Population:<br><br>People with symptoms of asthma as seen in primary and secondary care in England and Wales.<br><br>Cohort settings:<br><br>Start age: NR<br><br>Male: NR<br><br>Intervention<br>1. Bronchial challenge test with methacholine (MCT)<br>2. FeNO + bronchodilator reversibility (NObreath)<br>3. FeNO + bronchodilator reversibility (NIOX VERO)<br>4. FeNO + bronchodilator reversibility (NIOX MINO)</td>
<td>Total costs (mean per patient):<br><br>Intervention (£)<br>1. 1226<br>2. 686.08<br>3. 687.61<br>4. 688.33<br>5. 1265.78<br>6. 1267.32<br>7. 1268.03<br>8. 810.14<br>9. 811.67<br>10. 812.38<br>11. 1328.28<br>12. 819.94<br>13. 821.47<br>14. 822.18<br>15. 877.91<br>16. 886.27<br>17. 907.71<br><br>For incremental analysis see cost effectiveness column Currency & cost year:</td>
<td>Total QALYs<br><br>Intervention<br>1. 4.2834<br>2. 4.2829<br>3. 4.2829<br>4. 4.2829<br>5. 4.2812<br>6. 4.2812<br>7. 4.2812<br>8. 4.2783<br>9. 4.2783<br>10. 4.2783<br>11. 4.2774<br>12. 4.2771<br>13. 4.2771<br>14. 4.2771<br>15. 4.2719<br>16. 4.2710<br>17. 4.2686<br><br>For incremental analysis see cost effectiveness column</td>
<td>Full incremental analysis (pa): [a] [b]
<table>
<tr><th>Int</th><th>Cost (£)</th><th>QALY</th><th>Inc cost</th><th>Inc QALY</th><th>ICER</th><th>% most CE at £20K/£30K:</th></tr>
<tr><td>17</td><td>907.71</td><td>4.2686</td><td colspan="3">Dominated by 2</td><td>0%/0%</td></tr>
<tr><td>16</td><td>886.27</td><td>4.2710</td><td colspan="3">Dominated by 2</td><td>0%/0%</td></tr>
<tr><td>15</td><td>877.91</td><td>4.2719</td><td colspan="3">Dominated by 2</td><td>0%/0%</td></tr>
<tr><td>14</td><td>822.18</td><td>4.2771</td><td colspan="3">Dominated by 2</td><td>0%/0%</td></tr>
<tr><td>13</td><td>821.47</td><td>4.2771</td><td colspan="3">Dominated by 2</td><td>0%/0%</td></tr>
<tr><td>12</td><td>819.94</td><td>4.2771</td><td colspan="3">Dominated by 2</td><td>0%/0%</td></tr>
<tr><td>11</td><td>1328.28</td><td>4.2774</td><td colspan="3">Dominated by 2</td><td>0%/0%</td></tr>
<tr><td>10</td><td>812.38</td><td>4.2783</td><td colspan="3">Dominated by 2</td><td>0%/0%</td></tr>
</table>
</td>
</tr>
</table>

Unnecessary treatment costs and health losses resulting from misdiagnosis were explicitly captured in the model. Mortality was not modelled.

**Perspective:** UK NHS

**Time horizon:** 5 years (a)

**Discounting:** Costs: 3.5%, Outcomes: 3.5%

5. FeNO + sputum induction (Nobreath)
6. FeNO + sputum induction (NIOX VERO)
7. FeNO + sputum induction (NIOX MINO)
8. FeNO + FEV1 (Nobreath)
9. FeNO + FEV1 (NIOX VERO)
10. FeNO + FEV1 (NIOX MINO)
11. Sputum induction
12. FeNO (NObreath)
13. FeNO (NIOX VERO)
14. FeNO (NIOX MINO)
15. PEFv
16. Bronchodilator reversibility
17. FEV1/FVC

2012/2013 UK pounds

**Cost components Incorporated:**

Test costs included, maintenance costs of devices, primary care costs (measuring FeNO, spirometry and reversibility testing requires 2 GP visit and 1 nurse visit).

Secondary care costs (sputum induction and the metacholine challenge test) require 2 visits, 1 laboratory).

Cost of asthma management (in line with BTS/SIGN asthma guidelines).

Cost of resolving misdiagnosis (1 additional primary care appointment, 2 additional secondary care

| | | | | | | |
|---|---|---|---|---|---|---|
| 9 | 811.67 | 4.2783 | Dominated by 2 | | | 0%/0% |
| 8 | 810.14 | 4.2783 | Dominated by 2 | | | 2% |
| 7 | 1268.03 | 4.2812 | Dominated by 2 | | | 0%/0% |
| 6 | 1267.32 | 4.2812 | Dominated by 2 | | | 0%/0% |
| 5 | 1265.78 | 4.2812 | Dominated by 2 | | | 0%/0% |
| 4 | 688.33 | 4.2829 | Dominated by 2 | | | 0%/0% |
| 3 | 687.61 | 4.2829 | Dominated by 2 | | | 98%/95% |
| 2 | 686.08 | 4.2829 | Baseline | | | 0%/0% |
| 1 | 1226 | 4.2834 | 539.92 | 0.005 | £1,125,074 per QALY | 0%/0% |

FeNO + bronchodilator reversibility (NObreath) was the most cost-effective intervention at £20,000 per QALY.

A full incremental analysis is presented below with combinations excluded (interventions 2 to 10) for the purposes of the FeNO review question (probability most cost effective not available): [a] [b]

| Int | Cost (£) | QALY | Inc cost | Inc QALY | ICER |
|---|---|---|---|---|---|

and 1 laboratory visit).

Costs associated with loss of control for FN patients, (1 exacerbation per year)

| | | | | | |
|---|---|---|---|---|---|
| 17 | 907.71 | 4.2686 | Dominated by 12 | | |
| 16 | 886.27 | 4.2710 | Dominated by 12 | | |
| 15 | 877.91 | 4.2719 | Dominated by 12 | | |
| 14 | 822.18 | 4.2771 | Dominated by 12 | | |
| 13 | 821.47 | 4.2771 | Dominated by 12 | | |
| 12 | 819.94 | 4.2771 | Baseline | | |
| 11 | 1328.28 | 4.2774 | Dominated by 1 | | |
| 1 | 1226 | 4.2834 | 406.06 | 0.0063 | £64,454 per QALY |

FeNO (NObreath) was the most cost-effective intervention at £20,000 per QALY.

**Analysis of uncertainty:**

1. Deterministic analyses conducted. The results were robust in most cases. The model was sensitive to assumptions about the length of time needed to resolve misdiagnoses; assumptions about health losses incurred by patients who have false-negative results; the costs of asthma management; and the use of rule-in and rule-out diagnostic decision rules. The only sensitivity analysis

| | | | | |
|---|---|---|---|---|
| | | | | where FeNO + bronchodilator reversibility (NObreath) was no longer the most cost-effective intervention was when it was assumed all tests were conducted in secondary care (including FeNO). In this instance, Bronchial challenge test with methacholine (MCT) was dominant.<br><br>Results based on the point estimates of parameters reflect the results of PSA. |

**Data sources**

**Health outcomes:** Diagnostic accuracy of tests taken from a systematic review conducted alongside the economic model which identified 5 papers (Cordeiro 2011, Hunter 2002, Schleich 2012, Schneider 2008 and Sivan 2009). Schneider 2008 used to inform diagnostic accuracy of FeNO alone. Prevalence of asthma taken from the studies that informed diagnostic accuracy, with exception of Hunter 2002 due to study design. **Quality-of-life weights:** Utility of non-asthma population estimated using a general population EQ-5D regression model reported by Ara and Brazier. Disutility asthma estimate taken from Sullivan et al. (2011) which estimated this using community-based UK preferences applied to EQ-5D descriptive questionnaire responses in the US-based Medical Expenditure Panel Survey. Disutility associated with poor asthma control derived from EQ-5D estimates reported in McTaggart-Cowan 2008 (tariff not reported). **Cost sources:** Resource use taken from manufacturer, BTS/SIGN, published evidence (such as HTAs for asthma management and Jayaram et al for exacerbation rate for FN) and committee assumption. Unit costs taken from NHS reference costs, PSSRU unit costs, manufacturers, Healthcare Resource Group, previous HTA reports, BNF, and published studies (drug management costs from Main et al. and Shepherd et. al).

**Comments**

**Source of funding:** NIHR. **Limitations:** EQ-5D data was not identified via systematic review of literature and it is unclear if all are from UK representative population. Diagnostic accuracy of non-FeNO comparators were not identified through systematic review of the evidence. The study used to estimate sensitivity and specificity of FeNO + BDR (Cordeiro 2011) was excluded in the clinical review as it also used BDR as reference standard. Prevalence of asthma taken from the studies that informed diagnostic accuracy, which may not reflect UK specific asthma prevalence rates. Due to the limited evidence base the model necessarily makes a number of unadjusted (naive) indirect comparisons between the included studies. The model structure doesn't reflect a sequential testing pathway however author states due to evidence limitations they were not able to undertake this. Uncertainty surrounding health losses associated with misdiagnosis: model elicited estimates of the duration required to resolve a FN/FP diagnosis and these estimates were very uncertain. There was also uncertainty surrounding the magnitude of the HRQoL loss as well as the duration over which this loss is incurred. Authors noted that it is possible that health losses associated with FP diagnoses in patients with more serious underlying pathology are underestimated, although they are not clear how this uncertainty could have been resolved empirically. **Other:** Improved diagnostic accuracy has no impact on mortality. All FeNO tests (NIOX MINO, NIOX VERO and NObreath) are assumed to have equivalent diagnostic accuracy. Diagnostic accuracy taken from paediatric and adult populations.

**Overall applicability:**[(c)] Directly applicable **Overall quality:**[(d)] Potentially serious limitations

*Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); FeNO= fractional exhaled nitric oxide; FEV1= forced expiratory volume ; FN= false negative; FP= false positive; FVC=forced vital capacity; HRQoL= health related quality of life; ICER= incremental cost-effectiveness ratio; MCT= metacholine challenge test; NR= not reported; pa= probabilistic analysis; PSSRU= Personal and Social Services Research Unit; QALYs= quality-adjusted life years; TN= true negative; TP=true positive*

*(a) Intervention number in order of least to most effective (in terms of QALYs)*

*(b) Full incremental analysis of available strategies: first strategies are ruled out that are dominated (another strategy is more effective and has lower costs) or subject to extended dominance (the strategy is more effective and more costly but the incremental cost effectiveness ratio is higher than the next most effective option and so it would never be the most cost effective option); incremental costs, incremental effects and incremental cost effectiveness ratios are calculated for the remaining strategies by comparing each to the next most effective option*

*(c) Directly applicable / Partially applicable / Not applicable*

*(d) Minor limitations / Potentially serious limitations / Very serious limitations Intervention number in order of least to most effective (in terms of QALYs)*

# Appendix H – Excluded studies

## Clinical studies

**Table 11: Studies excluded from the clinical review**

| Study | Code [Reason] |
|---|---|
| Anderson, Sandra D, Charlton, Brett, Weiler, John M et al. (2009) Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. Respiratory research 10: 4 | - Index test not relevant to this review protocol<br>*No relevant combination of tests included, only methacholine and mannitol separately* |
| Arianto, L., Hallas, H., Stokholm, J. et al. (2019) Multiple Breath Washout for Diagnosing Asthma and Persistent Wheeze in Young Children. Annals of the American Thoracic Society 16(5): 599-605 | - Population not relevant to this review protocol<br>*Participants not presenting with respiratory symptoms* |
| Backer, V., Sverrild, A., Ulrik, C. S. et al. (2015) Diagnostic work-up in patients with possible asthma referred to a university hospital. European Clinical Respiratory Journal 2 | - ICS washout period not appropriate<br>*1-day washout* |
| Bao, Wuping, Zhang, Xue, Yin, Junfeng et al. (2021) Small-Airway Function Variables in Spirometry, Fractional Exhaled Nitric Oxide, and Circulating Eosinophils Predicted Airway Hyperresponsiveness in Patients with Mild Asthma. Journal of asthma and allergy 14: 415-426 | - Reference standard not relevant to this review protocol<br>*Methacholine challenge test without clinician decision used as reference standard* |
| Beretta, C., Rifflart, C., Evrard, G. et al. (2018) Assessment of eosinophilic airway inflammation as a contribution to the diagnosis of occupational asthma. Allergy 73(1): 206-213 | - Study aiming to diagnose a condition other than asthma<br>*Occupational asthma* |
| Breuer, O., Gangwar, R. S., Seaf, M. et al. (2018) Evaluation of Soluble CD48 Levels in Patients with Allergic and Nonallergic Asthma in Relation to Markers of Type 2 and Non-Type 2 Immunity: An Observational Study. Journal of Immunological Research 2018: 4236263 | - Population not relevant to this review protocol<br>*Participants diagnosed with asthma prior to study entry* |
| Brigham, E. P. and West, N. E. (2015) Diagnosis of asthma: diagnostic testing. International Forum of Allergy & Rhinology 5suppl1: 27-30 | - Review article but not a systematic review |
| Chen, D., Zhang, Y., Yao, C. et al. (2021) Increased levels of serum IL-17 and induced | - Population not relevant to this review protocol |

| Study | Code [Reason] |
| --- | --- |
| sputum neutrophil percentage are associated with severe early-onset asthma in adults. Allergy, Asthma, & Clinical Immunology : Official Journal of the Canadian Society of Allergy & Clinical Immunology 17(1): 64 | *Participants diagnosed with asthma prior to study entry* |
| Chen, L. C., Tseng, H. M., Kuo, M. L. et al. (2018) A composite of exhaled LTB4 , LXA4 , FeNO, and FEV1 as an "asthma classification ratio" characterizes childhood asthma. Allergy 73(3): 627-634 | - ICS washout period not appropriate<br>*2-day washout* |
| Chen, L. C., Tseng, H. M., Kuo, M. L. et al. (2018) A composite of exhaled LTB4 , LXA4 , FeNO, and FEV1 as an "asthma classification ratio" characterizes childhood asthma. Allergy 73(3): 627-634 | - Duplicate reference |
| Chen, L., Wu, L., Lu, D. et al. (2021) The value of fractional exhaled nitric oxide and impulse oscillometric and spirometric parameters for predicting bronchial hyperresponsiveness in adults with chronic cough. Journal of Asthma and Allergy 14: 1065-1073 | - Index test not relevant to this review protocol<br>*No relevant combination of tests included* |
| Ciolkowski, J., Emeryk, A., Hydzik, P. et al. (2019) Eosinophilic airway inflammation is a main feature of unstable asthma in adolescents. Respiratory Medicine 147: 7-12 | - Population not relevant to this review protocol<br>*Participants diagnosed with asthma prior to study entry* |
| Cordeiro, Danielle, Rudolphus, Arjan, Snoey, Erik et al. (2011) Utility of nitric oxide for the diagnosis of asthma in an allergy clinic population. Allergy and Asthma Proceedings 32(2): 119-126 | - Reference standard not relevant to this review protocol<br>*Reference standard includes bronchodilator reversibility as objective test - cannot assess diagnostic accuracy of FeNO+BDR against this* |
| Danvers, L.; Lo, D. K. H.; Gaillard, E. A. (2020) The role of objective tests to support a diagnosis of asthma in children. Paediatric Respiratory Reviews 33: 52-57 | - Review article but not a systematic review |
| Das, D. K.; Chakraborty, C.; Bhattacharya, P. S. (2016) Automated Screening Methodology for Asthma Diagnosis that Ensembles Clinical and Spirometric Information. Journal of Medical and Biological Engineering 36(3): 420-429 | - Population not relevant to this review protocol<br>*Participants diagnosed with asthma prior to study entry* |
| de Jong, C. C. M., Pedersen, E. S. L., Mozun, R. et al. (2020) Diagnosis of asthma in children: findings from the Swiss Paediatric Airway Cohort. European Respiratory Journal 56(5): 11 | - ICS washout period not appropriate<br>*1-day washout* |

| Study | Code [Reason] |
| --- | --- |
| de Jong, C.C.M., Pedersen, E.S.L., Mozun, R. et al. (2020) Diagnosis of asthma in children: Findings from the Swiss paediatric airway cohort. European Respiratory Journal 56(5): 2000132 | - Duplicate reference |
| de Meer, G, Postma, D S, Janssen, N A H et al. (2004) Bronchial hyper-responsiveness to hypertonic saline and blood eosinophilic markers in 8-13-year-old schoolchildren. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 34(8): 1226-31 | - Population not relevant to this review protocol<br>*Participants not presenting with respiratory symptoms* |
| del Giudice, Michele Miraglia, Brunese, F P, Piacentini, G L et al. (2004) Fractional exhaled nitric oxide (FENO), lung function and airway hyperresponsiveness in naive atopic asthmatic children. The Journal of asthma : official journal of the Association for the Care of Asthma 41(7): 759-65 | - Population not relevant to this review protocol<br>*Participants diagnosed with asthma prior to study entry* |
| Drake, S., Wang, R., Healy, L. et al. (2021) Diagnosing Asthma with and without Aerosol-Generating Procedures. The Journal of Allergy & Clinical Immunology in Practice 9(12): 4243-4251e7 | - ICS washout period not appropriate<br>*2-week washout* |
| Drake, Sarah, Wang, Ran, Healy, Laura et al. (2021) Diagnosing Asthma with and without Aerosol-Generating Procedures. The journal of allergy and clinical immunology. In practice 9(12): 4243-4251e7 | - Duplicate reference |
| Feng, Y., Zhang, S., Shang, Y. et al. (2022) The Use of Exercise Challenge Testing and Fractional Exhaled Nitric Oxide in Diagnosis of Chest Tightness Variant Asthma in Children. International Archives of Allergy & Immunology: 1-8 | - Reference standard not relevant to this review protocol<br>*Response to treatment used as reference standard* |
| Feng, Y., Zhang, S., Shang, Y. et al. (2022) The Use of Exercise Challenge Testing and Fractional Exhaled Nitric Oxide in Diagnosis of Chest Tightness Variant Asthma in Children. International Archives of Allergy and Immunology 183(7): 762-769 | - Duplicate reference |
| Gao, Q., Wu, Q., Li, F. et al. (2021) Fractional exhaled nitric oxide could identify early spirometry change in clinically suspected asthma patients without airway obstruction. | - Study design not relevant to this review protocol |

| Study | Code [Reason] |
|---|---|
| European Journal of Inflammation 19(nopagination) | *Not a diagnostic accuracy study - no reference standard* |
| Godinho Netto, A. C., Dos Reis, T. G., Matheus, C. F. et al. (2016) Fraction of exhaled nitric oxide measurements in the diagnoses of asthma in elderly patients. Clinical Interventions In Aging 11: 623-9 | - Data not reported in an extractable format or a format that can be analysed<br>*Sensitivity, specificity and 2x2 data not reported* |
| Grzelewski, T., Stelmach, W., Stelmach, R. et al. (2016) Spirometry-Adjusted Fraction of Exhaled Nitric Oxide Allows Asthma Diagnosis in Children, Adolescents, and Young Adults. Respiratory Care 61(2): 162-72 | - Inappropriate interval between index test and reference standard<br>*4 years between tests and diagnosis* |
| Hansen, T. E.; Evjenth, B.; Holt, J. (2015) Validation of a questionnaire against clinical assessment in the diagnosis of asthma in school children. Journal of Asthma 52(3): 262-7 | - Population not relevant to this review protocol<br>*Participants diagnosed with asthma prior to study entry* |
| Hao, H., Bao, W., Xue, Y. et al. (2021) Spirometric Changes in Bronchodilation Tests as Predictors of Asthma Diagnosis and Treatment Response in Patients with FEV1 >= 80% Predicted. The Journal of Allergy & Clinical Immunology in Practice 9(8): 3098-3108e4 | - Reference standard not relevant to this review protocol<br>*Change in FEV1 and ACT score after treatment used as reference standard* |
| Hou, L., Hao, H., Huang, G. et al. (2021) The value of small airway function parameters and fractional exhaled nitric oxide for predicting positive methacholine challenge test in asthmatics of different ages with FEV1 >= 80% predicted. Clinical and Translational Allergy 11(1): e12007 | - Duplicate reference |
| Jara-Gutierrez, P., Aguado, E., Del Potro, M. G. et al. (2019) Comparison of impulse oscillometry and spirometry for detection of airway hyperresponsiveness to methacholine, mannitol, and eucapnic voluntary hyperventilation in children. Pediatric Pulmonology 54(8): 1162-1172 | - Index test not relevant to this review protocol<br>*Spirometry and IOS used as index test* |
| Jara-Gutierrez, Pamela, Aguado, Erika, Del Potro, Manuela Garcia et al. (2019) Comparison of impulse oscillometry and spirometry for detection of airway hyperresponsiveness to methacholine, mannitol, and eucapnic voluntary hyperventilation in children. Pediatric pulmonology 54(8): 1162-1172 | - Duplicate reference |

| Study | Code [Reason] |
|---|---|
| Jenkins, M A, Clarke, J R, Carlin, J B et al. (1996) Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. International journal of epidemiology 25(3): 609-16 | - Population not relevant to this review protocol<br><br>*Participants not presenting with respiratory symptoms* |
| Jerzynska, J., Janas, A., Galica, K. et al. (2015) Total specific airway resistance vs spirometry in asthma evaluation in children in a large real-life population. Annals of Allergy, Asthma, & Immunology 115(4): 272-6 | - Index test not relevant to this review protocol<br><br>*IOS used as index test* |
| Jerzynska, J., Majak, P., Janas, A. et al. (2014) Predictive value of fractional nitric oxide in asthma diagnosis-subgroup analyses. Nitric Oxide 40: 87-91 | - Inappropriate interval between index test and reference standard<br><br>*3 years between tests and diagnosis* |
| Kaplan, A., Cao, H., FitzGerald, J. M. et al. (2021) Artificial Intelligence/Machine Learning in Respiratory Medicine and Potential Role in Asthma and COPD Diagnosis. Journal of Allergy and Clinical Immunology: In Practice 9(6): 2255-2261 | - Review article but not a systematic review |
| Katsoulis, K, Ganavias, L, Michailopoulos, P et al. (2013) Exhaled nitric oxide as screening tool in subjects with suspected asthma without reversibility. International archives of allergy and immunology 162(1): 58-64 | - Reference standard not relevant to this review protocol<br><br>*Methacholine challenge test without clinician diagnosis used as reference standard* |
| Kellerer, C., Wagenpfeil, S., Daines, L. et al. (2021) Diagnostic accuracy of FeNO [fractional exhaled nitric oxide] and asthma symptoms increased when evaluated with a superior reference standard. Journal of Clinical Epidemiology 129: 86-96 | - ICS washout period not appropriate<br><br>*12-hour washout* |
| Kim, K., Cho, H. J., Yoon, J. W. et al. (2018) Exhaled nitric oxide and mannitol test to predict exercise-induced bronchoconstriction. Pediatrics International 60(8): 691-696 | - Population not relevant to this review protocol<br><br>*Participants diagnosed with asthma prior to study entry* |
| Koca Kalkan, I., Koycu Buhari, G., Ates, H. et al. (2021) Can fractional exhaled Nitric Oxide with blood eosinophil count have a place in the diagnostic algorithm for Asthma?. Asthma Allergy Immunology 19(2): 100-109 | - Reference standard not relevant to this review protocol<br><br>*Methacholine challenge test determined asthma diagnosis without clinician decision* |
| Koca Kalkan, I., Koycu Buhari, G., Ates, H. et al. (2021) Can fractional exhaled Nitric Oxide with | - Duplicate reference |

| Study | Code [Reason] |
| --- | --- |
| blood eosinophil count have a place in the diagnostic algorithm for Asthma?. Asthma Allergy Immunology 19(2): 100-109 | |
| Lee, D. H., Kwon, J. W., Kim, H. Y. et al. (2020) Asthma predictive index as a useful diagnostic tool in preschool children: a cross-sectional study in Korea. Clinical and Experimental Pediatrics 63(3): 104-109 | - Population not relevant to this review protocol<br>*Participants age <5 years* |
| Lee, J. W., Shim, J. Y., Kwon, J. W. et al. (2015) Exhaled nitric oxide as a better diagnostic indicator for evaluating wheeze and airway hyperresponsiveness in preschool children. Journal of Asthma 52(10): 1054-9 | - Data not reported in an extractable format or a format that can be analysed<br>*Sensitivity, specificity and 2x2 data not reported* |
| Li, J. H., Han, R., Wang, Y. B. 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 | - ICS washout period not appropriate<br>*72-hour washout* |
| 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 | - Duplicate reference |
| 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 | - Duplicate reference |
| Li, X., Lu, Y., Yu, Q. et al. (2019) Analysis of the diagnostic value of fractional exhaled nitric oxide and IgE in children with asthma. International Journal of Clinical and Experimental Medicine 12(9): 11555-11562 | - Population not relevant to this review protocol<br>*Participants diagnosed with asthma prior to study entry* |
| Li, Y.; Chen, Y.; Wang, P. (2015) Application of impulse oscillometry and bronchial dilation test for analysis in patients with asthma and chronic obstructive pulmonary disease. International journal of clinical and experimental medicine 8(1): 1271-5 | - Population not relevant to this review protocol<br>*Participants diagnosed with asthma prior to study entry* |
| Liu, J., Xu, R., Zhan, C. 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 | - ICS washout period not appropriate<br>*7-day washout* |

| Study | Code [Reason] |
| --- | --- |
| Liu, L., Liu, W., Liu, C. et al. (2018) Study on small airway function in asthmatics with fractional exhaled nitric oxide and impulse oscillometry. The clinical respiratory journal 12(2): 483-490 | - Population not relevant to this review protocol<br>*Participants diagnosed with asthma prior to study entry* |
| Mallol, J., Riquelme, C., Aguirre, V. et al. (2020) Value of bronchial reversibility to salbutamol, exhaled nitric oxide and responsiveness to methacholine to corroborate the diagnosis of asthma in children. Allergologia et Immunopathologia 48(3): 214-222 | - Population not relevant to this review protocol<br>*Participants diagnosed with asthma prior to study entry* |
| Maloca Vuljanko, I., Turkalj, M., Nogalo, B. et al. (2017) Diagnostic value of a pattern of exhaled breath condensate biomarkers in asthmatic children. Allergologia et Immunopathologia 45(1): 2-10 | - Index test not relevant to this review protocol<br>*Exhaled breath condensate used as index test* |
| Murray, C., Foden, P., Lowe, L. et al. (2017) Diagnosis of asthma in symptomatic children based on measures of lung function: an analysis of data from a population-based birth cohort study. The Lancet Child & Adolescent Health 1(2): 114-123 | - Reference standard in study does not match that specified in protocol |
| Onell, A., Whiteman, A., Nordlund, B. et al. (2017) Allergy testing in children with persistent asthma: comparison of four diagnostic methods. Allergy 72(4): 590-597 | - Population not relevant to this review protocol<br>*Participants diagnosed with asthma prior to study entry* |
| Park, Sang Hoo, Im, Min Ji, Eom, Sang-Yong et al. (2017) Accuracy of maximal expiratory flow-volume curve curvilinearity and fractional exhaled nitric oxide for detection of children with atopic asthma. Korean journal of pediatrics 60(9): 290-295 | - Population not relevant to this review protocol<br>*Participants diagnosed with asthma prior to study entry* |
| Pino, J M, Garcia-Rio, F, Prados, C et al. (1996) Value of the peak expiratory flow in bronchodynamic tests. Allergologia et immunopathologia 24(2): 54-7 | - Index test not relevant to this review protocol<br>*No relevant combination of tests, PEF used as index test* |
| Racine, G., Castano, R., Cartier, A. et al. (2017) Diagnostic Accuracy of Inflammatory Markers for Diagnosing Occupational Asthma. The Journal of Allergy & Clinical Immunology in Practice 5(5): 1371-1377e1 | - Study aiming to diagnose a condition other than asthma<br>*Occupational asthma* |
| Sanchez-Garcia, S., Rodriguez del Rio, P., Escudero, C. et al. (2015) Exercise-induced | - Population not relevant to this review protocol |

| Study | Code [Reason] |
| --- | --- |
| bronchospasm diagnosis in children. Utility of combined lung function tests. Pediatric Allergy & Immunology 26(1): 73-9 | *Participants diagnosed with asthma prior to study entry* |
| Schleich, Florence N., Zanella, Delphine, Stefanuto, Pierre-Hugues et al. (2019) Exhaled Volatile Organic Compounds Are Able to Discriminate between Neutrophilic and Eosinophilic Asthma. American journal of respiratory and critical care medicine 200(4): 444-453 | - Population not relevant to this review protocol<br>*Participants diagnosed with asthma prior to study entry* |
| Selvanathan, J., Aaron, S. D., Sykes, J. R. et al. (2020) Performance Characteristics of Spirometry With Negative Bronchodilator Response and Methacholine Challenge Testing and Implications for Asthma Diagnosis. Chest 158(2): 479-490 | - Population not relevant to this review protocol<br>*Participants diagnosed with asthma prior to study entry* |
| Siersted, H C, Hansen, H S, Hansen, N C et al. (1994) Evaluation of peak expiratory flow variability in an adolescent population sample. The Odense Schoolchild Study. American journal of respiratory and critical care medicine 149(3pt1): 598-603 | - Population not relevant to this review protocol<br>*Participants not presenting with respiratory symptoms* |
| Sposato, B., Scalese, M., Migliorini, M. G. et al. (2014) Small airway impairment and bronchial hyperresponsiveness in asthma onset. Allergy, asthma & immunology research 6(3): 242-51 | - ICS washout period not appropriate<br>*3-week washout* |
| Stanbrook, M B; Chapman, K R; Kesten, S (1995) Gas trapping as a predictor of positive methacholine challenge in patients with normal spirometry results. Chest 107(4): 992-5 | - Index test not relevant to this review protocol<br>*No relevant combination of tests included* |
| 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 | - Index test not relevant to this review protocol<br>*Symptom score algorithm used as index test* |
| Tuomisto, L. E., Ilmarinen, P., Lehtimaki, L. et al. (2021) Clinical value of bronchodilator response for diagnosing asthma in steroid-naive adults. Erj Open Research 7(4) | - Population not relevant to this review protocol<br>*Participants diagnosed with asthma prior to study entry* |
| Urbankowski, T. and Przybylowski, T. (2022) Blood eosinophils, FeNO and small airways dysfunction in predicting airway hyperresponsiveness in patients with asthma- | - Reference standard not relevant to this review protocol |

| Study | Code [Reason] |
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| like symptoms. Journal of Asthma 59(7): 1376-1386 | *Methacholine challenge test without clinician decision used as reference standard* |
| Usta Guc, B.; Asilsoy, S.; Durmaz, C. (2014) The assessment and management of chronic cough in children according to the British Thoracic Society guidelines: Descriptive, prospective, clinical trial. Clinical Respiratory Journal 8(3): 330-337 | - Index test not relevant to this review protocol<br>*Bronchial obstruction reversibility used as sole index test - no relevant combination included* |
| Vugt, Saskia van, Broekhuizen, Lidewij, Zuithoff, Nicolaas et al. (2012) Airway obstruction and bronchodilator responsiveness in adults with acute cough. Annals of family medicine 10(6): 523-9 | - Index test not relevant to this review protocol<br>*No relevant combination of tests included* |
| Wordemann, M., Polman, K., Diaz, R.J. et al. (2006) The challenge of diagnosing atopic diseases: Outcomes in Cuban children depend on definition and methodology. Allergy: European Journal of Allergy and Clinical Immunology 61(9): 1125-1131 | - Population not relevant to this review protocol<br>*Participants not presenting with respiratory symptoms* |
| Yang, Y., Lo, D. K., Beardsmore, C. et al. (2022) Implementing spirometry and fractional exhaled nitric oxide testing in childhood asthma management in UK primary care: an observational study to examine training and implementation cost and impact on patient's health use and outcome. Archives of Disease in Childhood 107(1): 21-25 | - Population not relevant to this review protocol<br>*Participants diagnosed with asthma prior to study entry* |
| Zeng, G., Hu, H., Zheng, P. et al. (2018) The practical benefit of Phadiatop test as the first-line in vitro allergen-specific immunoglobulin E (sIgE) screening of aeroallergens among Chinese asthmatics: A validation study. Annals of Translational Medicine 6(8): 151 | - Index test not relevant to this review protocol<br>*No relevant combination of tests included* |
| Zhang, Yanli, Shi, Hongke, Su, Aifang et al. (2022) Angle beta combined with FeNO and FEV1/FVC% for the detection of asthma in school-aged children. The Journal of asthma : official journal of the Association for the Care of Asthma 59(4): 746-754 | - Population not relevant to this review protocol<br>*Participants diagnosed with asthma prior to study entry* |
| Zhu, H., Zhang, R., Hao, C. et al. (2019) Fractional Exhaled Nitric Oxide (FeNO) Combined with Pulmonary Function Parameters Shows Increased Sensitivity and Specificity for the Diagnosis of Cough Variant Asthma in | - ICS washout period not appropriate<br>*3-day washout* |

| Study | Code [Reason] |
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| Children. Medical Science Monitor 25: 3832-3838 | |
| Zhu, Zheng, Xia, Shu, Chen, Xi et al. (2020) Factors associated with exhaled nitric oxide in children with asthma and allergic rhinitis. The clinical respiratory journal 14(1): 9-15 | - Population not relevant to this review protocol<br>*Participants diagnosed with asthma prior to study entry* |
| 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 and Clinical Immunology 16(4): 239-246 | - Population not relevant to this review protocol<br>*Participants diagnosed with asthma prior to study entry* |

## 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.