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NICE National Institute for Health and Care Excellence

Healthcare Improvement Scotland | SIGN

Final

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

[F] Evidence reviews for diagnostic accuracy of fractional exhaled nitric oxide (FeNO) measures

BTS/NICE/SIGN collaborative guideline NG245

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Final

Developed by BTS, NICE and SIGN

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1. Accuracy and clinical and cost-effectiveness of FeNO in diagnosis of asthma

1.1. Review question

In people under investigation for asthma, what is the diagnostic test accuracy and clinical and cost-effectiveness of fractional exhaled nitric oxide (FeNO) measures?

1.1.1. Introduction

Asthma can be a difficult condition to diagnose, and it is not clear which tests are most useful in supporting a diagnosis. Nitric oxide is an endogenous signalling molecule with multiple roles and sources. In the airway it is generated in response to type 2 inflammation (the most common form of inflammation in asthma), largely under the influence of interleukin-13 (IL-13). It can be measured under controlled exhalation by commercially available instruments as fractional exhaled nitric oxide (FeNO). FeNO is therefore potentially useful in establishing a diagnosis of asthma and this evidence review was carried out to determine its clinical and cost-effectiveness as a diagnostic test.

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: Diagnostic Tests

Population	People with suspected asthma (presenting with respiratory symptoms). Ages stratified into the following 2 groups: • Children and young people (5-16 years old) • Adults (≥17 years) Stratified by smoking status: • Smokers • Non-smokers • Mixed populations Exclusion: • Children under 5 years old • People on steroid inhalers (washout period minimum of 4 weeks for inclusion)
Target condition	Asthma
Index test	Fractional exhaled nitric oxide (FeNO) with a cut-off threshold between 20-50ppb and a flow rate of 50ml/s or equivalent.
Reference standards	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test);

	• bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test)
Statistical measures	• Sensitivity (thresholds: upper 90%, lower 10%) • Specificity (thresholds: upper 80%, lower 50%) • Raw data to calculate 2x2 tables to calculate sensitivity and specificity • Negative predictive value (NPV), Positive predictive value (PPV)
Study design	• Cross sectional studies • Cohort studies will be included

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. WinBUGS was used for meta analyses where studies could be pooled.

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

1.1.4. Diagnostic evidence

1.1.4.1. Included studies

Twenty eight cross-sectional studies were included in the review; (Bai, et al., 2023, Bao, et al., 2021, Borhani Fard, et al., 2021, Chatkin, et al., 1999, Cordeiro, et al., 2011, Eom, et al., 2020, Fortuna, et al., 2007, Fukuhara, et al., 2011, He, et al., 2018, Heffler, et al., 2006, Jerzynska, et al., 2014, Katsoulis, et al., 2013, Kesler, et al., 2019, Kowal, et al., 2009, Livnat, et al., 2015, Louis, et al., 2023, Nekoee, et al., 2020, Porpodis, et al., 2017, Sato, et al., 2008, Schneider, et al., 2022, Schneider, et al., 2015, Simpson, 2024, Smith, et al., 2004, Tilemann, et al., 2011, Wang, et al., 2015, Woo, et al., 2012, Yang, et al., 2018, Zhou, et al., 2018) these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below.

Twenty-one of these studies were in adults, and seven studies were in children and young people. Five of these studies were in a mixed population of adults and children and young people but were categorised into age strata determined by the average population age. In the adult populations, six studies only included non-smoking participants, whilst the other fifteen included mixed groups of smokers and non-smokers, with one study conducting a subgroup analysis on smokers. Pooling was possible in all strata for at least one threshold, except in smoking adults where only one study was identified. Where exactly two studies reported the same threshold, data was reported separately in the GRADE tables to maintain transparency of the data identified.

The assessment of the evidence quality was conducted with emphasis on test sensitivity 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 (for studies reporting 2x2 data) in Appendix E, and study evidence tables in Appendix D.

1.1.4.2. Excluded studies

See the excluded studies list in Appendix J.

1.1.5. Summary of studies included in the diagnostic evidence

Table 2: Summary of studies in children and young people included in the evidence review

Study	Population	Target condition	Index test	Reference standard	Comments
Eom 2020(Eom et al., 2020)	Children aged 8-16 years, presenting with respiratory symptoms for at least 1 month, referred for evaluation of possible asthma. N=275; mean age (range): 11.5 (10.7-12.3) years. N=191 (69.5%) were diagnosed with Asthma South Korea	Asthma	FeNO Cut-off: >19.6 ppb	Clinical examination by paediatric pulmonologist; diagnosis determined according to the Global Initiative for Asthma guidelines, including bronchodilator reversibility (FEV of 12%)	Prospective study Strata: Age: Children/young people Exposure to cigarette smoking: Mixed ICS use: None within a month Indirectness: Downgraded by one increment due to index test (cut-off <20 ppb used) indirectness
Kesler 2019(Kesler et al., 2019)	Steroid naïve children aged 5-17 years with suspicious asthma. N=222 N=134 of which had atopy, n=88 non-atopy; N=114 had asthma (77/37 atopy/non-atopy); N=57 were atopic non-asthmatics. Germany	Atopic asthma and non-atopic asthma	FeNO Cut-offs: >24 and 34 ppb	Skin prick test (SPT), spirometry, MCT: Patients were categorized according to the results of the SPT as atopic or non-atopic and within these subgroups the findings of the MCT allowed discrimination of asthmatic and non-	Prospective study Strata: Age: Children/young people Passive smoking: 126 (56.8%) ICS use: Treatment naïve Indirectness: Downgraded by one increment due to reference standard (unclear if

Study	Population	Target condition	Index test	Reference standard	Comments
				asthmatic children.	clinician decision was involved in diagnosis) indirectness
Jerzynska 2014(Jerzynska et al., 2014)	Children aged 6-18 years with symptoms of allergic diseases such as Asthma and/or allergic rhinitis. N=1765; mean age (SD): 11.2 (6.3) Asthma confirmed in n=1054 (59.6%) Poland	Asthma	FeNO Cut-off: >23 ppb	Diagnosis of asthma was established by symptoms of asthma, the findings on physical examination of the respiratory system, and improvement in the pre-bronchodilator FEV1 >12% after administration of salbutamol	Retrospective cross-sectional study Strata: Age: Children/young people Smoking status: Not reported ICS use: Treatment naïve Indirectness: Downgraded by two increments due to population (mixed children and adolescents/young people and smoking status not reported) and reference standard (diagnosis confirmed 3 years after index test) indirectness
Livnat 2015 (Livnat et al., 2015)	Children aged 6-18 years referred for MCT at the pulmonary outpatient clinic of a tertiary university-affiliated medical centre. N=131 (n=63 positive MCT; n=68 negative MCT) Mean age (SD): 12.66 (3.77) Israel	Bronchial hyperresponsiveness	FeNO Cut-off: >23 ppb	Methacholine Challenge Test (threshold for positivity: <8mg/ml)	Prospective study Strata: Age: Children/young people Exposure to passive smoking: 28.2% ICS use: None within a month Downgraded by one increment due to reference standard (unclear if

Study	Population	Target condition	Index test	Reference standard	Comments
					clinician decision was involved in diagnosis) indirectness
Woo 2012(Woo et al., 2012)	Children 8-16 years presenting with non-specific respiratory symptoms (e.g. cough, wheezing, shortness of breath) N= 245; mean age (SD): atopic asthma: 11.7 (2.4) years; atopic non-asthma: 12.6 (2.6) years; non-atopic asthma: 11.6 (2.7) years; non-atopic non-asthma 11.4 (2.0) years South Korea	Asthma vs. non-asthma Asthma and non-asthma groups also sub-divided by atopic vs. nonatopic	FeNO Cut-off: >20, 21, 22, 23, 24, 25, 30, 35, 40, 45, and 50 ppb	History plus reversible airflow obstruction (≥12% improvement in FEV1 with inhaled β-agonist) and/or airway hyperresponsiveness (methacholine PC20 ≤8mg/mL)	Prospective study Strata: Age: Children/young people Smoking status: Not reported ICS use: None within 3 months of study
Zhou 2018(Zhou et al., 2018)	Children aged 6-14 years with cough of duration >4 weeks N=115 patients and N=25 healthy controls China	Cough-variant asthma	FeNO Cut-off: >25 ppb	American College of Chest Physicians guidelines; bronchodilator reversibility	Prospective cohort study Strata: Age: Children/young people Smoking status: Not reported ICS use: Unclear, drugs that could affect FeNO had been stopped for >2 weeks Indirectness: Downgraded by one increment due to population (unclear ICS use) indirectness

Table 3: Summary of studies in adults included in the evidence review

Study	Population	Target condition	Index test	Reference standard	Comments
Bai 2023 (Bai et al., 2023)	Adults with chronic cough (>8 weeks) attending a Pulmonary and Critical Care Department with an FEV1 >80% of predicted N=283 Mean age (SD): CVA; 47.8 (15.9), nCVA; 44.6 (15.2) years China	Cough variant asthma vs non-asthma chronic cough	FeNO Cut-off: >27 ppb	Asthma as per Chinese diagnosis guidelines: chronic cough, often with significant night cough, positive bronchial provocation test and positive response to anti-asthma treatment	Cross-sectional observational study Strata: Age: Adults Smoking status: Non-smokers ICS use: None within a month
Bao 2021 (Bao et al., 2021)	Adults with an FEV1 >80%, normal CT scan results and recurrent variable symptoms of dyspnoea, cough, wheeze or chest tightness for >8 weeks referred to a pulmonary outpatient clinic N= 692 Mean age (SD): positive MCT; 43.90 (12.56), negative MCT: 43.80 (14.90) China	Airway hyperresponsiveness to methacholine	FeNO Cut-off: >41 ppb	Airway hyperresponsiveness was diagnosed using methacholine challenge testing	Retrospective cross-sectional study Strata: Age: Adults Smoking status: Non-smokers ICS use: None within a month Indirectness: Downgraded by two increments due to index test (no information on FeNO standards or flow rate) and reference standard (unclear if clinician decision was involved in diagnosis)
Borhani Fard 2021(Borhani Fard et al., 2021)	People ≥18 years with at least one of the following respiratory signs: cough, shortness of breath, and chest tightness.	Asthma	FeNO Cut-off: >20.5, 29, 36, 37.5, 39.5, 40.5, 42.5 and 48.5 ppb	A standard questionnaire, spirometry with bronchodilator administration, or methacholine challenge test	Cross-sectional study Strata: Age: Adults Smoking status: Non-smokers

Study	Population	Target condition	Index test	Reference standard	Comments
	N=87; mean age (SD)= 34.5 (5.7) years. N=49 had a positive bronchodilator test and asthma was confirmed in n=21 with MCT. Iran				ICS use: Treatment naïve
Chatkin 1999 (Chatkin et al., 1999)	Adults with chronic cough (>3 weeks) of unknown cause referred for diagnosis (n=38); healthy controls (n=23) Mean age (SD): asthma: 41 (12) years; chronic cough non-asthma: 47 (15) years; healthy controls: 38 (8) years Canada	Asthma diagnosis vs. chronic cough non-asthma FeNO levels asthma vs. chronic cough non-asthma or vs. healthy controls	FeNO Cut-off: >30 ppb	Positive to methacholine challenge (PC20 ≤8mg/mL) Tests done within 24 hours	Cross-sectional observational study Strata: Age: Adults Smoking status: Non-smokers ICS use: None within 6 weeks Indirectness: Downgraded by one increment due to index test (flow rate of 45 mL/s used, not 50 as specified in the review protocol)
Cordeiro 2011(Cordeiro et al., 2011)	New referrals to outpatient allergy clinic. N = 114; Median age (range): Asthma: 39 (range 7-83) years; non-asthma: 38 (7-87) years. The Netherlands	Asthma	FeNO Cut-off: >27 ppb	History of typical respiratory symptoms and FEV1 improvement >12% and >200mL with 400µg salbutamol or PC20 histamine ≤8mg/mL	Cross-sectional observational study Strata: Age: Mixed ages Smoking status: Not reported ICS use: None within 6 weeks Indirectness: Downgraded by two increments due to population (mixed children and adolescents/young people and smoking status not reported) indirectness

Study	Population	Target condition	Index test	Reference standard	Comments
Fortuna 2007 (Fortuna et al., 2007)	Adults referred to hospital-based respiratory medicine outpatient clinic for diagnosis with a clinical history suggestive of asthma (dry cough, wheezing, and shortness of breath) N=50; mean age (range): 37.56 (18-68) years Spain	Asthma	FeNO Cut-off: >19 ppb	Clinical history suggestive of asthma and a positive methacholine challenge test (cut-off: PD20 ≤16 mg/mL	Prospective cross-sectional study Strata: Age: Adults Smoking status: Mixed (19% current smokers) ICS use: 4-week washout Indirectness: Downgraded by two increments due to population (mixed smoking status) and index test (cut-off <20 ppb, protocol specified 20-50)
Fukuhara 2011(Fukuhara et al., 2011)	People with at least 1 subjective symptom: recurrent cough, wheezing or dyspnoea (including chest tightness) N = 61; Mean age (range): 55.6 (48.5-66.2) years. Japan	Asthma	FeNO Cut-off: >39 ppb	At least 2 of the following: induced sputum eosinophilia, airway hyperresponsiveness, reversible airway obstruction.	Cross-sectional study Strata: Age: Adults Smoking status: Mixed ICS use: Current users excluded Indirectness: Downgraded by one increment due to population (mixed smoking status)
He 2018(He et al., 2018)	Adults with suspected Asthma N=400; mean age (SD): 44.06 (11.86) years. N=265 (66.3%) were identified to have Asthma China	Asthma	FeNO Cut-off: >23.5 ppb	Bronchial provocation test (BPT) and bronchial reversibility test (BDT) plus a history of recurrent wheeze, shortness of breath, chest tightness, and cough ≥3 months	Prospective study Strata: Age: Adults Smoking status: Not reported ICS use: Not reported Indirectness: Downgraded by two increments due to

Study	Population	Target condition	Index test	Reference standard	Comments
					population (ICS use and smoking status not reported)
Heffler 2006(Heffler et al., 2006)	Patients referred to allergy department for diagnostic evaluation of persistent rhinitis and asthma-like lower airways symptoms (cough, dyspnoea, chest tightness and wheezing) during the last 2 months N = 48 symptomatic + N = 30 healthy controls; Mean age (range): Asthma: 42.33 (17-69) years; non-asthma: 38.73 (11-75) years Italy	Asthma	FeNO Cut-off: >20, 25, 30, 34, 36, 40, 45 and 50 ppb	Typical symptoms and significant response to bronchodilator (≥12% improvement in FEV1 with salbutamol) or airway hyperresponsiveness to methacholine (PD20 FEV1 ≤800µg)	Prospective study Strata: Age: Adults Smoking status: Non-smokers ICS use: users excluded Indirectness: Downgraded by one increment due to population (mixed children and adolescents/young people) indirectness
Katsoulis 2013 (Katsoulis et al., 2013)	Adults admitted to the outpatient clinics of an army hospital who gave at least one answer for respiratory symptoms on a screening form. N= 112 (37 smokers) Greece	Bronchial hyperresponsiveness	FeNO Cut-off: >20, 25 and 30 ppb	Methacholine bronchial challenge test (PD20 <800 µg)	Prospective cross-sectional study Strata: Age: Adults Smoking status: Mixed, data reported for whole population and separately for smokers ICS use: Treatment naïve Indirectness: Downgraded by two increments due to population (mixed smoking status (full population only))

Study	Population	Target condition	Index test	Reference standard	Comments
					and reference standard (no clinician decision in diagnosis)
Kowal 2009(Kowal et al., 2009)	Young adult patients with chronic cough (at least 8 weeks); N = 540 symptomatic + N = 100 healthy controls. Mean age (range): symptomatic: 26.5 (18-45) years; healthy controls: 24 (18-39) years. Poland	Asthma (vs. Rhinitis/sinusitis or gastroesophageal reflux)	FeNO Cut-off: >20, 30, 40 and 50 ppb	Significant diurnal changes in PEF or significant improvement of FEV1 with 200µg salbutamol over next 6 months	Prospective study Strata: Age: Adults Smoking status: Non-smokers ICS use: Non-users or at least 4- week washout Indirectness: Downgraded by one increment due to reference standard (unclear clinician decision in diagnosis)
Louis 2023 (Louis et al., 2023)	Adults seeking medical attention at an asthma clinic, in whom asthma was suspected N= 303; mean age; 51 (16) years Belgium	Asthma	FeNO Cut-off: >25 and >33 ppb	Asthma was diagnosed as per GINA guidelines, combining symptoms with bronchodilator reversibility and/or methacholine bronchial challenge tests	Prospective cross-sectional study Strata: Age: Adults Smoking status: Mixed ICS use: Treatment naïve Indirectness: Downgraded by one increment due to population (mixed smoking status) indirectness
Nekoee 2020 (Nekoee et al., 2020)	Database record of patients who had been referred to an asthma clinic with respiratory symptoms suggestive of asthma by two respiratory physicians N= 702; mean age: 51 years	Asthma	FeNO Cut-off: >36 ppb	Asthma was diagnosed by a positive result with a bronchodilator test (≥12% and 200 mL) or methacholine challenge test (≥20% fall in FEV1 with ⩽8 mg·mL−1)	Retrospective cross-sectional study Strata: Age: Adults Smoking status: Mixed (57% never, 24% ex, 19% current ICS use: Treatment naïve

Study	Population	Target condition	Index test	Reference standard	Comments
	Location not reported				Indirectness: Downgraded by two increments due to population (mixed smoking status), index test (standard FeNO was performed to not reported) and reference standard (unclear clinician decision in diagnosis)
Porpodis 2017 (Porpodis et al., 2017)	N=88 people with asthma related symptoms in the past month visiting an asthma clinic for asthma diagnosis Age, mean (SD): 38.56 (16.73) years Greece	Asthma	FeNO Cut-off: >20 ppb	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 Strata: Age: Adults Smoking status: 15% current smokers ICS use: Treatment naïve Indirectness: Downgraded by one increment due to population (mixed smoking status)
Sato 2008(Sato et al., 2008)	Adults with prolonged cough or wheezing (>3 weeks) aged 20-78 years N = 71; mean age (95%CI): Bronchial asthma: 55.5 (48.9 to 62.5); Cough variant asthma: 48.2 (39.4 to 57.0); Eosinophilic bronchitis without asthma: 45.3 (33.3 to 57.2); Others: 55.5 (47.5 to 63.5)	Asthma	FeNO Cut-off: >38.8 ppb	Cough and wheezing for 3 weeks or longer, sputum eosinophilia and positive airway hyperresponsiveness or reversible airflow limitation	Prospective study Strata: Age: Adults Smoking status: Not reported ICS use: Treatment naïve Indirectness: Downgraded by one increment due to population (mixed smoking status)

Study	Population	Target condition	Index test	Reference standard	Comments
	Japan				
Schneider 2015(Schneider et al., 2015)	Adults with symptoms of obstructive airway disease (OAD) or the respective differential diagnoses (such as restrictive airway disease) N=553; n=393 identified via pneumologists practice, n=160 identified via a general practice. Mean age (SD): 43.41 (16.36) Germany	Asthma	FeNO Cut-offs: >20, 25, 30, 35, 40 and 47 ppb	Tiffeneau ratio (forced expiratory volume in 1 s/vital capacity) or airway resistance as assessed by whole body plethysmography, with additional bronchoprovocation or bronchodilator testing.	Prospective study Strata: Age: Adults Smoking status: Mixed ICS use: Unclear (some already taking medication for asthma; unclear if that included corticosteroids) Indirectness: Downgraded by two increments due to population (ICS use not reported and mixed smoking status)
Schneider 2022 (Schneider et al., 2022)	People presenting to pulmonology practices with complaints suggestive of asthma N=308 Mean age (SD): 44.7 (16.7) years Germany	Asthma	FeNO Cut-offs: >20, 21, 22, 25, 30, 31, 32, 33, 34, 35, 37, 40 and 50 ppb	Asthma diagnosis by a committee of experts who assessed each participant's medical history, clinical pattern and disease progression over 12 weeks in combination with whole body plethysmography and methacholine challenge tests	Prospective cross-sectional study Strata: Age: Adults Smoking status: Mixed (19 smokers and 119 ex-smokers) ICS use: 17% taking asthma medication (type not reported) Indirectness: Downgraded by two increments due to population (17% of participants were already taking medication against asthma, not specified what medication this included, and mixed smoking status)

Study	Population	Target condition	Index test	Reference standard	Comments
Simpson 2024 (Simpson, et al., 2024)	Patients referred by general practitioners with symptoms suggestive of asthma N=118; mean age (SD): 26 (12) years UK	Asthma	FeNO Cut-offs: >50 ppb and >39 ppb	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 Strata: Adults ICS use: 4-week washout Smoking status: Mixed (40 (35%) current or ex-smokers) Indirectness: Downgraded by one increment due to population (mixed smoking status of participants) indirectness
Smith 2004 (Smith et al., 2004)	Consecutive patients aged 8–75 years referred by their family practitioner for asthma diagnosis. Inclusion criteria: people having respiratory symptoms in the preceding 4 weeks. Exclusion criteria: used oral or inhaled corticosteroid in the preceding 4 weeks or had a typical respiratory tract infection in the previous 6 weeks N= 47; mean age (range): 35.3 (9-72) years New Zealand	Asthma	FeNO Cut-off: >20 ppb	Relevant symptom history (present in all patients), using American Thoracic Society criteria, and a positive test for BHR and/or a positive response to hypertonic saline.	Prospective cross-sectional study Strata: Age: Adults Smoking status: Mixed ICS use: 4-week washout Indirectness: Downgraded by two increments due to population (mixed children and adolescents/young people and mixed smoking and non-smoking participants)
Tilemann 2011	Adults presenting to	Asthma	FeNO	Whole-body plethysmograp	Prospective cross-sectional study

Study	Population	Target condition	Index test	Reference standard	Comments
(Tileman n et al., 2011)	their GP for the first time with complaints suggestive of obstructive airways disease. Patients had dyspnoea, coughing and/or expectoration persisting for at least 2 months. Patients were referred to the lung function laboratory of a university hospital for further examination. N= 210 Mean age (SD): Asthma; 38.0 (14.6), COPD; 56.8 (11.7), Partial reversibility; 57.9 (11.2), No OAD: 42.3 (14.4) Germany		Cut-off: >46 ppb	hy (patients with FEV1 <80% predicted repeated the test after inhaling 400µg salbutamol). Asthma was diagnosed if reversibility was ≥12% and 200mL compared to baseline. If no obstruction in WBP, methacholine challenge using a cut-off of PC20 ≤16 mg/mL	Strata: Age: Adults Smoking status: Mixed, 63 (30%) current smokers, 36 (17%) past smokers, 111 (53%) never smokers ICS use: Mixed (5.2% using ICS, 12-hour washout) Indirectness: Downgraded by two increments due to population (5.2% receiving ICS, 12-hour washout), and reference standard (unclear clinician decision in diagnosis)
Wang 2015(Wang et al., 2015)	People suspected of asthma N=923; n=515 included in the present analysis N=185/515 were diagnosed with Asthma Mean age (range): 46.92 (15-89) years China	Asthma	FeNO Cut-off: >41 ppb	Bronchodilator reversibility	Prospective study Strata: Age: Adults Smoking status: Mixed (30.87%) had a history of smoking. ICS use: 4-week washout Indirectness: Downgraded by two increments due to population (mixed children and adolescents/young people and mixed

Study	Population	Target condition	Index test	Reference standard	Comments
					smoking and non-smoking participants)
Yang 2018(Yang et al., 2018)	Patients referred for measurement of FeNO for suspected asthma. N=132; mean age (SD): 42.8 (16) N=79 (59.8%) diagnosed with asthma South Korea	Asthma	FeNO Cut-off: >28 and 29 ppb	Diagnosis by clinicians based on symptoms, physical examination and bronchodilator test and methacholine test according to the Global Initiative for Asthma standard.	Retrospective study Strata: Age: Adults Smoking status: Unclear ICS use: Unclear Indirectness: Downgraded by two increments due to population (ICS use not reported and smoking status not reported)

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 4: Clinical evidence summary: diagnostic test accuracy for FeNO in children/young people

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
FeNO (cut-off: >19.6 ppb) vs clinician diagnosis with bronchodilator reversibility test							
1 cross-sectional study	274	Not serious	Not serious	Serious[1]	Not serious	Sensitivity= 0.64 (0.57-0.71)	MODERATE
		Not serious	Not serious	Serious[1]	Serious[2]	Specificity= 0.84 (0.74-0.91)	LOW
FeNO (cut-off >20 ppb) vs clinician diagnosis with methacholine bronchial challenge or bronchodilator reversibility tests							
1 cross-sectional study	245	Not serious	Not serious	Not serious	Not serious	Sensitivity= 0.60 (0.53-0.68)	HIGH
		Not serious	Not serious	Not serious	Serious[2]	Specificity= 0.81 (0.70-0.89)	MODERATE
FeNO (cut-off >21 ppb) vs clinician diagnosis with methacholine bronchial challenge or bronchodilator reversibility tests							
1 cross-sectional study	245	Not serious	Not serious	Not serious	Not serious	Sensitivity= 0.57 (0.49-0.65)	HIGH
		Not serious	Not serious	Not serious	Serious[2]	Specificity= 0.87 (0.78-0.94)	MODERATE
FeNO (cut-off >22 ppb) vs clinician diagnosis with methacholine bronchial challenge or bronchodilator reversibility tests							
1 cross-sectional study	245	Not serious	Not serious	Not serious	Not serious	Sensitivity= 0.57 (0.49-0.65)	HIGH
		Not serious	Not serious	Not serious	Serious[2]	Specificity= 0.87 (0.78-0.94)	MODERATE
FeNO (cut-off: >23 ppb) vs diagnosis with methacholine bronchial challenge test or clinician diagnosis with methacholine bronchial challenge or bronchodilator reversibility tests							

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
3 cross-sectional studies	2142	Serious[3]	Very serious[4]	Serious[5]	Serious[6]	Sensitivity= 0.71 (0.24-0.95)	VERY LOW
		Serious[3]	Very serious[4]	Serious[5]	Very serious[7]	Specificity= 0.75 (0.29-0.96)	VERY LOW
FeNO (cut-off >24 ppb) vs diagnosis with methacholine bronchial challenge tests							
1 cross-sectional study	222	Very serious[8]	Serious[9]	Serious[10]	Not serious	Sensitivity= 0.22 (0.15-0.31)	VERY LOW
		Very serious[8]	Not serious	Serious[10]	Not serious	Specificity= 0.91 (0.84-0.95)	VERY LOW
FeNO (cut-off >24 ppb) vs clinician diagnosis with methacholine bronchial challenge or bronchodilator reversibility tests							
1 cross-sectional study	245	Not serious	Serious[9]	Not serious	Not serious	Sensitivity= 0.50 (0.42-0.58)	MODERATE
		Not serious	Not serious	Not serious	Not serious	Specificity= 0.91 (0.82-0.96)	HIGH
FeNO (cut-off: >25 ppb) vs clinician diagnosis with methacholine bronchial challenge or bronchodilator reversibility tests							
1 cross-sectional study	245	Not serious	Very serious[4]	Not serious	Not serious	Sensitivity= 0.50 (0.42-0.58)	LOW
		Not serious	Not serious	Not serious	Not serious	Specificity= 0.92 (0.84-0.97)	HIGH
FeNO (cut-off: >25 ppb) vs clinician diagnosis with bronchodilator reversibility tests							
1 cross-sectional study	115	Serious[11]	Very serious[4]	Serious[12]	Serious[6]	Sensitivity= 0.83 (0.61-0.95)	VERY LOW
		Serious[11]	Not serious	Serious[12]	Not serious	Specificity= 0.97 (0.91-0.99)	LOW
FeNO (cut-off >30 ppb) vs clinician diagnosis with methacholine bronchial challenge or bronchodilator reversibility tests							
1 cross-sectional study	245	Not serious	Not serious	Not serious	Not serious	Sensitivity= 0.43 (0.35-0.50)	HIGH
		Not serious	Not serious	Not serious	Not serious	Specificity= 0.92 (0.84-0.97)	HIGH
FeNO (cut-off >34 ppb) vs diagnosis with methacholine bronchial challenge test							
1 cross-sectional study	222	Very serious[8]	Not serious	Serious[9]	Not serious	Sensitivity= 0.32 (0.23-0.41)	VERY LOW

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
		Very serious[8]	Not serious	Serious[9]	Serious[2]	Specificity= 0.83 (0.75-0.90)	VERY LOW
FeNO (cut-off >35 ppb) vs clinician diagnosis with methacholine bronchial challenge or bronchodilator reversibility tests							
1 cross-sectional study	245	Not serious	Not serious	Not serious	Not serious	Sensitivity= 0.32 (0.25-0.40)	HIGH
		Not serious	Not serious	Not serious	Not serious	Specificity= 0.99 (0.93-1.00)	HIGH
FeNO (cut-off >40 ppb) vs clinician diagnosis with methacholine bronchial challenge or bronchodilator reversibility tests							
1 cross-sectional study	245	Not serious	Not serious	Not serious	Not serious	Sensitivity= 0.25 (0.18-0.32)	HIGH
		Not serious	Not serious	Not serious	Not serious	Specificity= 0.99 (0.93-1.00)	HIGH
FeNO (cut-off >45 ppb) vs clinician diagnosis with methacholine bronchial challenge or bronchodilator reversibility tests							
1 cross-sectional study	245	Not serious	Not serious	Not serious	Not serious	Sensitivity= 0.17 (0.12-0.24)	HIGH
		Not serious	Not serious	Not serious	Not serious	Specificity= 1.00 (0.95-1.00)	HIGH
FeNO (cut-off >50 ppb) vs clinician diagnosis with methacholine bronchial challenge or bronchodilator reversibility tests							
1 cross-sectional study	245	Not serious	Not serious	Not serious	Serious[13]	Sensitivity= 0.14 (0.09-0.21)	MODERATE
		Not serious	Not serious	Not serious	Not serious	Specificity= 1.00 (0.95-1.00)	HIGH

1. *Downgraded by one increment due to index test (cut-off <20 ppb) indirectness*
2. *Downgraded by one increment due to the 95%CI overlapping the threshold referring to 'high specificity' (80%)*
3. *Downgraded by one increment as the majority of the evidence was at risk of bias due to concerns arising from either the method of participant selection (method not reported) or the interpretation of the index test and reference standard (unclear if blinded)*
4. *Downgraded by two increments due to substantial differences between point estimates and 95%CI reported by the individual studies reporting the same threshold*
5. *Downgraded by one increment due to indirectness across the included studies (one study no indirectness, one study with reference standard indirectness, one study with population and reference standard indirectness)*
6. *Downgraded by one increment due to the 95%CI overlapping the threshold corresponding to 'high sensitivity' (90%)*
7. *Downgraded by two increments due to the 95%CI overlapping the thresholds corresponding to both 'low and high specificity' (50 and 80%)*
8. *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)*
9. *Downgraded by one increment due to considerable differences between point estimates and 95%CI reported by the individual studies reporting the same threshold*

10. *Downgraded by one increment due to reference standard (unclear clinician decision in diagnosis) indirectness*
11. *Downgraded by one increment due to concerns arising from the method of participant selection (method not reported)*
12. *Downgraded by one increment due to population (ICS use not reported) indirectness*
13. *Downgraded by one increment due to the 95%CI overlapping the threshold referring to 'low sensitivity' (10%)*

Table 5: Clinical evidence summary: diagnostic test accuracy for FeNO in smoking adults

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
FeNO (cut-off: >20 ppb) vs diagnosis with methacholine bronchial challenge test							
1 cross-sectional study	37	Very serious[1]	Not serious	Serious[2]	Not serious	Sensitivity= 0.29 (0.10-0.56)	VERY LOW
		Very serious[1]	Not serious	Serious[2]	Serious[3]	Specificity= 0.75 (0.51-0.91)	VERY LOW
FeNO (cut-off: >25 ppb) vs diagnosis with methacholine bronchial challenge test							
1 cross-sectional study	37	Very serious[1]	Not serious	Serious[2]	Serious[4]	Sensitivity= 0.18 (0.04-0.43)	VERY LOW
		Very serious[1]	Not serious	Serious[2]	Serious[3]	Specificity= 0.90 (0.68-0.99)	VERY LOW
FeNO (cut-off: >30 ppb) vs diagnosis with methacholine bronchial challenge test							
1 cross-sectional study	37	Very serious[1]	Not serious	Serious[2]	Serious[4]	Sensitivity= 0.12 (0.01-0.36)	VERY LOW
		Very serious[1]	Not serious	Serious[2]	Serious[3]	Specificity= 0.95 (0.75-1.00)	VERY LOW

1. *Downgraded by two increments due to concerns arising from the method of participant selection (method not reported) and from interpretation of the index test and reference standard (unclear if blinded)*
2. *Downgraded by one increment due to reference standard (diagnosis without clinician decision) indirectness*
3. *Downgraded by one increment due to the 95%CI overlapping the threshold referring to 'high specificity' (80%)*
4. *Downgraded by one increment due to the 95%CI overlapping the threshold referring to 'low sensitivity' (10%)*

Table 6: Clinical evidence summary: diagnostic test accuracy for FeNO in non-smoking adults

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
FeNO (cut-off: >20 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	48	Not serious	Not serious	Serious[1]	Serious[2]	Sensitivity= 1.00 (0.81-1.00)	LOW
		Not serious	Not serious	Serious[1]	Serious[3]	Specificity= 0.33 (0.17-0.53)	LOW
FeNO (cut-off: >20 ppb) vs diagnosis with peak flow variability or bronchodilator reversibility tests							
1 cross-sectional study	540	Very serious[4]	Not serious	Serious[5]	Not serious	Sensitivity= 0.96 (0.91-0.98)	VERY LOW
		Very serious[4]	Not serious	Serious[5]	Not serious	Specificity= 0.42 (0.37-0.48)	VERY LOW
FeNO (cut-off: >20.5 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
1 cross-sectional study	87	Not serious	Not serious	Not serious	Not serious	Sensitivity= 0.70 (0.58-0.80)	HIGH
		Not serious	Not serious	Not serious	Serious[6]	Specificity= 0.76 (0.50-0.93)	MODERATE
FeNO (cut-off: >25 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	48	Not serious	Not serious	Serious[1]	Serious[2]	Sensitivity= 1.00 (0.81-1.00)	LOW
		Not serious	Not serious	Serious[1]	Serious[3]	Specificity= 0.47 (0.28-0.66)	LOW
FeNO (cut-off: 27 ppb) vs clinician diagnosis with methacholine bronchial challenge test							
1 cross-sectional study	283	Very serious[4]	Not serious	Not serious	Not serious	Sensitivity= 0.79 (0.68-0.88)	LOW
		Very serious[4]	Not serious	Not serious	Serious[6]	Specificity= 0.79 (0.73-0.84)	VERY LOW
FeNO (cut-off: >29 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	87	Not serious	Not serious	Not serious	Not serious	Sensitivity= 0.63 (0.50-0.74)	HIGH
		Not serious	Not serious	Not serious	Serious[6]	Specificity= 0.88 (0.64-0.99)	MODERATE
FeNO (cut-off: >30 ppb) vs diagnosis with peak flow variability or bronchodilator reversibility, or clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
3 cross-sectional studies	626	Serious[7]	Not serious	Serious[8]	Serious[2]	Sensitivity= 0.86 (0.54-0.97)	VERY LOW
		Serious[7]	Very serious[9]	Serious[8]	Very serious[10]	Specificity= 0.70 (0.31-0.93)	VERY LOW
FeNO (cut-off: >34 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	48	Not serious	Not serious	Serious[1]	Serious[2]	Sensitivity= 0.78 (0.52-0.94)	LOW
		Not serious	Not serious	Serious[1]	Serious[3]	Specificity= 0.53 (0.34-0.72)	LOW
FeNO (cut-off: >36 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	87	Not serious	Not serious	Not serious	Not serious	Sensitivity= 0.53 (0.41-0.65)	HIGH
		Not serious	Not serious	Not serious	Serious[6]	Specificity= 0.88 (0.64-0.99)	MODERATE
FeNO (cut-off: >37.5 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	87	Not serious	Not serious	Not serious	Not serious	Sensitivity= 0.51 (0.39-0.64)	HIGH
		Not serious	Not serious	Not serious	Serious[6]	Specificity= 0.88 (0.64-0.99)	MODERATE
FeNO (cut-off: >39.5 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	87	Not serious	Not serious	Not serious	Not serious	Sensitivity= 0.49 (0.36-0.61)	HIGH
		Not serious	Not serious	Not serious	Serious[6]	Specificity= 0.94 (0.71-1.00)	MODERATE
FeNO (cut-off: >40 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
	48	Not serious	Serious[11]	Serious[1]	Not serious	Sensitivity= 0.61 (0.36-0.83)	LOW

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
1 cross-sectional study		Not serious	Serious[11]	Serious[1]	Serious[3]	Specificity= 0.63 (0.44-0.80)	VERY LOW
FeNO (cut-off: >40 ppb) vs diagnosis with peak flow variability or bronchodilator reversibility tests							
1 cross-sectional study	540	Very serious[4]	Serious[11]	Serious[5]	Serious[2]	Sensitivity= 0.88 (0.83-0.93)	VERY LOW
		Very serious[4]	Serious[11]	Serious[5]	Serious[6]	Specificity= 0.83 (0.78-0.86)	VERY LOW
FeNO (cut-off: >40.5 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	87	Not serious	Not serious	Not serious	Not serious	Sensitivity= 0.44 (0.32-0.57)	HIGH
		Not serious	Not serious	Not serious	Serious[6]	Specificity= 0.94 (0.71-1.00)	MODERATE
FeNO (cut-off: >41 ppb) vs diagnosis with methacholine bronchial challenge test							
1 cross-sectional study	692	Very serious[4]	Not serious	Very serious[12]	Not serious	Sensitivity= 0.65 (0.58-0.72)	VERY LOW
		Very serious[4]	Not serious	Very serious[12]	Serious[6]	Specificity= 0.78 (0.74-0.82)	VERY LOW
FeNO (cut-off: >41.5 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	87	Not serious	Not serious	Not serious	Not serious	Sensitivity= 0.43 (0.31-0.55)	HIGH
		Not serious	Not serious	Not serious	Serious[6]	Specificity= 0.94 (0.71-1.00)	MODERATE
FeNO (cut-off: >42.5 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	87	Not serious	Not serious	Not serious	Not serious	Sensitivity= 0.41 (0.30-0.54)	HIGH
		Not serious	Not serious	Not serious	Serious[6]	Specificity= 0.94 (0.71-1.00)	MODERATE
FeNO (cut-off: >45 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	48	Not serious	Not serious	Serious[1]	Not serious	Sensitivity= 0.61 (0.36-0.83)	MODERATE
		Not serious	Not serious	Serious[1]	Serious[6]	Specificity= 0.73 (0.54-0.88)	LOW
FeNO (cut-off: >48.5 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	87	Not serious	Not serious	Not serious	Not serious	Sensitivity= 0.30 (0.20-0.42)	HIGH
		Not serious	Not serious	Not serious	Serious[6]	Specificity= 0.94 (0.71-1.00)	MODERATE
FeNO (cut-off: >50 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	48	Not serious	Not serious	Serious[1]	Not serious	Sensitivity= 0.56 (0.31-0.78)	MODERATE
		Not serious	Not serious	Serious[1]	Serious[6]	Specificity= 0.77 (0.58-0.90)	LOW
FeNO (cut-off: >50 ppb) vs diagnosis with peak flow variability or bronchodilator reversibility tests							
1 cross-sectional study	540	Very serious[4]	Not serious	Serious[5]	Not serious	Sensitivity= 0.69 (0.62-0.76)	VERY LOW
		Very serious[4]	Not serious	Serious[5]	Not serious	Specificity= 0.91 (0.88-0.94)	VERY LOW

1. *Downgraded by one increment due to population (mixed children/young people and adults) indirectness*
2. *Downgraded by one increment due to the 95%CI overlapping the threshold referring to 'high sensitivity' (90%)*
3. *Downgraded by one increment due to the 95%CI overlapping the threshold referring to 'low specificity' (50%)*
4. *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)*
5. *Downgraded by one increment due to reference standard (unclear if clinician decision was involved in diagnosis) indirectness*
6. *Downgraded by one increment due to the 95%CI overlapping the threshold referring to 'high specificity' (80%)*
7. *Downgraded by one increment as two studies in the meta-analysis were at low risk of bias, whilst the third was at very serious risk of bias 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) and contained a large number of participants relative to the other two studies*
8. *Downgraded by one increment due to population (mixed children/young people and adults), index test (flow rate of 45 mL/s used, not 50 mL/s as specified in the protocol) and reference standard (unclear if clinician decision was involved in diagnosis) indirectness in each study*
9. *Downgraded by two increments due to substantial differences between point estimates and 95%CI in the pooled studies*
10. *Downgraded by two increments due to the 95%CI overlapping the thresholds referring to both 'low and high specificity' (50 and 80%)*
11. *Downgraded by one increment due to considerable differences between point estimates and 95%CI in studies reporting the same threshold*
12. *Downgraded by two increments due to index test (no information on standards used or flow rate FeNO measurements were conducted to) and reference standard (unclear if clinician decision was involved in diagnosis) indirectness*

Table 7: Clinical evidence summary: diagnostic test accuracy for FeNO in adults with mixed/not reported smoking status

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
FeNO (cut-off: >19 ppb) vs clinician diagnosis with methacholine bronchial challenge test							
1 cross-sectional study	50	Serious[1]	Not serious	Very serious[2]	Serious[3]	Sensitivity= 0.77 (0.55-0.92)	VERY LOW
		Serious[1]	Not serious	Very serious[2]	Very serious[4]	Specificity= 0.64 (0.44-0.81)	VERY LOW
FeNO (cut-off: >20 ppb) vs clinician diagnosis with bronchodilator reversibility and/or methacholine/saline bronchial challenge tests or diagnosis with methacholine bronchial challenge test,							
5 cross-sectional studies	1104	Not serious	Very serious[5]	Very serious[6]	Not serious	Sensitivity= 0.62 (0.41-0.81)	VERY LOW
		Not serious	Not serious	Very serious[6]	Serious	Specificity= 0.69 (0.52-0.83)	VERY LOW
FeNO (cut-off: >21 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	308	Not serious	Not serious	Very serious[7]	Not serious	Sensitivity= 0.60 (0.52-0.68)	LOW
		Not serious	Not serious	Very serious[7]	Not serious	Specificity= 0.70 (0.62-0.77)	LOW
FeNO (cut-off: >22 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	308	Not serious	Not serious	Very serious[7]	Not serious	Sensitivity= 0.57 (0.49-0.65)	LOW
		Not serious	Not serious	Very serious[7]	Serious[8]	Specificity= 0.75 (0.67-0.82)	VERY LOW
FeNO (cut-off: >23.5 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	400	Serious[1]	Not serious	Very serious[7]	Not serious	Sensitivity= 0.80 (0.75-0.85)	VERY LOW
		Serious[1]	Not serious	Very serious[7]	Serious[9]	Specificity= 0.55 (0.46-0.63)	VERY LOW

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
FeNO (cut-off: >25 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests or diagnosis with methacholine bronchial challenge test							
3 cross-sectional studies	1275	Not serious	Not serious	Very serious[6]	Not serious	Sensitivity= 0.47 (0.28-0.67)	LOW
		Not serious	Not serious	Very serious[6]	Serious[9]	Specificity= 0.75 (0.56-0.88)	VERY LOW
FeNO (cut-off: >27 ppb) vs clinician diagnosis with bronchodilator reversibility and histamine bronchial challenge tests							
1 cross-sectional study	114	Not serious	Not serious	Very serious[6]	Not serious	Sensitivity= 0.79 (0.63-0.90)	LOW
		Not serious	Not serious	Very serious[6]	Not serious	Specificity= 0.92 (0.83-0.97)	LOW
FeNO (cut-off: >28 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	131	Serious[10]	Not serious	Very serious[7]	Not serious	Sensitivity= 0.77 (0.66-0.86)	VERY LOW
		Serious[10]	Not serious	Very serious[7]	Serious[9]	Specificity= 0.83 (0.70-0.92)	VERY LOW
FeNO (cut-off: >29 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	131	Serious[10]	Not serious	Very serious[7]	Not serious	Sensitivity= 0.81 (0.71-0.89)	VERY LOW
		Serious[10]	Not serious	Very serious[7]	Serious[9]	Specificity= 0.85 (0.72-0.93)	VERY LOW
FeNO (cut-off: >30 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests or diagnosis with methacholine bronchial challenge test							
3 cross-sectional studies	972	Not serious	Not serious	Very serious[6]	Not serious	Sensitivity= 0.43 (0.20-0.71)	LOW
		Not serious	Not serious	Very serious[6]	Serious[9]	Specificity= 0.86 (0.62-0.96)	VERY LOW
FeNO (cut-off: >31 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	308	Not serious	Not serious	Very serious[7]	Not serious	Sensitivity= 0.42 (0.35-0.50)	LOW
		Not serious	Not serious	Very serious[7]	Not serious	Specificity= 0.93 (0.88-0.97)	LOW
FeNO (cut-off: >32 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	308	Not serious	Not serious	Very serious[7]	Not serious	Sensitivity= 0.42 (0.35-0.40)	LOW
		Not serious	Not serious	Very serious[7]	Not serious	Specificity= 0.93 (0.88-0.97)	LOW
FeNO (cut-off: >32 ppb) vs diagnosis with methacholine bronchial challenge test							
1 cross-sectional study	112	Very serious[11]	Not serious	Very serious[12]	Not serious	Sensitivity= 0.48 (0.33-0.63)	VERY LOW
		Very serious[11]	Not serious	Very serious[12]	Serious[9]	Specificity= 0.83 (0.71-0.91)	VERY LOW
FeNO (cut-off: >33 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	308	Not serious	Not serious	Very serious[7]	Not serious	Sensitivity= 0.40 (0.32-0.48)	LOW
		Not serious	Not serious	Very serious[7]	Not serious	Specificity= 0.93 (0.88-0.97)	LOW

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
FeNO (cut-off: >33 ppb) vs clinician diagnosis with bronchodilator reversibility and/or methacholine bronchial challenge tests							
1 cross-sectional study	166	Very serious[13]	Not serious	Serious[14]	Not serious	Sensitivity= 0.32 (0.24-0.42)	VERY LOW
		Very serious[13]	Not serious	Serious[14]	Serious[9]	Specificity= 0.84 (0.72-0.92)	VERY LOW
FeNO (cut-off: >34 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	308	Not serious	Not serious	Very serious[7]	Not serious	Sensitivity= 0.38 (0.30-0.46)	LOW
		Not serious	Not serious	Very serious[7]	Not serious	Specificity= 0.95 (0.90-0.98)	LOW
FeNO (cut-off: >35 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	308	Not serious	Not serious	Very serious[7]	Not serious	Sensitivity= 0.37 (0.30-0.45)	LOW
		Not serious	Not serious	Very serious[7]	Not serious	Specificity= 0.95 (0.90-0.98)	LOW
FeNO (cut-off: >35 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	553	Not serious	Not serious	Very serious[7]	Not serious	Sensitivity= 0.32 (0.26-0.39)	LOW
		Not serious	Not serious	Very serious[7]	Not serious	Specificity= 0.87 (0.83-0.90)	LOW
FeNO (cut-off: >36 ppb) vs diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	702	Very serious[15]	Not serious	Very serious[16]	Not serious	Sensitivity= 0.30 (0.25-0.35)	VERY LOW
		Very serious[15]	Not serious	Very serious[16]	Not serious	Specificity= 0.85 (0.81-0.89)	VERY LOW
FeNO (cut-off: >37 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	308	Not serious	Not serious	Very serious[7]	Not serious	Sensitivity= 0.34 (0.27-0.42)	LOW
		Not serious	Not serious	Very serious[7]	Not serious	Specificity= 0.96 (0.91-0.98)	LOW
FeNO (cut-off: >38.8 ppb) vs clinician diagnosis with methacholine bronchial challenge, bronchodilator reversibility and sputum eosinophil tests							
1 cross-sectional study	71	Serious[1]	Not serious	Serious[14]	Not serious	Sensitivity= 0.79 (0.65-0.90)	LOW
		Serious[1]	Not serious	Serious[14]	Serious[9]	Specificity= 0.91 (0.72-0.99)	VERY LOW
FeNO (cut-off: >39 ppb) vs clinician diagnosis with methacholine bronchial challenge, bronchodilator reversibility and sputum eosinophil tests							
1 cross-sectional study	61	Serious[10]	Serious[17]	Serious[14]	Not serious	Sensitivity= 0.79 (0.63-0.90)	VERY LOW
		Serious[10]	Not serious	Serious[14]	Serious[9]	Specificity= 0.89 (0.67-0.99)	VERY LOW
FeNO (cut-off: >39 ppb) vs expert panel diagnosis with multiple diagnostic tests							
1 cross-sectional study	118	Very serious[18]	Serious[17]	Serious[14]	Not serious	Sensitivity: 0.59 (0.46-0.70)	VERY LOW
		Very serious[18]	Not serious	Serious[14]	Serious[9]	Specificity: 0.85 (0.72-0.94)	VERY LOW
FeNO (cut-off: >40 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
	308	Not serious	Not serious	Very serious[7]	Not serious	Sensitivity= 0.32 (0.25-0.40)	LOW

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
1 cross-sectional study		Not serious	Not serious	Very serious[7]	Not serious	Specificity= 0.97 (0.93-0.99)	LOW
FeNO (cut-off: >40 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	553	Not serious	Not serious	Very serious[7]	Not serious	Sensitivity= 0.30 (0.24-0.36)	LOW
		Not serious	Not serious	Very serious[7]	Not serious	Specificity= 0.87 (0.83-0.90)	LOW
FeNO (cut-off: >41 ppb) vs diagnosis with bronchodilator reversibility test							
1 cross-sectional study	515	Serious[1]	Not serious	Very serious[6]	Not serious	Sensitivity= 0.72 (0.65-0.79)	VERY LOW
		Serious[1]	Not serious	Very serious[6]	Not serious	Specificity= 0.75 (0.70-0.79)	VERY LOW
FeNO (cut-off: >46 ppb) vs diagnosis with bronchodilator reversibility or methacholine bronchial challenge tests							
1 cross-sectional study	156	Very serious[19]	Not serious	Very serious[6]	Not serious	Sensitivity= 0.30 (0.19-0.42)	VERY LOW
		Very serious[19]	Not serious	Very serious[6]	Not serious	Specificity= 0.92 (0.85-0.97)	VERY LOW
FeNO (cut-off: >47 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	553	Not serious	Not serious	Very serious[7]	Not serious	Sensitivity= 0.26 (0.20-0.32)	LOW
		Not serious	Not serious	Very serious[7]	Not serious	Specificity= 0.93 (0.89-0.95)	LOW
FeNO (cut-off: >50 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests							
1 cross-sectional study	308	Not serious	Serious[17]	Very serious[7]	Not serious	Sensitivity= 0.24 (0.18-0.32)	VERY LOW
		Not serious	Not serious	Very serious[7]	Not serious	Specificity= 0.99 (0.96-1.00)	LOW
FeNO (cut-off: >50 ppb) vs expert panel diagnosis with multiple diagnostic tests							
1 cross-sectional study	118	Very serious[18]	Serious[17]	Serious[14]	Not serious	Sensitivity: 0.51 (0.39-0.64)	VERY LOW
		Very serious[18]	Not serious	Serious[14]	Serious[9]	Specificity: 0.88 (0.75-0.95)	VERY LOW

1. *Downgraded by one increment due to concerns arising from the interpretation of the index test and reference standard (unclear if blinded)*
2. *Downgraded by two increments due to population (mixed/not reported smoking status) and index test (cut-off <20 ppb, protocol specified 20-50 ppb) indirectness*
3. *Downgraded by one increment due to the 95%CI overlapping the threshold corresponding to 'high sensitivity' (90%)*
4. *Downgraded by two increments due to the 95%CI overlapping the thresholds corresponding to both 'low and high specificity' (50 and 80%)*
5. *Downgraded by two increments due to substantial differences between point estimates and 95%CI in the studies included in the analysis*
6. *Downgraded by two increments due to population indirectness in all studies (mixed children/young people and adults, mixed/not reported smoking status, ICS use unclear or not reported)*
7. *Downgraded by two increments due to population (unclear ICS use and mixed smoking and non-smoking participants) indirectness*
8. *Downgraded by one increment due to the 95%CI overlapping the threshold corresponding to 'high specificity' (80%)*
9. *Downgraded by one increment due to the 95%CI overlapping the threshold corresponding to 'low specificity' (50%)*
10. *Downgraded by one increment due to concerns arising from the method of participant recruitment (method not reported)*
11. *Downgraded by two increments due to concerns arising from the method of participant recruitment (method not reported) and interpretation of the index test and reference standard (unclear if blinded)*

12. *Downgraded by two increments due to population (mixed/not reported smoking status) and reference standard (unclear if clinician decision was involved in diagnosis) indirectness*
13. *Downgraded by two increments due to concerns arising from the method of participant selection (method not reported), interpretation of the index test and reference standard (unclear if blinded) and the flow and timing of participants through the study (data only reported for training cohort (n=166), not including validation cohort)*
14. *Downgraded by one increment due to population (mixed/not reported smoking status) indirectness*
15. *Downgraded by two increments due to concerns arising from the method of participant recruitment (method not reported), interpretation of the index test and reference standard (unclear if blinded) and the flow and timing of the study (not all participants diagnosed using the same reference standard)*
16. *Downgraded by two increments due to population (mixed/not reported smoking status), index test (standard FeNO was performed to not reported) and reference standard (unclear if clinician decision was involved in diagnosis) indirectness*
17. *Downgraded by one increment due to considerable differences between point estimates and 95%CI in studies reporting the same threshold*
18. *Downgraded by two increments due to concerns arising from the method of participant recruitment (method not reported) and interpretation of the index test and reference standard (not blinded with access to index test results whilst making reference standard diagnosis)*
19. *Downgraded by two increments due to concerns arising from the interpretation of the index test and reference standard (unclear if blinded) and the flow and timing of the study (56 participants excluded from analysis)*

1.1.7. Economic evidence

1.1.7.1. Included studies

One health economic study with the relevant comparison was included in this review(Harnan, et al., 2015). This is summarised in the health economic evidence profile below Table 8 and the health economic evidence table in Appendix H.

1.1.7.2. Excluded studies

Two economic studies relating to this review question were identified but were excluded due to a combination of limited applicability and methodological limitations and the availability of more applicable evidence(Berg, et al., 2008, Price, et al., 2009). These are listed in Appendix J, with reasons for exclusion given.

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

1.1.8. Summary of included economic evidence

Table 8: Health economic evidence profile: FeNO vs standard tests for asthma

<table>
<tr><th>Study</th><th>Applicability</th><th>Limitations</th><th>Other comments</th><th>Incremental cost[d]</th><th>Incremental effects</th><th>Cost effectiveness</th><th>Uncertainty</th></tr>
<tr>
<td>Harnan 2015(Harnan et al., 2015) (UK)</td>
<td>Directly applicable</td>
<td>Potentially serious limitations[a]</td>
<td>
• Probabilistic decision tree model based on a systematic review of the diagnostic accuracy of FeNO
• Cost-utility analysis (QALYs)
• Population: People with suspected asthma
• Comparators[b]:
1. Bronchial challenge test with methacholine (MCT)
2. FeNO[c]
3. PEF
4. Bronchodilator reversibility
5. FEV1/FVC
• Time horizon: 5 years
</td>
<td colspan="3">
<table>
<tr><th>Int</th><th>Cost[e]:</th><th>QALY</th><th>Inc cost</th><th>Inc QALY</th><th>ICER</th></tr>
<tr><td>5</td><td>£907.71</td><td>4.2686</td><td colspan="3">Dominated by 2</td></tr>
<tr><td>4</td><td>£886.27</td><td>4.2710</td><td colspan="3">Dominated by 2</td></tr>
<tr><td>3</td><td>£877.91</td><td>4.2719</td><td colspan="3">Dominated by 2</td></tr>
<tr><td>2</td><td>£821.20</td><td>4.2771</td><td colspan="3">Baseline</td></tr>
<tr><td>1</td><td>£1226</td><td>4.2834</td><td>404.8</td><td>0.0063</td><td>£64,253per QALY</td></tr>
</table>

FeNO was the most cost-effective intervention when compared to other single tests at £20,000 per QALY.
</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; 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.

Results based on the point estimates of parameters reflect the results of PSA.
</td>
</tr>
</table>

Abbreviations: 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; QALYs= quality-adjusted life years; TN= true negative; TP=true positive.

(a) 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. Unclear if FeNO prices are VAT exclusive or inclusive. 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.

(b) All comparators including combination of tests were excluded from the table and are presented in the evidence review of 1.11. Sputum induction was excluded as out of scope.

(c) 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.

(d) Full incremental analysis re-analysed here to exclude non-relevant comparators (combination tests and sputum).

(e) 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).

1.1.9. Economic model

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

1.1.10. Unit costs

Table 9 shows the figures used to calculate the mean per-test cost of FeNO. Device and consumables costs were provided directly by one of the main FeNO manufacturers. A discounting factor of 3.5% was used to calculate the annuatisation factor over the lifetime of the device.

Table 9: Mean per-test cost of FeNO

Characteristics	Low volume centre (Jersey Allergy Clinic)	Assumed average across NHS	High volume centre (Alder Hey Children's)	Source
Device lifetime (years)	5	5	5	NIOX Group
Use of FeNO	100% diagnosis	NA	30% diagnosis, 70% monitoring	Personal communication
No. of tests per year	100	300	450	Personal communication
Cost of device	£1,250	£1,250	£1,250	NIOX Group
Cost of test kits: 300	NA	£1,645	£1,645	NIOX Group
Cost of test kits: 100	£890	NA	NA	NIOX Group
Shipping cost per order	£75	£50	£0	NIOX Group
Annuatisation factor for specific device lifetime	4.67	4.67	4.67	Calculation
Annuatised mean per-test cost	**£12.32**	**£6.54**	**£6.08**	**Calculation**
Annuatised mean per-test cost (excluding shipping cost)	**£11.57**	**£6.37**	**£6.08**	**Calculation**

Note: All prices are VAT-exclusive

The mean per-tests costs of a FeNO device was calculated in three different scenarios varying for their testing volume. Jersey Allergy Clinic is a relatively small specialist clinic (106,000 population) dealing only in part with asthma and using FeNO only for diagnostic purposes. Hence, they report only 100 FeNO tests a year. With such a small volume, the mean per-test cost of FeNO is the highest amounting to around £11.57 excluding shipping costs. By contrast, Alder Hey Children's NHS Foundation Trust is a large and specialized centre, which uses FeNO both for diagnosis (30%) and monitoring (70%). Hence, they report a larger number of FeNO tests done every year, approximately 450. With this volume, the mean per-test cost of FeNO is the lowest and equal to £6.08. A third scenario using an average of 300 tests per years and a mean cost of £6.37 is also reported. This is based on Committee's expert opinion and reflects the figures used in Harnan 2015(Harnan et al., 2015).

Table 10 shows the cost of delivering a FeNO test including the cost of staff required. The committee were aware that FeNO is a relatively easy test to deliver and would not require more than 15 minutes of a GP practice nurse time.

Table 10: Cost of delivering the test

Resource	Quantity	Unit cost[(a)]	Total cost	Source
GP practice nurse	15 minutes	£63.38 per hour[(a)]	£15.84	PSSRU 2022(Jones, et al.)
Mean cost of FeNO	1 test	£6.37 (£6.08 to £11.57)	£6.37 (£6.08 to £11.57)	Table 9
Total			**£22.21 (£21.92 to £27.41)**	

a) Costs included qualification costs

1.1.11. Evidence statements

1.1.11.1. Economic evidence statement

- One cost–utility analysis found that FeNO was cost effective compared to: bronchial challenge test with methacholine, PEF, bronchodilator reversibility and FEV/FEV1 for diagnosing asthma. FeNO dominated all comparators (less costly and more effective) except for bronchial challenge test with methacholine, which had an ICER of £64,253 per QALY compared to FeNO. This analysis was assessed as directly applicable with potentially serious 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 purposed 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 FeNO 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 test would be recommended and 0.1 and 0.5 below which a test is of no clinical use. The committee were interested in establishing whether there was an optimal cut-off value of FeNO with sufficiently high sensitivity and specificity to be useful in making a diagnosis of asthma, but also in whether there are separate cut-off values which could usefully help either rule in or rule out an asthma diagnosis.

1.2.2. The quality of the evidence

Clinical and cost effectiveness

No relevant clinical studies were identified comparing the clinical effectiveness of diagnosis of asthma based on Fractional exhaled nitric oxide (FeNO) measures with a cut-off threshold between 20-50ppb and a flow rate of 50ml/s or equivalent, in terms of the clinical outcomes examined.

Diagnostic accuracy

Twenty-eight observational studies were included in this review. Twenty-one of these studies were in adults and seven were in children and young people. Five of these studies included a mixed population of adults and children/young people but were categorised into either group based on the average population age. In the adult-containing studies, six studies included only non-smokers, with the other fifteen studies including a mix of smoking and non-smoking participants, and one study providing a subgroup analysis of smokers only.

After looking at the evidence the committee emphasised there was great variability in the FeNO cut-offs used across the studies as well as in the characteristics of the populations included, which made it difficult to draw conclusions. The pre-specified stratification by smoking status helped with the interpretation of the evidence, although the considerable heterogeneity in population characteristics remained a problem. Other factors that the committee highlighted as potentially influencing the diagnostic accuracy of FeNO included severity and duration of symptoms, atopic status, the country where the study was conducted, and any details about ICS use. Where reported, this information is available in the evidence tables, and was used to guide the committee through the evidence to try and explain any findings.

Evidence in children and young people ranged from very low to high quality, with the majority being high quality. Where downgrading occurred, this was most frequently due to risk of bias resulting from an unclear method of participant recruitment and/or a lack of clarity over blinding of the results of the index test and reference standard. Indirectness was infrequent, but occurred in some studies where participants' ICS status was not reported or there was a lack of clarity over the involvement of a clinician in the final asthma diagnosis. Some inconsistency was seen in studies reporting the same diagnostic threshold although this was infrequent due to the wide variety of thresholds reported. Finally, some imprecision was seen, mainly in the specificity estimates where the 95%CI overlapped the upper and/or lower thresholds for decision making.

1.2.3. Benefits and harms

Children and young people

Evidence was identified using FeNO cut-offs ranging from 19.6 to 50 ppb for the diagnosis of asthma in children and young people. This evidence ranged from very low to high quality, with the majority being high quality. The maximum sensitivity was seen in very low-quality evidence, reporting a value of 0.83 using a cut-off of >25 ppb when compared to a clinician diagnosis with bronchodilator reversibility. Due to the very low certainty of the estimate reported, this finding was interpreted with caution by the committee. Focussing on high quality evidence, the best sensitivity seen was using a threshold of >20 ppb, resulting in a sensitivity of 0.60 when compared to a clinician diagnosis with bronchodilator reversibility or methacholine bronchial challenge tests. Nonetheless, no evidence reported a sensitivity that met the threshold of 0.90 for the recommendation of FeNO as a rule-in test for asthma. Very high specificities of 0.99-1.00 were seen at four diagnostic thresholds (>35, >40, >45 and >50 ppb), all being reported with high certainty of the estimates. This evidence was all from a single study, containing 245 participants and using a clinician diagnosis with bronchodilator reversibility or methacholine bronchial challenge tests as the reference standard. Additionally, specificities meeting the decision-making threshold of 0.80 were seen at cut-offs as low as >19.6 ppb, albeit from low quality evidence, with the only cut-off not meeting this threshold being >23 ppb (specificity= 0.75).

Smoking Adults

Very low-quality evidence from a single study reported the diagnostic accuracy of FeNO in a subgroup of adults that were current smokers. Three cut-offs were reported, >20, >25 and >30 ppb, showing sensitivities of 0.29, 0.18 and 0.12, and specificities of 0.75, 0.90 and 0.95, respectively. All evidence was limited by risk of bias arising from the method of participant selection and a lack of clarity over blinding of results, as well as using an indirect reference standard, methacholine bronchial challenge test alone, to diagnose asthma. The values reported in this evidence do not suggest that FeNO is an appropriate test for ruling out an asthma diagnosis in adults that smoke. However, the specificity data met the decision-making threshold at cut-offs greater than 25 ppb, indicating potential utility as a rule-in test in this population.

Non-smoking Adults

Evidence for FeNO as a diagnostic test in adults that do not smoke was seen at cut-offs ranging from 20-50 ppb. This evidence ranged from very low to high-quality, with the majority being very low-quality. The decision-making threshold for sensitivity was met in two studies using a cut-off of >20 ppb, and one using >25 ppb, reporting values of 1.00, 0.96 and 1.00, respectively. Evidence for these thresholds was low to very low-quality, with the low-quality evidence coming from the same study, containing 47 participants, and using clinician diagnosis with bronchodilator reversibility or methacholine bronchial challenge tests as the reference standard. A larger study, containing 540 participants, provided very low-quality evidence that was limited by risk of bias, resulting from an unclear method of participant

recruitment and unclear blinding of results, and indirectness due to the reference standard used. Specificities exceeding the decision-making threshold were seen at cut-offs >29 ppb, although this was not consistent in all evidence reporting cut-offs above this value. The majority of the moderate-quality evidence came from a single study containing 87 participants, comparing FeNO at thresholds ranging from >20.5 to 48.5 ppb to a clinician diagnosis with bronchodilator reversibility or methacholine bronchial challenge tests. In this study, a maximum specificity of 0.94 was reported at all thresholds from >39.5 ppb upwards, suggesting a cut-off around >40 ppb may be optimal without overly compromising sensitivity. However, very low-quality evidence from two other studies reported lower specificities of 0.63 and 0.83, casting doubt upon >40 ppb as a diagnostic threshold. The committee acknowledged the complexity of the data and agreed that setting a clear diagnostic threshold that would be accurate in a typical suspected asthma presentation is difficult.

Adults with mixed or unreported smoking status

Evidence for using FeNO as a diagnostic test in adults with mixed or unreported smoking status was reported at thresholds ranging from 19-50 ppb. All evidence was low or very low-quality, with the main reason for downgrading being the mixed or unreported smoking status. No diagnostic cut-off values met the decision-making threshold for sensitivity, with a maximum value of 0.81 being seen with a cut-off of >29 ppb. Specificities met the decision-making threshold at all cut-offs exceeding and including >27 ppb, with the exception of >41 ppb, although this was close to meeting the threshold value (0.75). The inferior specificity seen at >41 ppb is potentially explainable by the inclusion criteria of an FEV_1 >80%, thus excluding participants with more severe and easy to diagnose asthma. The highest specificity (0.99) was achieved at a cut-off of >50 ppb, although cut-offs as low as >37 ppb produced similar values (0.96). Due to the very low-quality of the evidence, it was difficult for the committee to draw conclusions from the data presented. The mixture of smoking and non-smoking participants added a layer of complexity that was absent in the stratified evidence. Furthermore, as was the case throughout the diagnostic reviews, there was a wide range of subject selection criteria and of definitions for the suspicion of asthma, reflected in the prevalence of asthma which ranged from 20-80.5%.

1.2.4. Cost effectiveness and resource use

Three health economic studies were identified for this question. Two were cost-comparison analyses that were selectively excluded for being outdated and less applicable than the third study, which was included.

The included study, Harnan 2015, was a cost-utility analysis comparing FeNO with standard diagnostic tests for asthma. Some comparators included combinations of FeNO with other tests and therefore were excluded as more relevant for another research question (evidence review 1.11). The study was assessed as directly applicable with potentially serious limitations. The main limitations were that the estimation of costs of FeNO were outdated, the accuracy of standard tests was not obtained through a systematic review, prevalence of asthma was estimated by non-UK specific RCTs, and there was uncertainty on resolution pathway of false negative and false positive. The model had a short-time horizon of five years and assumed that a wrong diagnosis would not affect mortality but only quality of life and healthcare costs. The analysis found FeNO dominant compared with spirometry, PEF and bronchodilator reversibility, as it was cheaper and it increased quality of life. When compared with methacholine challenge test, this latter was found more effective and more costly but the resulting cost per QALY of £64,253 meant that FeNO would still be cost-effective.

The committee raised the concern that the estimation of the cost of FeNO provided by Harnan 2015 could be inaccurate and, possibly, too low if compared with their clinical experience. Therefore, it was agreed that the mean cost of a FeNO test would be transparently recalculated using updated data and latest information from the manufacturers.

Data on the device were collected directly from one the main manufacturers. Information on resource use (number of tests per year) and shipping costs were obtained from two different NHS trusts, one with a low volume of tests per year (100), where FeNO was used exclusively for diagnosis purposes, and one trust with a high volume of tests (450) where FeNO was used both for diagnosing and monitoring asthma. An “average volume” case was also included assuming 300 tests per year as recommended by the committee and used in Harnan 2015. The mean per-test cost of FeNO was estimated to be £6.08, £6.37 and £11.57 in, respectively, the high, average and low volume cases. The average estimation was found to be very similar to the estimation of Harnan 2015 confirming that, although prices of FeNO devices and consumables have changed in recent years, the final cost per test has remained the same. The volume of tests done each year was found to be the most important factor behind the final cost per test. If a centre use FeNO only for diagnosis purposes, it is unlikely it would reach a number of tests per year higher than 100 and, therefore, its per-test price would be around £11-12. If a centre uses FeNO routinely for both diagnosing and monitoring asthma, the cost per test would be much lower: around £6.

The committee considered FeNO alongside or in combination with a variety of other tests for asthma within a diagnostic algorithm for children and adults (see evidence review 1.11). In children, FeNO with a cut-off of 35ppb was found to be the most cost-effective initial test, and therefore was included in the recommendation. In adults, the economic analysis found that blood eosinophils was a more cost-effective alternative as an initial test. However, the analysis found that at high thresholds, when FeNO reaches a specificity comparable to blood eosinophils, it could be a cost-effective alternative to a blood test. Hence, the committee agreed to recommend either blood eosinophils or FeNO as an initial test within a diagnostic pathway for asthma in adults.

1.2.5. Other factors the committee took into account

The committee noted that some people find it difficult to make a FeNO measurement and it may take several minutes to perform.

FeNO has been gaining popularity in past years and is progressively becoming available to more NHS practices, although it was noted that there is some geographic variation in availability.

The committee emphasised that FeNO is a marker of eosinophilic inflammation, and that the diagnosis of asthma would ideally also take tests of pulmonary function into account.

The suppression of FeNO levels in smokers is a limitation to its usefulness. However, it was agreed that this would still allow FeNO to be used as a specific test since it would be more unusual for a smoker to achieve a high level than a non-smoker.

There was consensus that the evidence indicated different cut-offs should be used in adults compared to children and young people. Ideally each individual’s FeNO level would be interpreted in light of normal data for their age, height and gender in the same way as is standard practice for lung function measurements. However, there are no internationally accepted normalised data yet, and current measuring devices do not produce FeNO read-outs in this fashion. To be practically useful therefore, a cut-off recommendation must be a compromise citing a single value. Based on their clinical experience, and after taking note of the health economic analysis which suggests that FeNO is best used as a specific test, the committee suggested a cut-off of 50 ppb in adults and 35 ppb in children.

1.2.6. Recommendations supported by this evidence review

Recommendations 1.2.1 and 1.2.5.

1.3 References

FeNO references: Test and treat

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Appendices

Appendix A – Review Protocol

Review protocol for fractional exhaled nitric oxide (FeNO) for the diagnosis of asthma

ID	Field	Content
0.	PROSPERO registration number	CRD42023438137
1.	Review title	Accuracy and clinical and cost-effectiveness of FeNO in diagnosis of asthma
2.	Review question	In people under investigation for asthma, what is the diagnostic test accuracy and clinical and cost-effectiveness of fractional exhaled nitric oxide (FeNO) measures?
3.	Objective	To evaluate the diagnostic test value of FeNO in diagnosing asthma This evidence review will have two stages: (1) Identify the clinical and cost effectiveness of diagnosis with the test (test plus treatment) (2) If evidence on clinical effectiveness is limited, the diagnostic accuracy will instead be determined
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos

		Searches will be restricted by: • Date limitations – clinical effectiveness searched from inception. Diagnostic accuracy searched from 2014 onwards in line with previous guideline. • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Asthma
6.	Population	People with suspected asthma (presenting with respiratory symptoms). Ages stratified into the following 2 groups: • Children and young people (5-16 years old) • Adults (≥17 years)

		Exclusion: • Children under 5 years old • People on steroid inhalers (washout period minimum of 4 weeks for inclusion) Stratification • Smokers vs non-smokers vs mixed populations
7.	Test	Fractional exhaled nitric oxide (FeNO) with a cut-off threshold between 20-50ppb and a flow rate of 50ml/s or equivalent.
8.	Reference standard	Effectiveness (test-and-treat) • Compare to each other Diagnostic accuracy • Reference standard Reference standard: Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test)

		Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold. Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis. Stratification: • Different reference standards Maximum interval between index test and reference standard: 12 months
9.	Types of study to be included	Clinical effectiveness (test and treat): • Systematic reviews of RCTs • Parallel RCTs Published NMAs and IPDs will be considered for inclusion. Diagnostic test accuracy: • Cross sectional studies • Cohort studies will be included
10.	Other exclusion criteria	• Non-English language studies. • Non comparative cohort studies • Before and after studies • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.

		• Studies in which >10% of people are on inhaled and/or systemic corticosteroid treatment • Not looking at occupational asthma /allergens • Not looking at validation studies, or studies comparing different methods of measuring FeNO. • Cross-sectional studies were included if they reported sensitivity or specificity, or the sensitivity and specificity could be calculated.
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:
		
		Clinical effectiveness (test and treat) outcomes:
		• Severe asthma exacerbations (defined as asthma exacerbations requiring oral corticosteroid use (dichotomous outcome at ≥6 months)
		• Mortality (dichotomous outcome at ≥6 months)
		• Quality of life (QOL; validated scale, including asthma specific questionnaires AQLQ; health-related) (continuous outcome at ≥3 months)
		• Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months)
		• Hospital admissions (dichotomous outcome at ≥6 months)
		• Reliever/rescue medication use (continuous outcome at ≥3 months)
		• Lung function (change in FEV1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 months). *Note: Extract FEV1 %pred over litres if both are reported. If only litres is reported, extract and analyse separately (do not extract both). For children, only use FEV1 %pred.*
		• Adverse events
		  ○ Linear growth (continuous outcome at ≥1 year),
		  ○ Pneumonia frequency (dichotomous outcome at ≥3 months)
		  ○ Adrenal insufficiency as defined by study, including short synacthen test and morning cortisol (dichotomous outcome at ≥3 months)

		○ Bone mineral density (continuous outcome at ≥6 months) • Inflammatory markers; exhaled nitric oxide (continuous outcome at ≥8 weeks) Diagnostic accuracy outcomes: Asthma diagnosis • Sensitivity (thresholds: upper 90%, lower 10%) • Specificity (thresholds: upper 80%, lower 50%) • Raw data to calculate 2x2 tables to calculate sensitivity and specificity • Negative predictive value (NPV), Positive predictive value (PPV)
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. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments

		Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • QUADAS-2 checklist
15.	Strategy for data synthesis	<u>Diagnostic intervention (test and treat):</u> Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the

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

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 National Guideline Centre 5b Named contact e-mail asthmachronicmanagement@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre]		
24.	Review team members	From the National Guideline Centre: Bernard Higgins (Guideline lead) Sharon Swain (Guideline lead) Melina Vasileiou (senior systematic reviewer) Qudsia Malik (systematic reviewer) Toby Sands (Systematic reviewer) Alfredo Mariani (Senior health economist) Lina Gulhane (Head of information specialists) Stephen Deed (Information specialist) Amy Crisp (Senior project manager)		
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 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: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
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 11: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).(National Institute for Health and Care Excellence) **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:*

	• UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2006 or later but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as 'Not applicable'. • Studies published before 2006 be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

In people under investigation for asthma, what is the diagnostic test accuracy and clinical and cost-effectiveness of fractional exhaled nitric oxide (FeNO) measures?

Clinical search literature search strategy

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

Table 12: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 28 Dec 2023	Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 28 Dec 2023	Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies Exclusions (conference abstracts, animal studies, letters, comments, editorials, case studies/reports) English language
The Cochrane Library (Wiley)	Cochrane Reviews to 2023 Issue 12 of 12 CENTRAL to 2023 Issue 12 of 12	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 28 Dec 2023	Exclusions (Cochrane reviews) English language

Medline (Ovid) search terms

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

6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case reports/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/
19.	exp Rodentia/
20.	(rat or rats or mouse or mice or rodent*).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language
24.	biological markers/
25.	breath tests/
26.	exhalation/
27.	24 or 25 or 26
28.	Nitric oxide/
29.	27 and 28
30.	Fractional Exhaled Nitric Oxide Testing/
31.	((FE or exhal* or fraction*) adj3 (NO or nitric or nitrogen)).ti,ab,kf.
32.	FENO.ti,ab,kf.
33.	or/29-32
34.	23 and 33
35.	exp "sensitivity and specificity"/
36.	(sensitivity or specificity).ti,ab.
37.	((pre test or pretest or post test) adj probability).ti,ab.
38.	(predictive value* or PPV or NPV).ti,ab.
39.	likelihood ratio*.ti,ab.
40.	likelihood function/
41.	((area under adj4 curve) or AUC).ti,ab.
42.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
43.	gold standard.ab.
44.	exp Diagnostic errors/
45.	(false positiv* or false negativ*).ti,ab.
46.	Diagnosis, Differential/
47.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab.
48.	or/35-47
49.	randomized controlled trial.pt.

50.	controlled clinical trial.pt.
51.	randomi#ed.ab.
52.	placebo.ab.
53.	randomly.ab.
54.	clinical trials as topic.sh.
55.	trial.ti.
56.	or/49-55
57.	Meta-Analysis/
58.	Meta-Analysis as Topic/
59.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
60.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
61.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
62.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
63.	(search* adj4 literature).ab.
64.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
65.	cochrane.jw.
66.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
67.	or/57-66
68.	Epidemiologic studies/
69.	Observational study/
70.	exp Cohort studies/
71.	(cohort adj (study or studies or analys* or data)).ti,ab.
72.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
73.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
74.	Controlled Before-After Studies/
75.	Historically Controlled Study/
76.	Interrupted Time Series Analysis/
77.	(before adj2 after adj2 (study or studies or data)).ti,ab.
78.	exp case control study/
79.	case control*.ti,ab.
80.	Cross-sectional studies/
81.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
82.	or/68-81
83.	34 and (48 or 56 or 67 or 82)

Embase (Ovid) search terms

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

7.	case report/ or case study/
8.	(letter or comment*).ti.
9.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
10.	or/4-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice or rodent*).ti.
20.	or/12-19
21.	3 not 20
22.	limit 21 to English language
23.	*biological marker/
24.	*breath analysis/
25.	*exhalation/
26.	23 or 24 or 25
27.	*nitric oxide/
28.	26 and 27
29.	nitric oxide breathanalyzer/
30.	((FE or exhal* or fraction*) adj3 (NO or nitric or nitrogen)).ti,ab,kf.
31.	FENO.ti,ab,kf.
32.	or/28-31
33.	22 and 32
34.	exp "sensitivity and specificity"/
35.	(sensitivity or specificity).ti,ab.
36.	((pre test or pretest or post test) adj probability).ti,ab.
37.	(predictive value* or PPV or NPV).ti,ab.
38.	likelihood ratio*.ti,ab.
39.	((area under adj4 curve) or AUC).ti,ab.
40.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
41.	diagnostic accuracy/
42.	diagnostic test accuracy study/
43.	gold standard.ab.
44.	exp diagnostic error/
45.	(false positiv* or false negativ*).ti,ab.
46.	differential diagnosis/
47.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab.
48.	or/34-47
49.	Clinical study/
50.	Observational study/

51.	Family study/
52.	Longitudinal study/
53.	Retrospective study/
54.	Prospective study/
55.	Cohort analysis/
56.	Follow-up/
57.	cohort*.ti,ab.
58.	56 and 57
59.	(cohort adj (study or studies or analys* or data)).ti,ab.
60.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
61.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
62.	(before adj2 after adj2 (study or studies or data)).ti,ab.
63.	exp case control study/
64.	case control*.ti,ab.
65.	cross-sectional study/
66.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
67.	or/49-55,58-66
68.	random*.ti,ab.
69.	factorial*.ti,ab.
70.	(crossover* or cross over*).ti,ab.
71.	((doubl* or singl*) adj blind*).ti,ab.
72.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
73.	crossover procedure/
74.	single blind procedure/
75.	randomized controlled trial/
76.	double blind procedure/
77.	or/68-76
78.	Systematic Review/
79.	Meta-Analysis/
80.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
81.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
82.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
83.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
84.	(search* adj4 literature).ab.
85.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
86.	cochrane.jw.
87.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
88.	or/78-87
89.	33 and (48 or 67 or 72 or 88)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Asthma] explode all trees
#2.	asthma*:ti,ab
#3.	#1 or #2
#4.	conference:pt or (clinicaltrials or trialsearch):so
#5.	#3 not #4
#6.	MeSH descriptor: [Biomarkers] this term only
#7.	MeSH descriptor: [Breath Tests] explode all trees
#8.	MeSH descriptor: [Exhalation] this term only
#9.	#6 or #7 or #8
#10.	MeSH descriptor: [Nitric Oxide] explode all trees
#11.	#9 and #10
#12.	MeSH descriptor: [Fractional Exhaled Nitric Oxide Testing] explode all trees
#13.	((FE or exhal* or fraction*) near/3 (NO or nitric or nitrogen)):ti,ab
#14.	FENO:ti,ab
#15.	#11 or #12 or #13 or #14
#16.	#5 and #15

Epistemonikos search terms

1.	(title:("Fractional Exhaled Nitric Oxide" OR FENO OR ((FE OR exhal* OR fraction*) AND (nitric OR nitrogen))) OR abstract:("Fractional Exhaled Nitric Oxide" OR FENO OR ((FE OR exhal* OR fraction*) AND (nitric OR nitrogen))))

Health economic literature search strategy

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

Table 13: Database parameters, filters and limits applied

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

Database	Dates searched	Search filters and limits applied
Embase (OVID)	Health Economics 1 January 2014 – 29 Dec 2023	Health economics studies Quality of life studies Modelling Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 29 Dec 2023	
	Modelling 1974 – 29 Dec 2023	
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 29 Dec 2023	English language

Medline (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/
6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case reports/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/

19.	exp Rodentia/
20.	(rat or rats or mouse or mice or rodent*).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language
24.	quality-adjusted life years/
25.	sickness impact profile/
26.	(quality adj2 (wellbeing or well being)).ti,ab.
27.	sickness impact profile.ti,ab.
28.	disability adjusted life.ti,ab.
29.	(qal* or qtime* or qwb* or daly*).ti,ab.
30.	(euroqol* or eq5d* or eq 5*).ti,ab.
31.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
32.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
33.	(hui or hui1 or hui2 or hui3).ti,ab.
34.	(health* year* equivalent* or hye or hyes).ti,ab.
35.	discrete choice*.ti,ab.
36.	rosser.ti,ab.
37.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
38.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
39.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
40.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
41.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
42.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
43.	or/24-42
44.	exp models, economic/
45.	*Models, Theoretical/
46.	*Models, Organizational/
47.	markov chains/
48.	monte carlo method/
49.	exp Decision Theory/
50.	(markov* or monte carlo).ti,ab.
51.	econom* model*.ti,ab.
52.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
53.	or/44-52
54.	Economics/
55.	Value of life/
56.	exp "Costs and Cost Analysis"/
57.	exp Economics, Hospital/
58.	exp Economics, Medical/

59.	Economics, Nursing/
60.	Economics, Pharmaceutical/
61.	exp "Fees and Charges"/
62.	exp Budgets/
63.	budget*.ti,ab.
64.	cost*.ti.
65.	(economic* or pharmaco?economic*).ti.
66.	(price* or pricing*).ti,ab.
67.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
68.	(financ* or fee or fees).ti,ab.
69.	(value adj2 (money or monetary)).ti,ab.
70.	or/54-69
71.	23 and 43
72.	23 and 53
73.	23 and 70

Embase (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.
7.	case report/ or case study/
8.	(letter or comment*).ti.
9.	(conference abstract or conference paper).pt.
10.	or/4-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice or rodent*).ti.
20.	or/12-19
21.	3 not 20
22.	limit 21 to English language
23.	quality adjusted life year/

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

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

NHS EED and HTA (CRD) search terms

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

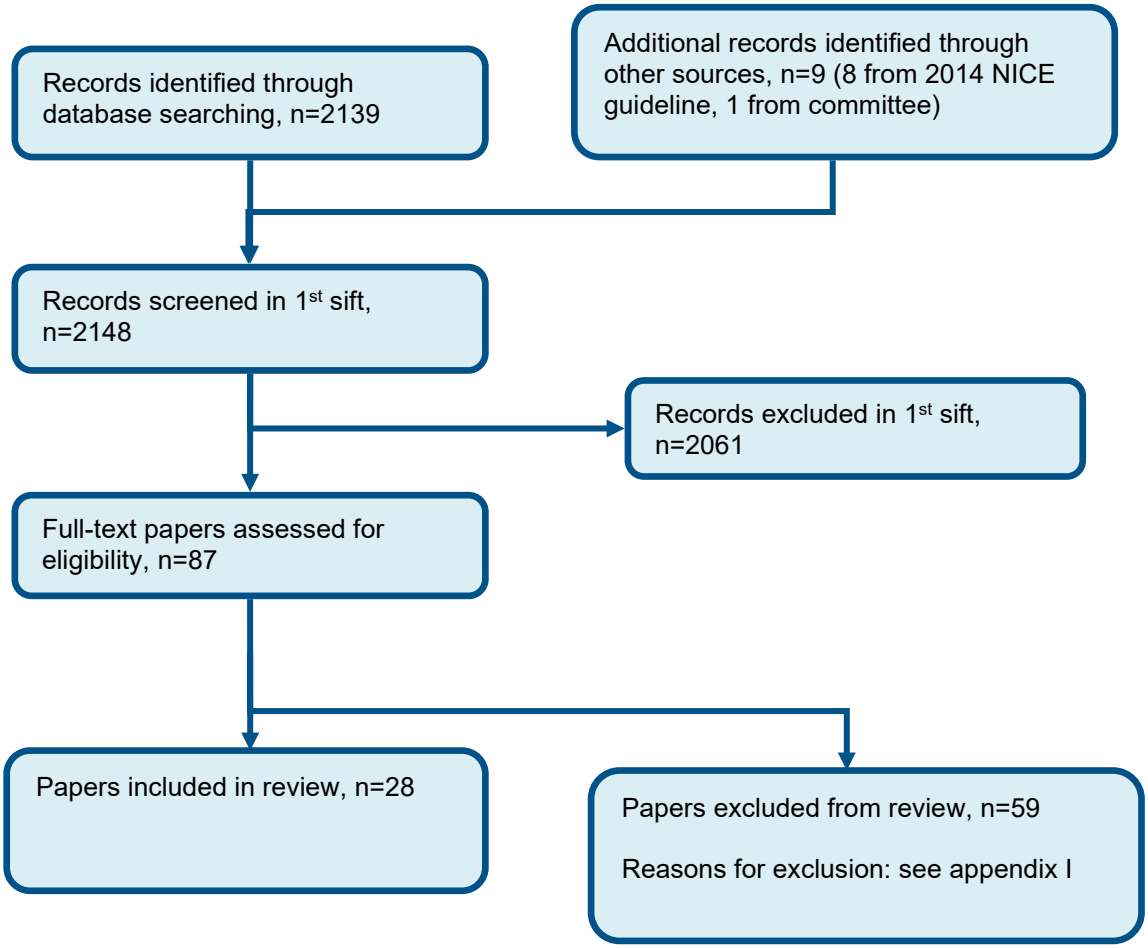
INAHTA search terms

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

Appendix C – Study selection

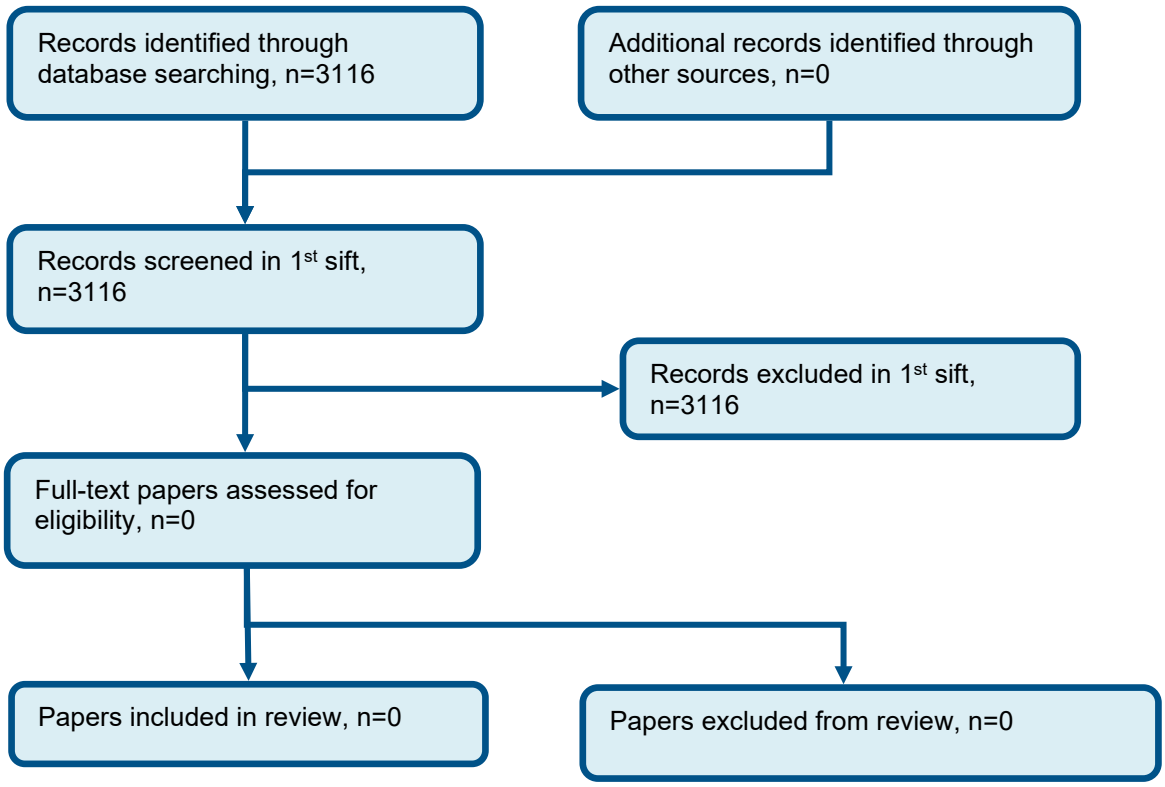
C.1 Diagnostic evidence: Accuracy of FeNO measures

Figure 1: Flow chart of clinical study selection for the review of diagnostic test accuracy of FeNO



C.2 Clinical Evidence: FeNO test and treat

Figure 2: Flow chart of clinical study selection for the review of FeNO diagnosis in asthma



Appendix D –Diagnostic evidence

Accuracy of FeNO measures

Reference	**Bai 2023 (Bai et al., 2023)**
Study type	Cross-sectional diagnostic study
Study methodology	Data source: patients attending the Department of Pulmonary and Critical Care Medicine Recruitment: not reported
Number of patients	n = 283
Patient characteristics	Age, mean (SD): cough variant asthma (CVA); 47.8 (15.9) years, non-cough variant asthma (NCVA); 44.6 (15.2) years Gender (male to female ratio): CVA; 27:44, NCVA; 85:127 Ethnicity: not reported Setting: secondary care Country: China Smoking status: non-smokers Inclusion criteria: >18 years of age, cough lasting at least 8 weeks, normal chest radiograph, FEV1/FVC >70% of predicted and FEV1 >80% of predicted and no corticosteroid use in the past month Exclusion criteria: current smoker or ex-smoker within 2 years, pregnant or lactating, acute upper respiratory tract infection within 8 weeks, use of corticosteroids within a month, or use of montelukast or LABAs within a week, severe cardiac insufficiency, severe liver and kidney insufficiency, mental and cognitive dysfunction, hearing and communication impairment and multiple causes of chronic cough
Target condition(s)	Cough variant asthma or non-asthma chronic cough

<table>
<tr><td>Reference</td><td colspan="5">Bai 2023 (Bai et al., 2023)</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5">Index test
Exhaled nitric oxide was measured using a breath analyser, following ATS/ERS recommendations via a mouthpiece at 50 and 200 mL/s.

Cut-off: >27 ppb (optimal threshold)

Only data from the 50 mL/s tests is included in this review as per the protocol specification

Reference standard
Diagnosis of cough variant asthma in accordance with Chinese national guidelines: chronic cough, often with significant night cough, positive bronchial provocation test and positive response to anti-asthma treatment

Spirometry
Spirometry assessments were made with a spirometer in accordance with the specifications and performance criteria recommended in the ATS/ERS guidelines

Bronchial provocation test
Histamine bronchial provocation tests were performed with the Jaeger APS Pro system by using a nebulizer, following the recommendations of the ATS/ERS. Provocative dose causing a 20% fall in FEV_1 was recorded, and bronchial hyperresponsiveness was defined as present if PD20- FEV_1 <7.8 µmol.

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>Total</td><td rowspan="4">Prevalence= 25.1%</td></tr>
<tr><td></td><td>Index test +</td><td>56</td><td>44</td><td>100</td></tr>
<tr><td></td><td>Index test −</td><td>15</td><td>168</td><td>183</td></tr>
<tr><td></td><td>Total</td><td>71</td><td>212</td><td>283</td></tr>
<tr><td>Statistical measures</td><td colspan="5">Sensitivity: 0.79 (95%CI 0.68-0.88)
Specificity: 0.79 (95%CI 0.73-0.84)
PPV: 56.0%
NPV: 91.8%</td></tr>
<tr><td>Source of funding</td><td colspan="5">Supported by the National Natural Science Foundation of China, the Project of Science and Technology Commission of Shanghai Municipality, the Program of Shanghai Academic Research Leader and the Fund of Shanghai Youth Talent Support Program</td></tr>
</table>

Reference	**Bai 2023 (Bai et al., 2023)**
Limitations	Risk of bias: Very serious risk of bias due to selection bias (unclear recruitment method) and concerns arising from interpretation of the index test and reference standard (unclear if blinded) Indirectness: None
Comments	2x2 data calculated using sensitivity, specificity and prevalence (25.1%) reported in the paper

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

Reference	**Bao 2021 (Bao et al., 2021)**				
Index test(s) and reference standard	Index test Retrospective FeNO data was used for this study. No information on protocol or standards measurements were performed to. Cut-off: 41 ppb (optimal threshold) Reference standard Methacholine challenge testing was used with a cut-off of ≤0.48 mg to indicate airway hyperresponsiveness. Time between measurement of index test and reference standard: Not reported				
2×2 table		Reference standard +	Reference standard −	Total	Prevalence= 24.6%
	Index test +	111	114	225	
	Index test −	59	408	467	
	Total	170	522	692	
Statistical measures	Sensitivity: 0.65 (95%CI 0.58-0.72) Specificity: 0.78 (95%CI 0.74-0.82) PPV: 49% NPV: 87%				
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) 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 (24.6%) data reported in paper				

Reference	**Borhani Fard 2021(Borhani Fard et al., 2021)**
Study type	Cross-sectional
Study methodology	Data source: Lung clinic of Shahid Sadoughi hospital and the occupational medicine clinic of Shahid Rahamoun hospitals. Recruitment: Consecutive people with respiratory signs (cough, shortness of breath and chest tightness)
Number of patients	n = 87

Reference	Borhani Fard 2021(Borhani Fard et al., 2021)
Patient characteristics	Age, mean (SD, range): 34.5 (5.7, 18-77) years Gender (male to female ratio): 52/35 Ethnicity: not specified Setting: Shahid Sadoughi University of Medical Sciences. Country: Iran Smoking status: Non-smokers Inclusion criteria: >18-years of age with at least one of the following respiratory signs: cough, shortness of breath and chest tightness. Exclusion criteria: inability to perform acceptable FeNO or spirometry manoeuvres, smoking or being a former smoker during the past year, occupational respiratory exposure, acute respiratory infection six weeks before the study, chronic lung diseases, consumption of oral or inhaled corticosteroids, NO-releasing drugs (e.g., isosorbide dinitrate, trinitroglycerin, sildenafil, etc.), and treatment with effective medications on leukotriene (montelukast and zafirlukast, etc.). Most common respiratory symptoms were wheezing (72.4%), cough (66.6%), and dyspnoea (63.2%). In addition, 25.2%, 26.4%, and 22.9% of the participants had a history of childhood asthma, allergic rhinitis, and atopy. It is not specified for how long the symptoms had been present.
Target condition	Asthma
Index test(s) and reference standard	**Index test: FeNO** FeNO measurement manoeuvres were performed according to ATS guidelines. To measure FENO, the patients were asked to do a deep inspiration to reach the full capacity of the lung, and then immediately, send out the air through the mouthpiece at a constant speed as much as possible. This was repeated at least three times and the average of the results was recorded. Cut-off: >20.5 – 48.5 ppb (39.5 ppb optimal threshold) **Reference standard** A standard questionnaire, spirometry with bronchodilator administration, and methacholine challenge test were used to diagnose asthma. **Venable questionnaire**

Reference	**Borhani Fard 2021(Borhani Fard et al., 2021)**				
	At first, the subjects with respiratory symptoms were evaluated by the Venable questionnaire, along with a few additional questions about chronic respiratory symptoms, age, sex, employment duration, history of lung diseases and smoking, the presence of respiratory exposures and personal family history of asthma or atopy. At least, three positive answers in the Venable questionnaire could detect asthma or, at least increased responsiveness of the airways. The questionnaire was filled out by the patients under the supervision of a physician. **Spirometry** Spirometry was performed for all patients. **Bronchodilator reversibility** For patients with obstructive pattern in spirometry, the post-bronchodilator test was performed; i.e. 15 min after administration of 400 µg of inhaled Salbutamol, spirometry was performed again in the same condition. Values of the FEV_1 and FVC before and after using a bronchodilator were compared. Patients who responded to bronchodilator according to the ATS guidelines (>12% and >200 mL increase in FEV_1 or FVC) were diagnosed as suffering from asthma. Those who did not respond to bronchodilator therapy were treated with an inhaled corticosteroid, and spirometry was repeated 4-6 weeks later to confirm or reject asthma. **Methacholine challenge** For patients who initially had normal spirometry, a methacholine challenge test was conducted according to the ATS guidelines. For this purpose, a baseline spirometry was performed without medication and when saline and various concentrations of methacholine (from the lowest level) were administered to the subject by a nebulizer. The patient used a nose clip, and spirometry was performed 30 and 90 s after administration of different concentrations of methacholine, and FEV_1 was recorded. If a decline in FEV_1 after each concentration was 20% or more, the same level was assumed as diagnostic level and test was stopped. After 10 min of waiting, spirometry was repeated to confirm or reject the diagnosis. Time between measurement of index test and reference standard: Up to 6 weeks				
2×2 table FeNO >20.5 ppb		Reference standard +	Reference standard −	Total	Prevalence= 80.5%
	Index test +	49	4	53	
	Index test −	21	13	34	
	Total	70	17	87	
2×2 table FeNO >29 ppb		Reference standard +	Reference standard −	Total	
	Index test +	44	2	46	
	Index test −	26	15	41	
	Total	70	17	87	

Reference	Borhani Fard 2021(Borhani Fard et al., 2021)			
2×2 table FeNO >36 ppb		Reference standard +	Reference standard −	Total
	Index test +	37	2	39
	Index test −	33	15	48
	Total	70	17	87
2×2 table FeNO >37.5 ppb		Reference standard +	Reference standard −	Total
	Index test +	36	2	38
	Index test −	34	15	49
	Total	70	17	87
2×2 table FeNO >39.5 ppb		Reference standard +	Reference standard −	Total
	Index test +	34	1	35
	Index test −	36	16	52
	Total	70	17	87
2×2 table FeNO >40.5 ppb		Reference standard +	Reference standard −	Total
	Index test +	31	1	32
	Index test −	39	16	55
	Total	70	17	87
2×2 table FeNO >41.5 ppb		Reference standard +	Reference standard −	Total
	Index test +	30	1	31
	Index test −	40	16	56
	Total	70	17	87
2×2 table FeNO >42.5 ppb		Reference standard +	Reference standard −	Total
	Index test +	29	1	30
	Index test −	41	16	57
	Total	70	17	87
2×2 table FeNO >48.5 ppb		Reference standard +	Reference standard −	Total
	Index test +	21	1	22
	Index test −	49	16	65
	Total	70	17	87

Reference	Borhani Fard 2021(Borhani Fard et al., 2021)
Statistical measures	FeNO >20.5 ppb Sensitivity: 0.70 (95%CI 0.58-0.80) Specificity: 0.76 (95%CI 0.50-0.93) PPV: 92% NPV: 38% FeNO >29 ppb Sensitivity: 0.63 (95%CI 0.50-0.74) Specificity: 0.88 (95%CI 0.64-0.99) PPV: 96% NPV: 37% FeNO >36 ppb Sensitivity: 0.53 (95%CI 0.41-0.65) Specificity: 0.88 (95%CI 0.64-0.99) PPV: 95% NPV: 31% FeNO >37.5 ppb Sensitivity: 0.51 (95%CI 0.39-0.64) Specificity: 0.88 (95%CI 0.64-0.99) PPV: 95% NPV: 31% FeNO >39.5 ppb Sensitivity: 0.49 (95%CI 0.36-0.61) Specificity: 0.94 (95%CI 0.71-1.00) PPV: 97% NPV: 31% FeNO >40.5 ppb Sensitivity: 0.44 (95%CI 0.32-0.57) Specificity: 0.94 (95%CI 0.71-1.00) PPV: 97% NPV: 29% FeNO >41.5 ppb

Reference	Borhani Fard 2021(Borhani Fard et al., 2021)
	Sensitivity: 0.43 (95%CI 0.31-0.55) Specificity: 0.94 (95%CI 0.71-1.00) PPV: 97% NPV: 29% FeNO >42.5 ppb Sensitivity: 0.41 (95%CI 0.30-0.54) Specificity: 0.94 (95%CI 0.71-1.00) PPV: 97% NPV: 28% FeNO >48.5 ppb Sensitivity: 0.30 (95%CI 0.20-0.42) Specificity: 0.94 (95%CI 0.71-1.00) PPV: 95% NPV: 25%
Source of funding	Not specified
Limitations	Risk of bias: No concerns Indirectness: No concerns
Comments	2x2 data calculated using sensitivity, specificity and prevalence (80.5%) reported in the paper

Reference	Chatkin 1999 (Chatkin et al., 1999)
Study type	Cross sectional observational study
Study methodology	Data source: Data collected for this study Recruitment: Consecutive adults refereed to an asthma outpatient clinic or tertiary referral centre with chronic cough
Number of patients	n = 61
Patient characteristics	Age, mean (SD): 41 (12) years; chronic cough non-asthma: 47 (15) years; healthy controls: 38 (8) years Gender (male to female ratio): chronic cough 11:27, controls 8:15 Ethnicity: not reported

Reference	Chatkin 1999 (Chatkin et al., 1999)
	Setting: asthma centre (tertiary referral centre) or affiliated community respiratory clinics Country: Canada Smoking status: Non-smokers Inclusion criteria: chronic cough (>3 weeks) of unknown cause referred for diagnosis; normal CXR and FEV_1 >80% predicted Exclusion criteria: use of codeine or any other medication for chronic cough, upper respiratory infection within 4 weeks; use of corticosteroids within 6 weeks; current smoking; any significant medical conditions; contraindications to methacholine challenge.
Target condition(s)	Asthma diagnosis vs. chronic cough non-asthma
Index test(s) and reference standard	Index test: FeNO A chemiluminescent NO analyser was used. Participants were seated, and inserted a mouthpiece and inhaled to total lung capacity from a reservoir of compressed air that contained <1 ppb NO. The subject then exhaled via a high resistance and maintained a mouth pressure of 20 mm Hg, which was displayed on a pressure gauge. The resultant expiratory flow was 45 ml/s. The steady-state NO plateau was taken as the ENO value. Repeated exhalations were performed to achieve three ENO values that agreed at the 5% level. Optimal cut-off: >30 ppb (optimal threshold) Reference standard The clinical diagnosis of asthma was made by an experienced respiratory physician using a diagnostic algorithm without access to FeNO measurements. Each participants underwent a standard clinical assessment, which included history and physical examination, medical questionnaire, laboratory tests and chest roentgenogram, spirometry before and after bronchodilator, allergy skin testing to 12 common allergens, and methacholine challenge. **Bronchodilator response** Participants who's FEV_1 increased by ≥12% and 200 mL 15 minutes after receiving 360 mcg salbutamol were considered to have asthma and were not subjected to the methacholine challenge. **Methacholine challenge** Participants who did not demonstrate a bronchodilator response underwent a methacholine challenge. Participants were considered to have asthma if their PC20 FEV_1 was ≤8 mg/mL. **Skin prick test** Participants were considered atopic if they had at least one positive skin prick test.

Reference	**Chatkin 1999 (Chatkin et al., 1999)**				
	Time between measurement of index test and reference standard: Not stated				
2×2 table		Reference standard +	Reference standard −	Total	Prevalence= 21.1%
	Index test +	6	4	10	
	Index test −	2	26	28	
	Total	8	30	38	
Statistical measures	Sensitivity: 0.75 (95%CI 0.35-0.97) Specificity: 0.87 (95%CI 0.69-0.96) PPV: 60% NPV: 93%				
Source of funding	Primary author received a grant from CAPES				
Limitations	Risk of bias: No concerns Indirectness: Downgraded by one increment due to index test indirectness – flow rate of 45 mL/s used, not 50 mL/s as specified in this review protocol				

Reference	**Cordeiro 2011 (Cordeiro et al., 2011)**
Study type	Cross sectional observational study
Study methodology	Data source: Routine prospective database Recruitment:
Number of patients	n = 114
Patient characteristics	Age, median (range): Asthma: 39 (range 7-83); non-asthma 38 (7-87) Gender (male to female ratio): 43:71 Smoking status: Not reported Ethnicity: Not reported

Reference	Cordeiro 2011 (Cordeiro et al., 2011)
	Setting: General outpatient allergy clinic Country: The Netherlands Inclusion criteria: New referrals to outpatient allergy clinic Exclusion criteria: Patients using inhaled corticosteroids or oral corticosteroids within 6 weeks
Target condition(s)	Asthma diagnosis vs non-asthma
Index test(s) and reference standard	Index test FeNO was measured online at a constant flow rate of 50 mL/s in accordance with the ATS/ERS guideline. All FeNO tests were performed before any other tests. Optimal cut-off: >27 ppb (optimal threshold) Reference standard The clinical assessment of the diagnosis of asthma was based on a history of typical respiratory symptoms and an FEV_1 improvement of 12% and 200 mL or PC20 histamine of 8 mg/mL, according to the GINA guidelines. **Questionnaire** All patients had to complete a standardised questionnaire at their first visit and allergic symptoms were scored. Symptoms were divided into nasal and ocular complaints (rhinorrhea, watery eyes, nasal itching, sneezing, headache, facial pain, loss of smell, and nasal blockage), pulmonary complaints (wheezing, coughing, shortness of breath, and exercise intolerance), skin complaints (rash, pruritus, and urticaria), and general complaints (fatigue and nausea). **Skin prick test/IgE** Atopic status was assessed with skin-prick test or determination of specific plasma IgE in patients with eczema or other skin conditions. All subjects were tested for a panel of eight common inhalant allergens: house-dust mite; dog, cat, and horse dander; Aspergillus fumigatus; mugwort; and birch and grass pollen. Skin prick test cutaneous response was compared with a histamine-positive control and a saline solution. An skin prick test was considered positive when a wheal diameter of 3 mm was recorded after 15 minutes. IgE and specific plasma IgE were determined with a solid-phase two-step chemiluminescent immunoassay. Eosinophilic leukocytes were determined using a hematocytometer with VCS detection. **Spirometry and bronchodilator reversibility**

Reference	**Cordeiro 2011 (Cordeiro et al., 2011)**				
	Lower airways obstruction was determined with FEV_1 measurement. FEV_1 was determined by standard spirometry before and 15 minutes after inhalation of salbutamol (400 mcg). **Histamine challenge** When a participants' history was suspect for asthma, a PC20 histamine challenge was performed before the second outpatient visit within 6 weeks. In the inhalation challenge test, histamine was administered according to a standardised tidal breathing method. Time between measurement of index test and reference standard: 6 weeks				
2×2 table		Reference standard +	Reference standard −	Total	Prevalence= 36.8%
	Index test +	33	6	39	
	Index test −	9	66	75	
	Total	42	72	114	
Statistical measures	Sensitivity: 0.79 (95%CI 0.63-0.90) Specificity: 0.92 (95%CI 0.83-0.97) PPV: 86% NPV: 87%				
Source of funding	Asthma diagnosis vs. non-asthma				
Limitations	Risk of bias: No concerns Indirectness: Downgraded by two increments due to population (mixed children/young people and adults, and smoking status not reported) indirectness				

Reference	**Eom 2020 (Eom et al., 2020)**
Study type	Prospective study
Study methodology	Data source: children aged 6-18 years referred for evaluation of possible asthma. Recruitment: consecutive
Number of patients	n = 275
Patient characteristics	Age, mean (range): for non-asthmatics 11.5 (10.7-12.3); asthmatics 11.6 (11.1-12.1) Gender (male to female ratio): 180/95 Height (m): non-asthmatics 1.44 (1.41-1.48); asthmatics 1.47 (1.44-1.49)

Reference	Eom 2020 (Eom et al., 2020)
	Exposure to cigarette smoke (%): non-asthmatics 45.2; asthmatics 40.6 Ethnicity: not specified Setting: out-patient clinic, Chungbuk National University Hospital, Cheongju Country: South Korea Inclusion criteria: Children presenting with respiratory symptoms including cough, wheezing, or breathlessness for at least 1 month duration. Exclusion criteria: Individuals with symptoms of respiratory tract infection or those with other systemic or inflammatory disease were not included in the study. All of included patients did not receive inhaled short-acting β2-agonists for at least 8 hours and were also not receiving a regular treatment with controller medications for 1 month or more before evaluation of FeNO and lung function.
Target condition	Asthma
Index test(s) and reference standard	**Index test: FeNO** FeNO was measured using a NO analyzer with electrochemical sensors, according to the ATS/ERS guidelines. Participants were instructed to avoid eating, drinking and exercise 2 hours before FeNO measurements. Participants exhaled at a 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 taken if there was a >10% difference between the first two measurements. Cut-off: >19.6 ppb (optimal threshold) **Reference standard** Asthma was assessed by a paediatric pulmonologist after at least 6 months of follow-up. The diagnosis of asthma was determined according to the GINA 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 in addition to spirometry with bronchodilator reversibility **Spirometry and bronchodilator reversibility** Lung function was measured by a spirometer according to the ATS/ERS recommendations. FVC, FEV_1, FEF25-75 and FEV_1 /FVC were obtained from the best of three reproducible forced expiratory manoeuvres. Bronchodilator response was measured 15 minutes after administration of four puffs (400 µg) of salbutamol using metered dose inhaler with a spacer according to ATS/ERS guidelines Time between measurement of index test and reference standard: at least 6 months

Reference	**Eom 2020 (Eom et al., 2020)**				
2×2 table		Reference standard +	Reference standard −	Total	Prevalence= 69.1%
	Index test +	121	14	136	
	Index test −	68	71	139	
	Total	190	85	275	
Statistical measures	Sensitivity: 0.64 (95%CI 0.57-0.71) Specificity: 0.83 (95%CI 0.74-0.91) PPV: 90% (95%CI 84-93) NPV: 50% (95%CI 45-56)				
Source of funding	Not specified				
Limitations	Risk of bias: No concerns Indirectness: Downgraded by one increment due to index test (cut-off below 20 ppb, protocol specified 20-50 ppb) indirectness				
Comments	2x2 data calculated from sensitivity, specificity and prevalence (69.1%) data reported in paper				

Reference	**Fortuna 2007 (Fortuna et al., 2007)**
Study type	Prospective cross-sectional diagnostic study
Study methodology	Data source: Consecutive patients referred to respiratory medicine outpatient clinic for asthma diagnosis Recruitment: Consecutive
Number of patients	n = 50
Patient characteristics	Age, mean (range): asthma diagnosis: 38 (18-64), non-asthma diagnosis: 37 (18-68) years Gender (male to female ratio): 21:29 Ethnicity: Not reported Smoking status: 14% current smokers Atopy: Mean induced sputum eosinophil count: 3.16% Setting: Secondary care

<table>
<tr><td>Reference</td><td colspan="5">Fortuna 2007 (Fortuna et al., 2007)</td></tr>
<tr><td></td><td colspan="5">Country: Spain

Inclusion criteria: patients referred to hospital-based respiratory medicine outpatient clinic for diagnosis with a clinical history suggestive of asthma (dry cough, wheezing, and shortness of breath)

Exclusion criteria: patients with conditions that could affect FeNO or Eos% measurement for reasons other than asthma: subjects with symptoms of respiratory tract infection in the previous 6 weeks or with systemic manifestations of atopy (rash, digestive symptoms, etc.) and patients who had received treatment with inhaled or oral corticosteroids in the last 4 weeks</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"><u>Index test</u>
FeNO measurement was performed with a conventional chemoluminescence analyser according to ATS/ERS guidelines. The standardised single breath technique was used; each patient inhaled to total lung capacity once and then exhaled at a constant flow rate of 50 mL/s for approximately 10 s. A resistance with a pressure above 5–20 cm H2O was provided to ensure velum closure and to exclude contamination from nasal NO. The mean value of FENO from three technically valid measurements was recorded.

Cut-off: >19 ppb (pre-specified)

<u>Reference standard</u>
A subject who presented with a clinical history suggestive of asthma and a positive methacholine challenge test was diagnosed with asthma. The methacholine challenge was performed according to international guidelines as a dose–response test of increasing doses of methacholine chloralhydrate (0.1–32 mg/mL) every 5 min. The test was stopped when the highest concentration (32 mg/mL) was tolerated, or if a fall of 20% in FEV1 from baseline was induced after methacholine was inhaled. A methacholine challenge test was considered positive if the PD20 was ≤16 mg/mL.

Time between measurement of index test and reference standard: 1 day</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">Prevalence= 44%</td></tr>
<tr><td></td><td>Index test +</td><td>17</td><td>10</td><td>27</td></tr>
<tr><td></td><td>Index test −</td><td>5</td><td>18</td><td>23</td></tr>
<tr><td></td><td>Total</td><td>22</td><td>28</td><td>50</td></tr>
<tr><td>Statistical measures</td><td colspan="5"><u>Index text</u>
Sensitivity: 0.77 (95%CI 0.55-0.92)
Specificity: 0.64 (95%CI 0.44-0.81)
PPV: 63%
NPV: 78%</td></tr>
</table>

Reference	**Fortuna 2007 (Fortuna et al., 2007)**
Source of funding	None reported
Limitations	Risk of bias: Downgraded by one increment due to concerns arising from the interpretation of the index test and reference standard (unclear if blinded) Indirectness: Downgraded by two increments due to population (mixed smoking and non-smoking participants) and index test (cut-off below 20 ppb, protocol specified 20-50 ppb) indirectness
Comments	Sensitivity and specificity calculated from reported 2x2 tables

Reference	**Fukuhara 2011 (Fukuhara et al., 2011)**
Study type	Cross sectional study
Study methodology	Data source: Not reported Recruitment: Not reported
Number of patients	n = 61
Patient characteristics	Age, mean (range): 55.6 (17-81) years Gender (male to female ratio): 31:30 Ethnicity: Not reported Smoking status: Not reported Setting: Outpatients from the Department of Pulmonary Medicine University Hospital Country: Japan Inclusion criteria: At least 1 of the subjective symptoms: recurrent cough, wheezing or dyspnoea (including chest tightness) Exclusion criteria: Prior history of asthma, taking oral or inhaled steroids or anti-leukotriene agents
Target condition(s)	Asthma
Index test(s) and reference standard	Index test: FeNO FeNO was measured using the online method in accordance with ATS/ERS recommendations using a chemiluminescence analyser. Measurement was performed with the patient in a sitting position, after resting ventilation, and without a nose clip. While mouth pressure

Reference	Fukuhara 2011 (Fukuhara et al., 2011)
	was being monitored, the patient was asked to exhale for 10 seconds at a constant mouth pressure of 16 cm H2O and a flow of 50 mL/s. The FeNO level was recorded once FeNO concentrations reached a constant level on the monitor. The FeNO level was measured 3 times, with differences in measured values within 10%. The means of 3 measurements were used as data for statistical analysis. FeNO levels were measured before examination of pulmonary function and airway hyperresponsiveness and induced sputum testing. Bronchial asthma was diagnosed using FeNO-based criteria when (1) at least 1 of the subjective symptoms of recurrent cough, wheezing, and dyspnea was present; (2) FeNO level was 40 ppb or higher; and (3) other diseases were ruled out in the same manner as with conventional criteria. Cut-off: >39 ppb (pre-specified) <u>Reference standard</u> Bronchial asthma was diagnosed with the conventional criteria when (1) at least 1 of the subjective symptoms of recurrent cough, wheezing, and dyspnea was present; (2) at least 2 of the 3 criteria of induced sputum eosinophilia, airway hyperresponsiveness, and reversible airway obstruction were satisfied; and (3) other diseases were ruled out using chest radiography, computed tomography, and other laboratory tests **Spirometry and bronchodilator reversibility** Pulmonary function was measured using rolling seal spirometers to measure FVC and FEV1. Tests were performed by experienced respiratory technicians according to ATS guidelines. For airway reversibility testing, reversibility was defined as a change in FEV1 of 200 mL or greater and 12% or greater from baseline before and after inhalation of a short-acting beta-2-agonist or from initial presentation to weeks 2 through 4 of treatment with an inhaled steroid or bronchodilator. **Methacholine challenge** Airway responsiveness to inhaled methacholine was measured using the Astrograph method. The participant began by inhaling physiologic saline as a control and then inhaled methacholine diluted in physiologic saline at concentrations of 49, 98, 195, 390, 781, 1,563, 3,125, 6,250, and 12,500 mcg/mL, increasing minute. Airway resistance was continuously measured and used to plot a dose-response curve of methacholine concentrations and airway resistance. The dose of methacholine at which airway resistance began to rise was calculated as a marker of airway hyperresponsiveness. Positive airway hyperresponsiveness was defined as a value less than 12.5 U. **Induced sputum** The participant first inhaled 5 mL of 5% hypertonic saline using an ultrasonic nebulizer. Sputum samples were stained with Papanicolaou stain and observed by microscopy. Observers were experienced technicians masked to clinical information. Sputum samples were judged as adequate if alveolar macrophages were present and the percentage of squamous cells was less than 10%. A total of 400 cells were counted on each slide. Eosinophilia was defined as an eosinophil count of 3% or greater of the total cell count.

Reference	**Fukuhara 2011 (Fukuhara et al., 2011)**				
	Blood tests Blood tests included measurement of peripheral blood eosinophil count, serum nonspecific IgE levels, and antigenspecific IgE levels. The CAP radioallergosorbent fluoroimmunoassay test for antigen specific IgE was performed for weeds, mites, house dust, cats, dogs, cedar, cypress, orchard grass, moths, Aspergillus, Candida, and mixed molds. Nonspecific IgE level was measured using a fluorescence enzyme immunoassay. If either the nonspecific IgE concentration was 250 IU/mL or greater or any specific IgE test result was positive (≥0.69 UA/mL), the patient was considered to be atopic. Time between measurement of index test and reference standard: Up to 4 weeks				
2×2 table		Reference standard +	Reference standard −	Total	Prevalence= 68.9%
	Index test +	33	2	35	
	Index test −	9	17	26	
	Total	42	19	61	
Statistical measures	Sensitivity: 0.79 (95%CI 0.63-0.90) Specificity: 0.89 (95%CI 0.67-0.99) PPV: 94.3% NPV: 65.4%				
Source of funding	Not stated				
Limitations	Risk of bias: Downgraded by one increment due to concerns arising from the method of participant selection (method not reported) Indirectness: Downgraded by one increment due to population (smoking status not reported) indirectness				

Reference	**He 2018 (He et al., 2018)**
Study type	Prospective study
Study methodology	Data source: Outpatients who visited hospital for the first time for the evaluation of suspected asthma from October 2014 to June 2015. Recruitment: Consecutive
Number of patients	n = 400 (265 of which were eventually diagnosed with asthma)
Patient characteristics	Age, mean (SD): asthma 44.4 (12.3); non-asthma 43.4 (10.9); range: 18 to 72 years Gender (male to female ratio): 132/268 Ethnicity: not specified

Reference	He 2018 (He et al., 2018)
	Height (SD) (cm): asthma 159 (8.2); non-asthma 157.3 (7.6) Atopy (%) in Asthma patients 164 (61.9); in non-asthma patients 39 (28.9) Setting: Outpatient respiratory department Country: China Smoking status: Not reported Inclusion criteria: Outpatients who visited hospital for the first time for the evaluation of suspected asthma from October 2014 to June 2015. Exclusion criteria: Patients were excluded when they presented with one of the following: (i) upper respiratory tract infection during four weeks before visit; (ii) severe cardiovascular diseases such as fatal arrhythmia and myocardial infarction; (iii) other severe pulmonary diseases with an influence in lung function including but not limited to severe pneumonia, bronchiectasis, emphysema, pneumothorax, pulmonary fibrosis, allergic bronchopulmonary aspergillosis, tuberculosis and lung cancer; or (iv) refusing FeNO, BPT or BDT measurements.
Target condition	Asthma
Index test(s) and reference standard	Index test: FeNO FeNO concentration was measured by chemiluminescence using an NO monitor at an expiratory flow rate of 50 ml/sec, which was performed at least twice until at least two NO plateau values were obtained within 10 per cent of each other. FeNO measurements were performed prior to spirometry measurements. Cut-off: >23.5 ppb (optimal threshold) Reference standard The diagnostic criteria of asthma included: (i) a history of recurrent wheeze, shortness of breath, chest tightness, and cough ≥3 months; (ii) positive BPT or BDT; and (iii) obvious alleviation of symptoms after treatment with ICS or plus long-acting beta2 agonist for a month **Spirometry** Spirometry was performed three or more times until three acceptable spirograms have been obtained when the two largest values of FVC/FEV_1 were within 0.150 L of each other **Methacholine challenge**

Reference	**He 2018 (He et al., 2018)**
	If FEV_1 was ≥70% of predicted, a bronchial provocation test was performed with methacholine, and the cumulative methacholine dosage with a 20 per cent decrease in FEV_1 (PD20) was recorded. **Bronchodilator reversibility** If FEV_1 was <70% of predicted, bronchodilator reversibility testing was conducted with a positive cut-off of an increase in FEV_1 >12% and >200 mL from baseline. Time between measurement of index test and reference standard: not specified

2×2 table

	Reference standard +	Reference standard −	Total	Prevalence= 66.3%
Index test +	212	61	273	
Index test −	53	74	127	
Total	265	135	400	

Statistical measures	Sensitivity: 0.80 (95%CI 0.75-0.85) Specificity: 0.55 (95%CI 0.46-0.63) PPV: 77.9% NPV: 58.1%
Source of funding	None
Limitations	Risk of bias: Downgraded by one increment due to concerns arising from the interpretation of the index test and reference standard (unclear if blinded) Indirectness: Downgraded by two increments due to population (ICS use and smoking status not reported) indirectness
Comments	2x2 data calculated from sensitivity, specificity and prevalence (66%) data reported in paper

Reference	**Heffler 2006 (Heffler et al., 2006)**
Study type	Prospective study
Study methodology	Data source: Collected for this study Recruitment: Consecutive people with persistent rhinitis and asthma-like symptoms
Number of patients	n = 48
Patient characteristics	Age, mean (range): Asthma: 42.33 (17-69); non-asthma: 38.73 (11-75) Gender (male to female ratio): 21:27

Reference	**Heffler 2006 (Heffler et al., 2006)**				
	Ethnicity: Not reported Setting: Allergy outpatient clinics Country: Italy Smoking status: Non-smokers Inclusion criteria: Patients referred to allergy department for diagnostic evaluation of persistent rhinitis and asthma-like lower airways symptoms (cough, dyspnoea, chest tightness and wheezing) during the last 2 months Exclusion criteria: Use of steroids or any other anti-inflammatory medications in last 2 months, current smoking (in previous 12 months), previous diagnosis of asthma, respiratory infection in last 6 weeks				
Target condition(s)	Asthma				
Index test(s) and reference standard	Index test: FeNO Exhaled NO concentration (FENO) was measured using a chemiluminescence analyser. The online single exhalation technique with exhalation rate 50 ml/s and positive expiratory mouth pressure of 10 cm H2O was applied. The mean FeNO of three acceptable last 3 s end-expiratory plateau measurements was calculated. Cut-off: >20-50 (36 ppb optimal threshold) Reference standard The diagnosis of asthma was based on typical symptoms and on a positive bronchodilator response (≥12% improvement in FEV1 in response to salbutamol) or methacholine challenge test result (PD20 FEV1 ≤800 mcg) No information on protocols applied for bronchodilator reversibility or methacholine challenge testing. Time between measurement of index test and reference standard: Same time				
2×2 table FeNO >20 ppb		Reference standard +	Reference standard −	Total	Prevalence= 37.5%
	Index test +	18	20	38	
	Index test −	0	10	10	
	Total	18	30	48	
2×2 table		Reference standard +	Reference standard −	Total	

Reference	**Heffler 2006 (Heffler et al., 2006)**			
FeNO >25 ppb	Index test +	18	16	34
	Index test −	0	14	14
	Total	18	30	48
2×2 table FeNO >30 ppb		Reference standard +	Reference standard −	Total
	Index test +	14	15	29
	Index test −	4	15	19
	Total	18	30	48
2×2 table FeNO >34 ppb		Reference standard +	Reference standard −	Total
	Index test +	14	14	28
	Index test −	4	16	20
	Total	18	30	48
2×2 table FeNO >36 ppb		Reference standard +	Reference standard −	Total
	Index test +	14	12	26
	Index test −	4	18	22
	Total	18	30	48
2×2 table FeNO >40 ppb		Reference standard +	Reference standard −	Total
	Index test +	11	11	22
	Index test −	7	19	26
	Total	18	30	48
2×2 table FeNO >45 ppb		Reference standard +	Reference standard −	Total
	Index test +	11	8	19
	Index test −	7	22	29
	Total	18	30	48
2×2 table FeNO >50 ppb		Reference standard +	Reference standard −	Total
	Index test +	10	7	17
	Index test −	8	23	31
	Total	18	30	48

Reference	Heffler 2006 (Heffler et al., 2006)
Statistical measures	FeNO >20 ppb Sensitivity: 1.00 (95%CI 0.81-1.00) Specificity: 0.33 (95%CI 0.17-0.53) PPV: 47% NPV: 100% FeNO >25 ppb Sensitivity: 1.00 (95%CI 0.81-1.00) Specificity: 0.47 (95%CI 0.28-0.66) PPV: 53% NPV: 100% FeNO >30 ppb Sensitivity: 0.78 (95%CI 0.52-0.94) Specificity: 0.50 (95%CI 0.31-0.69) PPV: 48% NPV: 79% FeNO >34 ppb Sensitivity: 0.78 (95%CI 0.52-0.94) Specificity: 0.53 (95%CI 0.34-0.72) PPV: 50% NPV: 80% FeNO >36 ppb Sensitivity: 0.78 (95%CI 0.52-0.94) Specificity: 0.60 (95%CI 0.41-0.77) PPV: 54% NPV: 82% FeNO >40 ppb Sensitivity: 0.61 (95%CI 0.36-0.83) Specificity: 0.63 (95%CI 0.44-0.80) PPV: 50% NPV: 73% FeNO >45 ppb

Reference	Heffler 2006 (Heffler et al., 2006)
	Sensitivity: 0.61 (95%CI 0.36-0.83) Specificity: 0.73 (95%CI 0.54-0.88) PPV: 58% NPV: 76% FeNO >50 ppb Sensitivity: 0.56 (95%CI 0.31-0.78) Specificity: 0.77 (95%CI 0.58-0.90) PPV: 59% NPV: 74%
Source of funding	Regione Peimonte-Ricerca Sanitaria Finalizzata 2003
Limitations	Risk of bias: No concerns Indirectness: Downgraded by one increment due to population (mixed children/young people and adults) indirectness

Reference	Jerzynska 2014 (Jerzynska et al., 2014)
Study type	Retrospective cross-sectional study
Study methodology	Data source: prospective data from medical documentation of 1767 children with symptoms of allergic diseases such as asthma and/or allergic rhinitis, attending the Allergic Outpatient Clinic (Medical university of Lodz) from January 2005 to December 2012 Recruitment: not specified
Number of patients	n = 1767
Patient characteristics	Age, mean (SD, range): 11.2 (6.3; 6-18) years Gender (male to female ratio): 1048/719 Ethnicity: not specified Setting: Allergic Outpatient Clinic Country: Poland Inclusion criteria: children aged 6-18 years with symptoms of allergic diseases such as asthma and/or allergic rhinitis; and who had the following tests done during diagnostic procedures: FeNO, spirometry (to exclude bronchoconstriction), specific IgE results

<table>
<tr><td>Reference</td><td colspan="5">Jerzynska 2014 (Jerzynska et al., 2014)</td></tr>
<tr><td></td><td colspan="5">Exclusion criteria: chronically treated with inhaled corticosteroids and/or leukotriene inhibitors</td></tr>
<tr><td>Target condition</td><td colspan="5">Asthma</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5">Index test: FeNO
The NO measurements were performed according to the ERS/ATS recommendations, with a chemiluminescence analyser. All participants were tested in a sitting position, without wearing a nose clip. The subjects exhaled at a constant flow rate (50 mL/s) from total lung capacity to residual volume without breath holding. They maintained a constant mouth pressure (17 cm H2O) by monitoring a visual display in order to eliminate contamination from nasal NO. Dead space and nasal NO (which are reflected by the NO concentration peak during exhalation) and NO from the lower respiratory tract (determined by the plateau value after the peak) were recorded automatically. Three FeNO measurements of the plateau phase were obtained, with less than 10% variation. The mean value of 3 successive, reproducible recordings was retained for statistical analysis.

Cut-off: >23 ppb (optimal threshold)

Reference standard
The diagnosis of asthma, allergic rhinitis were universally established by the allergist doctors (different allergist than in retrospective time was seeing the patients in real time and was assessing the asthma diagnoses in the charts) according to standard definitions of diseases in the latest guidelines by GINA and WHO. Diagnosis of asthma was universally established by symptoms of asthma, the findings on physical examination of the respiratory system, and improvement in the pre-bronchodilator FEV_1 >12% after administration of salbutamol (200 µg) in all participants

Time between measurement of index test and reference standard: 3 years</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">Prevalence= 59.6%</td></tr>
<tr><td></td><td>Index test +</td><td>948</td><td>342</td><td>1290</td></tr>
<tr><td></td><td>Index test −</td><td>105</td><td>371</td><td>476</td></tr>
<tr><td></td><td>Total</td><td>1053</td><td>713</td><td>1767</td></tr>
<tr><td>Statistical measures</td><td colspan="5">Sensitivity: 0.90 (95%CI 0.88-0.98)
Specificity: 0.52 (95%CI 0.48-0.56)
PPV: 25% (95%CI 16-37)
NPV: 97% (95%CI 88-99)</td></tr>
<tr><td>Source of funding</td><td colspan="5">Study self-funded</td></tr>
<tr><td>Limitations</td><td colspan="5">Risk of bias: Downgraded by one increment due to concerns arising from in the interpretation of the index test and reference standard (unclear if blinded)</td></tr>
</table>

Reference	**Jerzynska 2014 (Jerzynska et al., 2014)**
	Indirectness: Downgraded by two increments due to population (mixed children/young people and adults, and smoking status not reported) and reference standard (confirmation of asthma diagnosis made after 3 years of treatment) indirectness
Comments	2x2 data calculated from sensitivity, specificity and prevalence (59.6%) data reported in paper

Reference	**Katsoulis 2013 (Katsoulis et al., 2013)**
Study type	Prospective cross-sectional study
Study methodology	Data source: Patients admitted to outpatient clinics of an Army General Hospital and University Hospital who had given at least one positive answer for respiratory symptoms related to asthma on a questionnaire based on the European Community Respiratory Health Survey (12-item questionnaire, considering symptoms such as wheezing, coughing, tightness, shortness of breath, allergies, use of reliever medication and history of possible asthma attacks) Recruitment: Not reported
Number of patients	n = 112
Patient characteristics	Age, mean (range): 25 (22-37) Gender (male to female ratio): 95:17 Ethnicity: Not reported Setting: Outpatient clinics (secondary care) Country: Greece Smoking status: Mixed (37 smokers) Inclusion criteria: Reported at least one symptom on a questionnaire based on the European Community Respiratory Health Survey Exclusion criteria: Previous diagnosis of asthma, treated with asthma-related medication (ICS, LABA or LTRA), positive bronchodilator response (≥12% and 200 mL response to salbutamol), respiratory infection in the last 8 weeks and recent smoking quitters
Target condition	Bronchial hyperresponsiveness to methacholine
Index test(s) and reference standard	Index test: FeNO FeNO was measured using a portable nitric oxide analyser that provided measurements at 50 ml/s exhalation flow rate. FeNO was measured in the morning between 08.00 and 10.00 a.m in all participants

Reference	**Katsoulis 2013 (Katsoulis et al., 2013)**				
	Cut-offs: 10-32 ppb (pre-specified range 10-30, 32 ppb optimal threshold) *Only cut-offs ≥20 ppb included in this review (protocol specified cut-offs between 20-50 ppb)* <u>Reference standard</u> Bronchial hyperresponsiveness to methacholine was deemed positive with a value of PD20 ≤4 µmol Time between measurement of index test and reference standard: One day				
2×2 table FeNO >20 ppb full population		Reference standard +	Reference standard −	Total	Prevalence= 42.9%
	Index test +	31	26	57	
	Index test −	17	38	55	
	Total	48	64	112	
2×2 table FeNO >25 ppb full population		Reference standard +	Reference standard −	Total	
	Index test +	25	16	41	
	Index test −	23	48	71	
	Total	48	64	112	
2×2 table FeNO >30 ppb full population		Reference standard +	Reference standard −	Total	
	Index test +	23	12	35	
	Index test −	24	53	77	
	Total	48	64	112	
2×2 table FeNO >32 ppb full population		Reference standard +	Reference standard −	Total	
	Index test +	23	11	34	
	Index test −	25	53	78	
	Total	48	64	112	
2×2 table FeNO >20 ppb smokers		Reference standard +	Reference standard −	Total	Prevalence= 45.9%
	Index test +	5	5	10	
	Index test −	12	15	27	
	Total	17	20	37	
2×2 table		Reference standard +	Reference standard −	Total	
	Index test +	3	2	5	

Reference	**Katsoulis 2013 (Katsoulis et al., 2013)**				
FeNO >25 ppb smokers	Index test −	14	18	32	
	Total	17	20	37	
2×2 table FeNO >30 ppb smokers		Reference standard +	Reference standard −	Total	
	Index test +	2	1	3	
	Index test −	15	19	34	
	Total	17	20	37	
Statistical measures	**Full population** Index test: FeNO >20 ppb Sensitivity: 0.65 (95%CI 0.49-0.78) Specificity: 0.59 (95%CI 0.46-0.71) PPV: 54% NPV: 69% Index test: FeNO >25 ppb Sensitivity: 0.52 (95%CI 0.37-0.67) Specificity: 0.75 (95%CI 0.63-0.85) PPV: 61% NPV: 68% Index test: FeNO >30 ppb Sensitivity: 0.49 (95%CI 0.34-0.64) Specificity: 0.82 (95%CI 0.70-0.90) PPV: 67% NPV: 68% Index test: FeNO >32 ppb Sensitivity: 0.48 (95%CI 0.33-0.63) Specificity: 0.83 (95%CI 0.71-0.91) PPV: 67% NPV: 68% **Smokers** Index test: FeNO >20 ppb Sensitivity: 0.29 (95%CI 0.10-0.56) Specificity: 0.75 (95%CI 0.51-0.91)				

Reference	Katsoulis 2013 (Katsoulis et al., 2013)
	PPV: 50% NPV: 56% Index test: FeNO >25 ppb Sensitivity: 0.18 (95%CI 0.04-0.43) Specificity: 0.90 (95%CI 0.68-0.99) PPV: 60% NPV: 56% Index test: FeNO >30 ppb Sensitivity: 0.12 (95%CI 0.01-0.36) Specificity: 0.95 (95%CI 0.75-1.00) PPV: 67% NPV: 56%
Source of funding	Not reported
Limitations	Risk of bias: Downgraded by two increments due to concerns arising from the method of participant selection (method not reported) and from interpretation of the index test and reference standard (unclear if blinded) Indirectness: Downgraded by two increments due to population (mixed smoking and non-smoking participants in full population analysis) and reference standard (diagnosis without clinician decision) indirectness
Comments	2x2 data calculated from sensitivity, specificity and prevalence (42.9% for full population, 45.9% for smokers) data reported in paper

Reference	Kesler 2019 (Kesler et al., 2019)
Study type	Prospective study
Study methodology	Data source: Steroid naive children (5–17 years) with symptoms suggestive of asthma and admitted for diagnostic work up at a practice for paediatric pulmonology and allergology Recruitment: consecutive
Number of patients	n = 222 (n=77 atopic asthma; n=57 atopic non-asthmatics; n=37 non-atopic asthma, n=51 non-atopy, non-asthma)
Patient characteristics	Age, mean (SD): 9.7 (3.2) Gender (male to female ratio): 122/100 Ethnicity: not specified

Reference	Kesler 2019 (Kesler et al., 2019)
	Passive smoking (n (%)): 126 (56.8%) Setting: Rostock University Medical Hospital, Rostock, Germany Country: Germany Inclusion criteria: Steroid naive children (5–17 years) with symptoms suggestive of asthma and admitted for diagnostic work up to a practice for paediatric pulmonology and allergology; free of infections for at least two weeks prior to the scheduled examination. Patients were asked to refrain from inhaled short-acting β2-agonists, leukotriene receptor antagonist or antihistamines for at least 3 days prior to the scheduled examination Exclusion criteria: not specified
Target condition	Atopic asthma and non-atopic asthma
Index test(s) and reference standard	Index test: FeNO FENO was measured by means of an online electrochemical nitric oxide monitor according to the ATS/ERS guidelines, i.e. before spirometry and without nose clip at a constant flow rate of 50 ml/s. Cut-offs: >34, 24, ppb (pre-specified) * Only cut-offs ≥20 ppb included in this review (protocol specified cut-offs between 20-50 ppb)* Reference standard All examinations were done during a single visit and consisted of a skin prick test, assessment of FeNO and spirometry prior and during methacholine challenge testing. Patients were categorized according to the results of the skin prick test as atopic or non-atopic and within these subgroups the findings of the methacholine challenge test allowed discrimination of asthmatic and non-asthmatic children. **Skin prick test** The skin prick test was performed at the volar surface of the forearm with application of an extract containing a mixture of common aeroallergens (hazel, birch, alder, beech, ribwort, mugwort, ambrosia, house dust mite, *Aspergillus fumigatus, Penicillium notatum*, *Alternaria*. For positive and negative controls, histamine and saline were used, respectively. Dog and cat were tested only when patients reported contact to either species. Results were recorded 15 min after exposure and were defined positive when the mean diameter was at least 3 mm greater than the negative control. **Spirometry, methacholine challenge testing and bronchodilator reversibility** Spirometry was conducted according to ATS/ERS guidelines. Patients underwent continuous pulse oximetry and performed two to three manoeuvres for assessment of lung function and to rule out any contraindication for the MCT, i.e. a FEV_1 (%predicted) below 75% or O2-

<table>
<tr><td>Reference</td><td colspan="5">Kesler 2019 (Kesler et al., 2019)</td></tr>
<tr><td></td><td colspan="5">saturation below 95%. Subsequently, methacholine challenge testing was performed using the APS dosimeter technique and the one concentration procedure. Dissolved methacholine (16 mg/ml) was nebulized using an incremental protocol yielding delivery of 0.01, 0.1, 0.4, 0.8 and 1.6 mg with corresponding cumulative dosages of 0.01, 0.11, 0.51, 1.31 and 2.91 mg, respectively. Two minutes after each inhalation, spirometry was performed and the individual provocation dose that caused a 20% drop in FEV_1 was calculated. For participants responding already to the administration of 0.01 mg methacholine, this concentration was used for calculation of the PD-20. After the MCT, patients inhaled two puffs of Salbutamol (100 µg each) and underwent spirometry 5 min later. Patients were judged as asthmatic when ≤ 1 mg of methacholine was required to induce a 20% drop in FEV_1.

Time between measurement of index test and reference standard: Same time</td></tr>
<tr><td>2×2 table
FeNO >34 ppb</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">Prevalence= 51.4%</td></tr>
<tr><td></td><td>Index test +</td><td>14</td><td>7</td><td>21</td></tr>
<tr><td></td><td>Index test −</td><td>100</td><td>101</td><td>201</td></tr>
<tr><td></td><td>Total</td><td>114</td><td>108</td><td>222</td></tr>
<tr><td>2×2 table
FeNO >24 ppb</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4"></td></tr>
<tr><td></td><td>Index test +</td><td>25</td><td>10</td><td>35</td></tr>
<tr><td></td><td>Index test −</td><td>89</td><td>98</td><td>187</td></tr>
<tr><td></td><td>Total</td><td>114</td><td>108</td><td>222</td></tr>
<tr><td>Statistical measures</td><td colspan="5">Index text: FeNO >34 ppb
Sensitivity: 0.12 (95%CI 0.07-0.20)
Specificity: 0.94 (95%CI 0.87-0.97)
PPV: 67%
NPV: 50%

Index text: FeNO >24 ppb
Sensitivity: 0.22 (95%CI 0.15-0.31)
Specificity: 0.91 (95%CI 0.84-0.95)
PPV: 71%
NPV: 52%</td></tr>
<tr><td>Source of funding</td><td colspan="5">None declared</td></tr>
<tr><td>Limitations</td><td colspan="5">Risk of bias: Downgraded by two increments due to concerns arising from the method of participant selection (recruitment method and exclusion criteria not specified) and interpretation of the index test and reference standard (unclear if blinded)
Indirectness: Downgraded by one increment due to reference standard (unclear if clinician decision involved) indirectness</td></tr>
</table>

Reference	**Kesler 2019 (Kesler et al., 2019)**
Comments	Study reports sensitivity and specificity for atopic and non-atopic groups separately. Analyst has used prevalence data reported in paper (57.5% in atopic people, 42% in non-atopic people, 51.4% overall) to calculate 2x2 data and combine data for atopic and non-atopic groups.

Reference	**Kowal 2009 (Kowal et al., 2009)**
Study type	Prospective study
Study methodology	Data source: Collected for this study Recruitment: Method not reported, participants were referred to an asthma clinic by their family doctor for evaluation of chronic cough
Number of patients	n = 640
Patient characteristics	Age, mean (range): Symptomatic: 26.5 (18-45); healthy controls: 24 (18-39) Gender (male to female ratio): Not reported Ethnicity: Not reported Setting: Asthma clinic Country: Poland Smoking status: Non-smokers Inclusion criteria: Young adult patients with chronic cough (at least 8 weeks) referred to asthma clinic for evaluation Exclusion criteria: Use of any antiasthma medication, treatment with angiotensin converting enzyme inhibitors, use of codeine or other cough suppressant, upper respiratory tract infection within 4 weeks before study, presence of any systemic disease, contra-indications to bronchial histamine test; people with seasonal allergies if cough appeared in pollen season or up to 4 weeks after the season
Target condition(s)	Asthma vs rhinitis/sinusitis or gastroesophageal reflux
Index test(s) and reference standard	Index test: FeNO Concentration of nitric oxide in the expired air was evaluated “on-line” using a chemiluminescence analyser. Measurements were performed according to ATS recommendations. Briefly, each patient exhaled against the fixed expiratory resistance of 16-cm H20, which resulted in a constant flow of 50 mL/s. Exhaled air was directed through a bacterial and viral filter attached and further through a nonrebreathing valve into a Teflon tubing system connected to the analyser. A plateau of NO concentration in the exhaled air at the

Reference	**Kowal 2009 (Kowal et al., 2009)**				
	selected exhalation rate was automatically selected by the computer software according to the ATS recommendations. At each timepoint measurements were repeated three times and the mean value was used for analysis. Cut-off: >20-50 ppb (40 ppb optimal threshold) <u>Reference standard</u> Participants were followed up over a 6-month period. Those deemed to have bronchial asthma demonstrated significant diurnal changes in PEF or significant improvement of FEV_1 with 200 µg salbutamol, as per GINA guidelines. **Histamine challenge** All patients inhaled doubling concentrations of histamine starting with a concentration of 0.62 mg/mL. Aerosol was generated using a nebulizer attached to a dosimeter. All subjects performed five inspiratory-capacity breaths of given histamine concentration. Forced expiratory manoeuvres were performed 90 seconds after each fifth inhalation. The procedure was continued until either at least a 20% decrease of FEV_1, or a histamine concentration of 32 mg/mL was reached. **Skin prick test** All persons were skin tested using prick methodology with a screening panel of aeroallergens including the following allergen extracts: dust mite, tree mix, grass, weed mix and cat fur. Time between measurement of index test and reference standard: 6 months				
2×2 table FeNO >20 ppb		Reference standard +	Reference standard −	Total	Prevalence= 33%
	Index test +	170	209	379	
	Index test −	8	153	161	
	Total	178	362	540	
2×2 table FeNO >30 ppb		Reference standard +	Reference standard −	Total	
	Index test +	162	114	276	
	Index test −	16	248	264	
	Total	178	362	540	
2×2 table FeNO >40 ppb		Reference standard +	Reference standard −	Total	
	Index test +	157	63	220	
	Index test −	21	299	320	
	Total	178	362	540	
2×2 table		Reference standard +	Reference standard −	Total	

Reference	**Kowal 2009 (Kowal et al., 2009)**				
FeNO >50 ppb	Index test +	123	31	154	
	Index test −	55	331	386	
	Total	178	362	540	
Statistical measures	FeNO >20 ppb Sensitivity: 0.96 (95%CI 0.91-0.98) Specificity: 0.42 (95%CI 0.37-0.48) PPV: 44% NPV: 95% FeNO >30 ppb Sensitivity: 0.91 (95%CI 0.86-0.95) Specificity: 0.69 (95%CI 0.63-0.73) PPV: 59% NPV: 94% FeNO >40 ppb Sensitivity: 0.88 (95%CI 0.82-0.93) Specificity: 0.83 (95%CI 0.78-0.86) PPV: 72.6% NPV: 94% FeNO >50 ppb Sensitivity: 0.69 (95%CI 0.62-0.76) Specificity: 0.91 (95%CI 0.88-0.94) PPV: 80% NPV: 86%				
Source of funding	Medical University of Bialystok				
Limitations	Risk of bias: Downgraded by two increments due to concerns arising from the method of participant selection (method not reported) and the interpretation of the index test and reference standard (unclear if blinded) Indirectness: Downgraded by one increment due to reference standard (unclear if clinician decision was involved in diagnosis) indirectness				
Comments	2x2 data calculated from sensitivity, specificity and prevalence (33%) reported in paper for optimal threshold.LR+ and LR- used for all other thresholds				

Reference	**Livnat 2015 (Livnat et al., 2015)**
Study type	Prospective cohort study
Study methodology	Data source: Children aged 6-18 years referred for methacholine challenge test (MCT) during a 14-month period (July 2011- September 2012) Recruitment: Consecutive
Number of patients	n = 131 (63 MCT positive, 68 MCT negative)
Patient characteristics	Age, mean (SD): negative MCT: 12.9 (3.9); positive MCT: 12.4 (3.6) Gender (male to female ratio): negative MCT: 41/27; positive MCT: 38/25 Exposure to passive smoking: negative MCT 28 (41.2%); positive MCT 28 (44.4%) Ethnicity: not specified ICS use: not specified Setting: Pulmonary Outpatient Clinic of a tertiary university-affiliated medical centre. Country: Israel Inclusion criteria: Children aged 6-18 years referred for methacholine challenge test (MCT) during a 14-month period (July 2011-September 2012) Exclusion criteria: baseline FEV_1 <65%, presence of other systemic or lung disease, anti-inflammatory drugs, or upper respiratory tract infection in the last month.
Target condition	Bronchial hyperresponsiveness
Index test(s) and reference standard	Index test: FeNO Participants performed three online single breath manoeuvres according to ATS/ERS guidelines. They inspired NO-free air to total lung capacity and exhaled through a static flow restrictor for 6–10 s. An animation biofeedback assisted the children in maintaining flow rate at 50 ml/sec during the total length of the exhalation. The mean value of at least two successful FeNO measurements was entered in the analysis. Cut-off: >23 ppb (optimal threshold)

Reference	Livnat 2015 (Livnat et al., 2015)
	Reference standard: Methacholine Challenge Test (MCT) Nebulized methacholine was inhaled for 2 min, with 5-min intervals between doses, until the maximal concentration or the end point was reached. PC20– FEV_1 was determined by the provocative concentration that reduced FEV_1 by 20 % from baseline. On completing the MCT, 200 mg of albuterol inhaler was given to all patients by a spacer device to restore airway calibre. Patients with a positive MCT (PC20 >8 mg/ml) were considered as Group I, while patients with a negative MCT (PC20 <8 mg/ml) were considered as Group II. Time between measurement of index test and reference standard: not specified

2×2 table

	Reference standard +	Reference standard −	Total	Prevalence= 48%
Index test +	38	19	57	
Index test −	25	49	74	
Total	63	68	131	

Statistical measures	Sensitivity: 0.60 (95%CI 0.47-0.72) Specificity: 0.72 (95%CI 0.60-0.82) PPV: 67% NPV: 66%
Source of funding	Not specified
Limitations	Risk of bias: Downgraded by one increment due to concerns arising from the interpretation of the index test and reference standard (unclear if blinded) Indirectness: Downgraded by one increment due to reference standard (unclear clinician decision in diagnosis) indirectness
Comments	2x2 data calculated from sensitivity, specificity and prevalence (48%) reported in paper

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

Reference	**Louis 2023 (Louis et al., 2023)**				
	Smoking status: 62 smokers, 84 ex-smokers, 157 non-smokers Atopy: 136 atopic Ethnicity: Not reported Setting: Secondary care Country: Belgium Inclusion criteria: Untreated patients aged ≥18 years who sought medical attention and in whom asthma was suspected Exclusion criteria: None specified				
Target condition	Asthma				
Index test(s) and reference standard	Index test: FeNO FeNO was measured at a flow rate of 50 mL/s prior to spirometry Cut-off: 25 ppb (pre-specified) and 33 ppb (optimal threshold) Reference standard As per GINA guidelines, asthma diagnosis was based on the presence of typical symptoms (wheezing, dyspnoea, cough, sputum production and chest tightness) combined with ⩾12% and ⩾200 mL FEV_1 reversibility after inhalation of 400 µg salbutamol and/or a PC20 methacholine causing a 20% fall in FEV_1 ⩽8 mg·mL−1 when FEV_1 is ⩾70% predicted Time between measurement of index test and reference standard: 1-2 weeks				
2×2 table >25 ppb		Reference standard +	Reference standard −	Total	Prevalence= 61.1%
	Index test +	68	40	108	
	Index test −	117	78	195	
	Total	185	118	303	
2×2 table >33 ppb		Reference standard +	Reference standard −	Total	Prevalence= 63.3%
	Index test +	34	10	44	
	Index test −	71	51	122	
	Total	105	61	166	

Reference	**Louis 2023 (Louis et al., 2023)**
Statistical measures	FeNO >25 ppb Sensitivity: 0.37 (95%CI 0.30-0.44) Specificity: 0.66 (95%CI 0.57-0.75) PPV: 63% NPV: 40% FeNO >33 ppb Sensitivity: 0.32 (95%CI 0.24-0.42) Specificity: 0.84 (95%CI 0.72-0.92) PPV: 76% NPV: 41%
Source of funding	Funding from the European Union, FEDER APPS INTERREG
Limitations	Risk of bias: Downgraded by two increments due to concerns arising from the method of participant recruitment (method not reported) and the interpretation of the index test and reference standard (unclear if blinded). Additionally, 33 ppb cut-off has further concerns due to the flow and timing of participants through the study, including data on the training cohort (n=166) only, not including the validation cohort. Indirectness: Downgraded by one increment due to including a mix of smoking and non-smoking participants
Comments	2x2 data for 33 ppb cut-off calculated from sensitivity, specificity and prevalence (63.3%) reported in paper

Reference	**Nekoee 2020 (Nekoee et al., 2020)**
Study type	Retrospective cross-sectional diagnostic accuracy study
Study methodology	Data source: Retrospective study of database data of untreated patients referred to an asthma clinic by two respiratory physicians for chronic or episodic respiratory symptoms suggestive of asthma Recruitment: Not reported
Number of patients	n = 702
Patient characteristics	Age, mean: 51 years Gender (% female): 58% Smoking status: 57% never smokers, 24% ex-smokers, 19% current smokers Atopy: Not reported

<table>
<tr><td>Reference</td><td colspan="5">Nekoee 2020 (Nekoee et al., 2020)</td></tr>
<tr><td></td><td colspan="5">Ethnicity: Not reported

Setting: Asthma clinic (secondary care)

Country: Not reported

Inclusion criteria: Underwent investigations at an asthma clinic prior to receiving maintenance therapy

Exclusion criteria: None reported</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"><u>Index test</u>
FeNO – method/protocol followed to obtain measurements not reported

Cut-off: >36 ppb (optimal threshold)

<u>Reference standard</u>
Asthma was diagnosed by either bronchodilator reversibility (⩾12% from baseline and 200 mL) and/or bronchial hyperresponsiveness to methacholine (provocative concentration causing a 20% fall in FEV_1 ⩽8 $mg \cdot mL^{-1}$). Patients who were negative tested negative to both tests

Time between measurement of index test and reference standard: 1-2 weeks</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>eference standard −</td><td>Total</td><td rowspan="4">Prevalence= 49.7%</td></tr>
<tr><td></td><td>Index test +</td><td>105</td><td>53</td><td>158</td></tr>
<tr><td></td><td>ndex test −</td><td>244</td><td>300</td><td>544</td></tr>
<tr><td></td><td>Total</td><td>349</td><td>353</td><td>702</td></tr>
<tr><td>Statistical measures</td><td colspan="5"><u>Index text</u>
Sensitivity: 0.30 (95%CI 0.25-0.35)
Specificity: 0.85 (95%CI 0.81-0.89)
PPV: 66%
NPV: 55%</td></tr>
</table>

Reference	**Nekoee 2020 (Nekoee et al., 2020)**
Source of funding	Supported by a Federal Belgian Government Excellence of Science grant
Limitations	Risk of bias: Downgraded by two increments due to concerns arising from patient selection (method of selection not reported), unclear interpretation of the index test and reference standard (unclear if blinded) and the flow and timing of participants through the study (not all participants were diagnosed with the same reference standard) Indirectness: Downgraded by two increments due to population (mixed smoking and non-smoking participants) index test (no information on protocol or flow rate FeNO measurements were conducted with) and reference standard (unclear clinician involvement in diagnosis) indirectness
Comments	2x2 data calculated from sensitivity, specificity and prevalence (49.7%) data reported in paper

Reference	**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 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 Gender (male to female ratio): 41:47 Ethnicity: Not reported Smoking status: 55 non-smokers, 16 ex-smokers, 17 current smokers ICS use: Treatment naïve Setting: Secondary care Country: Greece Inclusion criteria: Asthma related symptoms in the previous month but without previous diagnosis of asthma and without initiation of treatment. Exclusion criteria: Any other known cardiopulmonary or systematic disease

Reference	**Porpodis 2017 (Porpodis et al., 2017)**
Target condition(s)	Asthma
Index test(s) and reference standard	Index test FeNO levels were measured with the a nitric oxide analyser according to ATS Guidelines. The cut-off point of 20 ppb was defined as an increased level of FeNO at a flow rate of 0.05 L/s compliant to ATS Guidelines. Cut-off: >20 ppb (pre-specified) Reference standard 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 FEV_1 after albuterol, along with new symptoms of coughing, wheezing, or shortness of breath over the past month, and no previous diagnosis of asthma Time between measurement of index test and reference standard: Unclear

2×2 table

	Reference standard +	Reference standard −	Total	Prevalence= 76.1%
Index test +	26	4	30	
Index test −	41	17	58	
Total	67	21	88	

Statistical measures	Index text Sensitivity: 0.39 (95%CI 0.27-0.51) Specificity: 0.81 (95%CI 0.58-0.95) PPV: 87% NPV: 29%
Source of funding	None reported
Limitations	Risk of bias: Downgraded by two increments due to unclear method of patient selection (method not reported) and unclear interpretation of the index test and reference standard (unclear if clinician diagnosing asthma was blinded to methacholine challenge result) Indirectness: Downgraded by one increment due to population (mixed smoking and non-smoking participants) indirectness
Comments	Sensitivity and specificity calculated from 2x2 data reported in paper

Reference	**Sato 2008 (Sato et al., 2008)**
Study type	Prospective study
Study methodology	Data source: Collected for this study

Reference	**Sato 2008 (Sato et al., 2008)**
	Recruitment: Consecutive Patients attending the Department of Pulmonary Medicine at a university hospital with complaints of prolonged cough or wheezing lasting for more than 3 weeks
Number of patients	n = 71
Patient characteristics	Age, mean (95%CI): Bronchial asthma: 55.5 (48.9 to 62.5); Cough variant asthma: 48.2 (39.4 to 57.0); Eosinophilic bronchitis without asthma: 45.3 (33.3 to 57.2); Others: 55.5 (47.5 to 63.5) Gender (male to female ratio): Bronchial asthma: 20:10; Cough variant asthma: 7:11; Eosinophilic bronchitis without asthma: 4:4; Others: 8:7 Ethnicity: Not reported Setting: Department of Pulmonary Medicine Country: Japan Inclusion criteria: Prolonged cough or wheezing >3 weeks attending Department of Pulmonary Medicine; age 20-78 years; no abnormalities on CXR or CT scan; no prior history of treatment for pulmonary disease; never used oral or inhaled corticosteroids Exclusion criteria: None
Target condition(s)	Asthma group = bronchial asthma + cough variant asthma together; compared with non-asthma group = eosinophilic bronchitis without asthma (EB), post-infectious cough, post-nasal drip, COPD, chronic bronchitis, cough with GERD or sino-bronchial syndrome (i.e. one comparator group)
Index test(s) and reference standard	Index test: FeNO FeNO was measured in accordance with ATS/ERS recommendations using a chemiluminescence analyser. Measurement was performed with patients in a sitting position and without wearing a nose clip. From total lung capacity without breath holding, the patient exhaled at a constant flow of 50 mL/sec. To eliminate contamination from nasal NO, patients maintained a constant mouth pressure of 16 cm H2O. FeNO was measured three times, with differences in measured values within 10%. The mean value of three measurements was used as data for statistical analysis. FeNO was measured before pulmonary function and airway hyperresponsiveness testing. Optimal cut-off: >38.8 ppb (optimal threshold) Reference standard Patients with allergic airway inflammation associated with prolonged cough are classified as follows: bronchial asthma (BA); cough and wheezing for 3 weeks or longer, sputum eosinophilia, and positive airway hyperresponsiveness or presence of reversible airflow limitation, cough variant asthma (CVA); cough without wheezing for 3 weeks or longer, sputum eosinophilia, and positive airway hyperresponsiveness or presence of reversible airflow limitation, eosinophilic bronchitis without asthma (EB); cough without wheezing for

Reference	**Sato 2008 (Sato et al., 2008)**				
	3 weeks or longer, sputum eosinophilia, but negative airway hyperresponsiveness and no reversible airflow limitation. Within this classification, patients with BA and CVA are defined as the asthmatic group. In patients not meeting these criteria for allergic airway inflammatory disease, a specific diagnosis was made, if possible, based on clinical examination, pulmonary function tests, and imaging studies. These are classified as ‘‘Others’’ disorders. Bronchial asthma: cough and wheezing for 3 weeks or longer, sputum eosinophilia and positive airway hyperresponsiveness (methacholine <12.5 units) or reversible airflow limitation (improvement in FEV1 of 200mL and ≥12% from baseline after salbutamol 200 μg or long-acting β2-agonist). Cough variant asthma (CVA): As above except without wheezing. **Spirometry and bronchodilator reversibility** Pulmonary function testing was performed using spirometers to measure FVC and FEV_1. Tests were performed by experienced respiratory technicians according to ATS guidelines. For airway reversibility testing, a positive result was defined as an improvement in FEV_1 of 200 mL and 12% from baseline when measured 20 min after inhalation of a short-acting b2 agonist (salbutamol 200 mg from a pressurized inhaler), or the same improvement after treatment with a long acting b2 agonist. **Methacholine challenge** Airway hyperresponsiveness testing using methacholine was performed by the Astrograph method. Patients inhaled methacholine diluted in physiologic saline (starting with physiologic saline only as a control) at gradually increasing concentrations of 49 mg/mL, 98 mg/mL, 195 mg/mL, 390 mg/mL, 781 mg/mL, 1563 mg/mL, 3125 mg/mL, 6250 mg/mL, and 12500 mg/mL, and airway resistance was continuously measured. A dose-response curve was drawn for methacholine and airway pressure, and the minimum dose of methacholine was calculated as an index of airway responsiveness. Positive airway hyperresponsiveness was defined as a value <12.5 units. **Induced sputum** Induced sputum testing was conducted using with inhalation of 5 mL of 5% hypertonic saline using an ultrasonic nebulizer. The sputum samples were stained with Papanicolaou stain and examined by microscopy. Sputum samples were judged to be adequate if alveolar macrophages were present and total percentage of squamous cells was <10%. On each slide, 400 cells other than squamous cells were counted. Observers who counted the cells were blinded to clinical information about the patient. Eosinophilia in the induced sputum was defined as an eosinophil count 3% of the total cell count. Time between measurement of index test and reference standard: same time				
2×2 table		Reference standard +	Reference standard −	Total	Prevalence= 67.7%
	Index test +	38	2	40	
	Index test −	10	21	31	
	Total	48 (BA + CVA)	23 (EB + other)	71	

Reference	**Sato 2008 (Sato et al., 2008)**
Statistical measures	Sensitivity: 0.79 (95%CI 0.65-0.90) Specificity: 0.91 (95%CI 0.72-0.99) PPV: 95% NPV: 68%
Source of funding	Not stated
Limitations	Risk of bias: Downgraded by one increment due to concerns arising from the interpretation of the index test and reference standard (unclear if blinded) Indirectness: Downgraded by one increment due to population (smoking status not reported) indirectness

Reference	**Schneider 2015 (Schneider et al., 2015)**
Study type	Prospective diagnostic study
Study methodology	Data source: diagnostic-naïve patients suspected of suffering from obstructive airway disease from 10 general practices and 1 private practice, between February 2006 and June 2007 Recruitment: consecutive
Number of patients	n = 553 (393 at pulmonology practices, 160 at general practices)
Patient characteristics	Age, mean (SD): 43.41 (16.36) calculated across groups reported Gender (male to female ratio): 233/320 Ethnicity: not specified Setting: general practices in Heidelberg, Germany Country: Germany Inclusion criteria: patients visiting their GP for the first time, with symptoms suggestive of obstructive airway disease or the respective differential diagnoses, such as restrictive airway disease. The participants had to present with symptoms such as dyspnoea, cough or expectoration of more than two months, thus leading to the clinical suspicion of obstructive or restrictive airway disease. Exclusion criteria: respiratory tract infections within the last 6 weeks preceding the evaluation, previously established diagnosis of obstructive airways disease, contraindications for bronchodilator reversibility testing or bronchial provocation, namely untreated hyperthyreosis, unstable coronary artery disease and cardiac arrhythmia and pregnancy.

Reference	**Schneider 2015 (Schneider et al., 2015)**				
Target condition	Asthma				
Index test(s) and reference standard	Index test: FeNO All patients underwent standard measurement of FeNO at a flow rate of 50 mL/s, according to the ATS/ERS guidelines. FeNO was performed prior to whole body plethysmography and bronchial provocation. Cut-offs: >4-99 ppb (unclear selection) *Only cut-offs between 20 and 50 ppb extracted for this review, as per protocol specification* Reference standard Asthma as determined by pneumologist based on medical history, physical examination, Whole body plethysmography investigation and bronchial provocation results. **Whole body plethysmography** Participants with an FEV_1 <80% predicted received salbutamol with an additional WBP investigation 20min later. An obstructive airways disease was diagnosed in FEV_1/VC was ≤0.70. Asthma was classified if clinical symptoms and history fitted, and if the change in FEV_1 compared to baseline was both ≥12% and ≥200mL, and lung function returned to the predicted normal range. An incomplete bronchodilator response was stated if the response was ≥12% and ≥200 mL, but where lung volumes remained below predicted. Participants in meeting this criterion were labelled as having asthma-COPD overlap syndrome. Participants were classified as COPD if clinical symptoms and history fitted and the bronchodilator response of FEV_1 after salbutamol was both <12% compared to baseline and <200mL. **Bronchial provocation** If there was no bronchial obstruction, bronchial provocation was performed to determine bronchial hyperresponsiveness. Trained lung function technicians measured response to methacholine according to the ATS guidelines. An asthma diagnosis required a 20% fall in FEV_1 from baseline after inhaling methacholine stepwise until the maximum concentration (16 mg/mL), and, alternatively, a doubling of airway resistance and its increase to ≥2.0 kPa. Time between measurement of index test and reference standard: not specified				
2×2 table FeNO >20 ppb		Reference standard +	Reference standard −	Total	Prevalence= 41.4%
	Index test +	137	122	259	
	Index test −	92	202	294	
	Total	229	324	553	
2×2 table		Reference standard +	Reference standard −	Total	

Reference	**Schneider 2015 (Schneider et al., 2015)**			
FeNO >25 ppb	Index test +	112	82	194
	Index test −	117	242	359
	Total	229	324	553
2×2 table FeNO >30 ppb		Reference standard +	Reference standard −	Total
	Index test +	87	60	147
	Index test −	142	264	406
	Total	229	324	553
2×2 table FeNO >35 ppb		Reference standard +	Reference standard −	Total
	Index test +	74	43	117
	Index test −	155	281	436
	Total	229	324	553
2×2 table FeNO >40 ppb		Reference standard +	Reference standard −	Total
	Index test +	88	42	110
	Index test −	161	282	443
	Total	229	324	553
2×2 table FeNO >47 ppb		Reference standard +	Reference standard −	Total
	Index test +	59	24	83
	Index test −	170	300	470
	Total	229	324	553
Statistical measures	Index test: FeNO (cut-off >20 ppb) Sensitivity: 0.60 (95%CI 0.53-0.66) Specificity: 0.62 (95%CI 0.57-0.68) PPV: 53% NPV: 69% Index test: FeNO (cut-off >25 ppb) Sensitivity: 0.49 (95%CI 0.42-0.56) Specificity: 0.75 (95%CI 0.70-0.79) PPV: 58% NPV: 67%			

Reference	Schneider 2015 (Schneider et al., 2015)
	Index text: FeNO (cut-off >30 ppb) Sensitivity: 0.38 (95%CI 0.32-0.45) Specificity: 0.81 (95%CI 0.77-0.86) PPV: 59% NPV: 65% Index test: FeNO (cut-off >35 ppb) Sensitivity: 0.32 (95%CI 0.26-0.39) Specificity: 0.87 (95%CI 0.83-0.90) PPV: 63% NPV: 64% Index text: FeNO (cut-off >40 ppb) Sensitivity: 0.30 (95%CI 0.24-0.36) Specificity: 0.87 (95%CI 0.83-0.90) PPV: 62% NPV: 64% Index text: FeNO (cut-off >47 ppb) Sensitivity: 0.26 (95%CI 0.20-0.32) Specificity: 0.93 (95%CI 0.89-0.95) PPV: 71% NPV: 64%
Source of funding	The part of the study in the general practices was funded by the Federal Ministry of Education and Research (BMBF); grant number 01GK0515
Limitations	Risk of bias: No concerns Indirectness: Downgraded by two increments due to population (ICS use not reported and mixed smoking and non-smoking participants) indirectness
Comments	2x2 data calculated from sensitivity, specificity and prevalence data (39.2% in pneumology practices, 46.9% in general practices) reported in paper and combined those identified in pneumology practices and general practices

Reference	Schneider 2022 (Schneider et al., 2022)
Study type	Prospective cross-sectional study
Study methodology	Data source: Patients coming for the first time for diagnostic work-up with complaints suggestive of asthma

Reference	**Schneider 2022 (Schneider et al., 2022)**
	Recruitment: Consecutive
Number of patients	n = 308
Patient characteristics	Age, mean (SD): 44.7 (16.7) years Gender (male to female ratio): 122:186 Ethnicity: Not reported Setting: Three private practices of pneumologists Country: Germany Smoking status: Mixed (19 smokers, 117 ex-smokers) Inclusion criteria: Presenting for the first time with complaints of asthma Exclusion criteria: Previously established diagnosis of obstructive airways disease, smoked on the day of assessment, consumed a nitrate-rich meal <3 hours prior to FeNO measurement, had a respiratory infection <6 weeks prior to assessment, contra-indications for bronchodilator reversibility testing or bronchial provocation tests, untreated hyperthyreosis, unstable coronary artery disease, cardiac arrhythmia and pregnancy
Target condition	Asthma
Index test(s) and reference standard	Index test: FeNO The FeNO measurement was performed with the electrochemically-based NO-measuring device. The FeNO measurements were performed once for each patient, following ATS/ERS recommendations. Cut-off: Multiple cut-offs ranging from >5-158 ppb (pre-specified and optimal threshold) *Only cut-offs between 20 and 50 ppb extracted for this review, as per protocol specification* Reference standard A committee of experts reviewed each diagnosis in consideration of the participant's medical history, WBP and BP results. The decisions made were based on the diagnostic test performed in combination with the clinical pattern of the participants and course of the disease over 12 weeks.

Reference	**Schneider 2022 (Schneider et al., 2022)**				
	Whole body plethysmography including spirometry An obstructive airway disease was diagnosed when Forced Expiratory Volume in the first second / Vital Capacity (FEV1/ VC) was ≤0.70. A reversible airway obstruction was diagnosed if the bronchodilation test was positive (change in FEV1 >12% and >200 mL). If there was no bronchial obstruction, bronchial provocation was performed. **Methacholine challenge** Positivity was confirmed if FEV1 decreased by ≥20% after inhalation of a maximum cumulative methacholine dose of 960 µg and/or specific airway resistance increased simultaneously by ≥100% and to ≥2.0 kPa*s, and/or if airway resistance increased simultaneously by at least 100% and ≥0.5 kpa*s/L. Time between measurement of index test and reference standard: 12 weeks				
2×2 table FeNO >50 ppb		Reference standard +	Reference standard −	Total	Prevalence= 52.3%
	Index test +	39	1	40	
	Index test −	122	145	267	
	Total	161	146	308	
2×2 table FeNO >40 ppb		Reference standard +	Reference standard −	Total	
	Index test +	52	4	56	
	Index test −	110	143	252	
	Total	161	147	308	
2×2 table FeNO >37 ppb		Reference standard +	Reference standard −	Total	
	Index test +	55	6	61	
	Index test −	106	141	247	
	Total	161	147	308	
2×2 table FeNO >35 ppb		Reference standard +	Reference standard −	Total	
	Index test +	60	7	67	
	Index test −	101	140	241	
	Total	161	147	308	
2×2 table FeNO >34 ppb		Reference standard +	Reference standard −	Total	
	Index test +	61	7	68	
	Index test −	100	140	240	
	Total	161	147	308	

Reference	Schneider 2022 (Schneider et al., 2022)			
2×2 table FeNO >33 ppb		Reference standard +	Reference standard −	Total
	Index test +	64	10	75
	Index test −	97	137	233
	Total	161	147	308
2×2 table FeNO >32 ppb		Reference standard +	Reference standard −	Total
	Index test +	68	10	78
	Index test −	93	137	230
	Total	161	147	308
2×2 table FeNO >31 ppb		Reference standard +	Reference standard −	Total
	Index test +	68	10	78
	Index test −	93	137	230
	Total	161	147	308
2×2 table FeNO >30 ppb		Reference standard +	Reference standard −	Total
	Index test +	71	13	84
	Index test −	90	134	224
	Total	161	147	308
2×2 table FeNO >25 ppb		Reference standard +	Reference standard −	Total
	Index test +	84	26	110
	Index test −	77	120	198
	Total	161	147	308
2×2 table FeNO >22 ppb		Reference standard +	Reference standard −	Total
	Index test +	92	37	129
	Index test −	69	110	179
	Total	161	147	308
2×2 table FeNO >21 ppb		Reference standard +	Reference standard −	Total
	Index test +	97	44	141
	Index test −	64	103	167
	Total	161	147	308

Reference	**Schneider 2022 (Schneider et al., 2022)**				
2×2 table FeNO >20 ppb		Reference standard +	Reference standard −	Total	
	Index test +	105	48	153	
	Index test −	56	98	155	
	Total	161	147	308	
Statistical measures	Index text: FeNO; cut-off: >50 ppb Sensitivity: 0.24 (95%CI 0.18-0.32) Specificity: 0.99 (95%CI 0.96-1.00) PPV: 95% (95%CI 83-99) NPV: 54% (95%CI 48-60) Index text: FeNO; cut-off: >40 ppb Sensitivity: 0.32 (95%CI 0.25-0.40) Specificity: 0.97 (95%CI 0.93-0.99) PPV: 93% (95%CI 82-98) NPV: 57% (95%CI 50-63) Index text: FeNO; cut-off: >37 ppb Sensitivity: 0.34 (95%CI 0.27-0.42) Specificity: 0.96 (95%CI 0.91-0.98) PPV: 90% (95%CI 80-96) NPV: 57% (95%CI 51-63) Index text: FeNO; cut-off: >35 ppb Sensitivity: 0.37 (95%CI 0.30-0.45) Specificity: 0.95 (95%CI 0.90-0.98) PPV: 89% (95%CI 79-96) NPV: 58% (95%CI 51-64) Index text: FeNO; cut-off: >34 ppb Sensitivity: 0.38 (95%CI 0.30-0.46) Specificity: 0.95 (95%CI 0.90-0.98) PPV: 90% (95%CI 80-96) NPV: 58% (95%CI 52-65) Index text: FeNO; cut-off: >33 ppb Sensitivity: 0.40 (95%CI 0.32-0.48)				

Reference	Schneider 2022 (Schneider et al., 2022)
	Specificity: 0.93 (95%CI 0.87-0.97) PPV: 85% (95%CI 75-92) NPV: 58% (95%CI 52-65) Index text: FeNO; cut-off: >32 ppb Sensitivity: 0.42 (95%CI 0.34-0.50) Specificity: 0.93 (95%CI 0.87-0.96) PPV: 86% (95%CI 76-93) NPV: 59% (95%CI 52-66) Index text: FeNO; cut-off: >31 ppb Sensitivity: 0.42 (95%CI 0.35-0.50) Specificity: 0.93 (95%CI 0.88-0.97) PPV: 86% (95%CI 77-93) NPV: 60% (95%CI 53-66) Index text: FeNO; cut-off: >30 ppb Sensitivity: 0.44 (95%CI 0.36-0.52) Specificity: 0.91 (95%CI 0.85-0.95) PPV: 85% (95%CI 75-91) NPV: 60% (95%CI 53-66) Index text: FeNO; cut-off: >25 ppb Sensitivity: 0.52 (95%CI 0.44-0.60) Specificity: 0.82 (95%CI 0.75-0.88) PPV: 76% (95%CI 67-84) NPV: 61% (95%CI 54-68) Index text: FeNO; cut-off: >22 ppb Sensitivity: 0.57 (95%CI 0.49-0.65) Specificity: 0.75 (95%CI 0.67-0.82) PPV: 71% (95%CI 63-79) NPV: 61% (95%CI 54-69) Index text: FeNO; cut-off: >21 ppb Sensitivity: 0.60 (95%CI 0.52-0.68) Specificity: 0.70 (95%CI 0.62-0.77)

Reference	Schneider 2022 (Schneider et al., 2022)
	PPV: 69% (95%CI 60-76) NPV: 61% (95%CI 54-69) Index text: FeNO; cut-off: >20 ppb Sensitivity: 0.65 (95%CI 0.57-0.73) Specificity: 0.67 (95%CI 0.59-0.75) PPV: 69% (95%CI 61-76) NPV: 64% (95%CI 56-71)
Source of funding	None reported – Circassia Germany gave 25% discount on FeNO devices
Limitations	Risk of bias: None Indirectness: Downgraded by two increments due to population (17% of participants were already taking medication against asthma, not specified what medication this included, and mixed smoking and non-smoking participants) indirectness
Comments	2x2 data calculated from sensitivity, specificity and prevalence (52%) data reported in paper

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 Recruitment: Not reported
Number of patients	n = 118
Patient characteristics	Age, mean (SD): 36 (12) Gender (male to female ratio): 43:75 Smoking status: 40 (35%) current or ex-smokers Atopy: 75/115 (65%) with ≥1 positive skin prick test result Ethnicity: Not reported Setting: Asthma clinic Country: UK

Reference	**Simpson 2024 (Simpson et al., 2024)**				
	Inclusion criteria: Presenting with symptoms of wheeze, chest tightness, cough and/or breathlessness 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 FeNO analysis was conducted in accordance with manufacturer instructions and international recommendations. Participants exhaled fully, then took a deep inhalation through the device filter followed by a controlled exhalation for 10 seconds at a standardised flow rate (50 mL/s). Cut-offs: >39 and >50 ppb 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 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. Time between measurement of index test and reference standard: 8-12 weeks				
2×2 table FeNO >39 ppb		Reference standard +	Reference standard −	Total	Prevalence= 59.3%
	Index test +	41	7	48	
	Index test −	29	41	70	
	Total	70	48	118	
2×2 table FeNO >50 ppb		Reference standard +	Reference standard −	Total	
	Index test +	36	6	42	
	Index test −	34	42	76	
	Total	70	48	118	

Reference	Simpson 2024 (Simpson et al., 2024)
Statistical measures	Index text FeNO >39 ppb Sensitivity: 0.59 (95%CI 0.46-0.70) Specificity: 0.85 (95%CI 0.72-0.94) PPV: 85% (74-92) NPV: 59% (51-66) Index text FeNO >50 ppb Sensitivity: 0.51 (95%CI 0.39-0.64) Specificity: 0.88 (95%CI 0.75-0.95) PPV: 86% (73-93) NPV: 55% (49-62)
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) Indirectness: Downgraded by one increment due to population (mixed smoking status of participants) indirectness

Reference	Smith 2004 (Smith et al.)
Study type	Prospective cross-sectional diagnostic accuracy study
Study methodology	Data source: 47 consecutive patients aged 8–75 years referred by their family practitioner to Dunedin Hospital Recruitment: Consecutive patients
Number of patients	n = 47
Patient characteristics	Age, mean (range): Diagnosed with asthma: 41.6 (9-72), without asthma: 31.8 (9-64) Gender (male to female ratio): 20: 27 Smoking status: 42 non-smokers, 5 ex-smokers Atopy: Not reported

<table>
<tr><td>Reference</td><td colspan="5">Smith 2004 (Smith et al.)</td></tr>
<tr><td></td><td colspan="5">Ethnicity: Not reported

Setting: Primary care

Country: New Zealand

Inclusion criteria: people having respiratory symptoms in the preceding 4 weeks

Exclusion criteria: used oral or inhaled corticosteroid in the preceding 4 weeks or if they had a typical respiratory tract infection in the previous 6 weeks</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"><u>Index test</u>
Exhaled nitric oxide was measured before any forced expiratory manoeuvres, according to ATS guidelines at 50 mL/second. All readings were obtained by technical staff who were blinded as to the clinical status of the patients. FeNO levels were read at the first NO plateau

Cut-off: >20 ppb (optimal threshold)

<u>Reference standard</u>
Diagnosis of asthma was ascertained on the basis of the following: relevant symptom history (present in all patients), using American Thoracic Society criteria, and a positive test for BHR and/or a positive response to bronchodilator. These were defined as: provocative dose of hypertonic saline resulting in a 15% fall in FEV_1 (PD15) of less than 20 ml and an increase in FEV_1 of 12% or greater from baseline 15 minutes after inhaled albuterol, respectively

Time between measurement of index test and reference standard: 2-4 weeks</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">Prevalence= 36.4%</td></tr>
<tr><td></td><td>Index test +</td><td>14</td><td>6</td><td>20</td></tr>
<tr><td></td><td>Index test −</td><td>2</td><td>22</td><td>24</td></tr>
<tr><td></td><td>Total</td><td>16</td><td>28</td><td>44</td></tr>
<tr><td>Statistical measures</td><td colspan="5">Sensitivity: 0.88 (95%CI 0.62-0.98)
Specificity: 0.79 (95%CI 0.59-0.92)
PPV: 70%
NPV: 92%</td></tr>
</table>

Reference	**Smith 2004 (Smith et al.)**
Source of funding	Supported by the Otago Medical Research Foundation and the Otago Respiratory Research Trust. GlaxoSmithKline provided a personal educational grant to A.D.S. as GSK Research Fellow
Limitations	Risk of bias: No concerns Indirectness: Downgraded by two increments due to population (mixed children/young people and adults and mixed smoking and non-smoking participants) indirectness
Comments	2x2 data reported in paper, sensitivity and specificity calculated by analyst

Reference	**Tilemann 2011 (Tilemann et al., 2011)**
Study type	Prospective cross-sectional study
Study methodology	Data source: Adults presenting to their GP for the first time with complaints suggestive of obstructive airways disease. Patients had dyspnoea, coughing and/or expectoration persisting for at least 2 months. Patients were referred to the lung function laboratory of a university hospital for further examination. Recruitment: Consecutive
Number of patients	n = 156 (study contained 210 participants, with 54 missing FeNO measurements)
Patient characteristics	Age, mean (SD): Asthma: 38.0 (14.6), COPD: 56.8 (11.7), Partial reversibility: 57.9 (11.2), No OAD: 42.3 (14.4) Gender (male to female ratio): 86:124 Ethnicity: Not reported Smoking status: 63 (30%) current smokers, 36 (17%) past smokers, 111 (53%) never smokers ICS use: 11 patients (5.2%) had been started on inhaled corticosteroids by their GP. Setting: Secondary care Country: Germany Inclusion criteria: Patients presenting to their GP with respiratory symptoms for the first time Exclusion criteria: Patients with respiratory tract infections 6 weeks prior to investigation
Target condition(s)	Asthma

<table>
<tr><td>Reference</td><td colspan="5">Tilemann 2011 (Tilemann et al., 2011)</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5">Index test: FeNO
Patients underwent measurement of FeNO at a mouth flow rate of 50mL/s over 10s, as per guideline recommendations.

Cut-off: >46 ppb (optimal threshold)

Reference standard
All subjects with underwent body plethysmography in the lung function laboratory. Patients with an FEV_1 <80% of predicted received a bronchodilator test with additional whole-body plethysmography 20 minutes after inhaling 400µg salbutamol. An obstructive airway disease was diagnosed if FEV_1 /VC was ≤0.7. The obstruction was classified as irreversible (indicating COPD) if the post-bronchodilator FEV_1 was <12% compared with baseline and was <200mL. The obstruction was classified as fully reversible (indicating asthma) if the degree of reversibility in FEV_1 was >12% and >200mL from baseline and lung volume returned to predicted normal range. An incomplete bronchodilator response (indicating partial reversibility) was considered to be present if the bronchodilation response was >12% and >200 mL compared with baseline but lung volumes remained below the predicted levels. If there was no obstruction in the first lung function test, a bronchial provocation test with methacholine was performed according to ATS guidelines to determine bronchial hyperresponsiveness. Asthma was diagnosed if there was a fall of >20% in FEV_1 after inhaling methacholine stepwise up to the maximum concentration (PC20 ≤16mg/mL).

In some cases, asthma and COPD could hardly be differentiated. Repeated measurements after trials of medication were required, particularly to identify asthma with fixed obstruction

Time between measurement of index test and reference standard: Within 2 weeks</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">Prevalence= 41%</td></tr>
<tr><td></td><td>Index test +</td><td>19</td><td>7</td><td>26</td></tr>
<tr><td></td><td>Index test −</td><td>45</td><td>85</td><td>130</td></tr>
<tr><td></td><td>Total</td><td>64</td><td>92</td><td>156</td></tr>
<tr><td>Statistical measures</td><td colspan="5">Sensitivity: 0.30 (95%CI 0.19-0.42)
Specificity: 0.92 (95%CI 0.85-0.97)
PPV: 71%
NPV: 65%</td></tr>
<tr><td>Source of funding</td><td colspan="5">Funded by the Federal Ministry of Education and Research</td></tr>
<tr><td>Limitations</td><td colspan="5">Risk of bias: Downgraded by two increments due to concerns arising from the interpretation of the index test and reference standard (unclear if blinded and not all participants received the same reference standard) and flow and timing of participants through the study (56 participants excluded from analysis due to not having FeNO measurements)</td></tr>
</table>

Reference	**Tilemann 2011 (Tilemann et al., 2011)**
	Indirectness: Downgraded by two increments due to population indirectness (5.2% of patients on ICS with <4-week washout and mixed smoking and non-smoking participants) and reference standard indirectness (no clinician decision in diagnosis)
Comments	2x2 data not reported, calculated from reported sensitivity and specificity using prevalence of 41%

Reference	**Wang 2015 (Wang et al., 2015)**
Study type	Prospective study
Study methodology	Data source: Suspected asthmatics consecutively referred to Daping Hospital, Chongqing, China during December 2012 to July 2014 Recruitment: Consecutive
Number of patients	n = 923 (n=515 diagnosed using the bronchodilation test and included in the present review)
Patient characteristics	Age, mean (range): Asthma: 45 (15-89), non-asthma: 48 (9-85) Gender (male to female ratio): 251/264 Ethnicity: Not specified Setting: Daping Hospital, Chongqing, China Country: China Inclusion criteria: Patients suspected of asthma based on their symptoms (recurrent wheezing, dyspnoea, chest tightness and/or cough, duration over 6 months), physical examination results and history of atopy. Exclusion criteria: Patients with serious cardiovascular system diseases or other diseases (such as emphysema, pneumothorax, pulmonary fibrosis and lung cancer etc) that can damage lung function were excluded from this study. Other exclusion criteria including: (1) Vigorous exercise in 1 hour before FeNO measurement; (2) Smoking or drinking or used bronchodilators in 4 hours before FeNO measurement; (3) Had clear respiratory infection in 7 days before FeNO measurement; (4) Used systemic steroids in 2 days before FeNO measurement; (5) Used inhaled corticosteroids or had allergic rhinitis attack in 4 weeks before FeNO measurement; (6) Chest imaging showed there were pulmonary infections or tumours or other abnormalities. Characteristics: smoking history: yes n=159 (30.87%)
Target condition	Asthma

<table>
<tr><td>Reference</td><td colspan="5">Wang 2015 (Wang et al., 2015)</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5">Index test: FeNO
FeNO was measured by a nitric oxide analyser according to the ATS guidelines. After inhalation of ambient air through a nitric oxide scrubber to total lung capacity, testers then exhaled against expiratory resistance to exclude nasal air. The exhaled platform time duration was more than 2 seconds with a 2-min analysis period. Repeated exhalations (two values that agree within 5% or 3 that agree within 10%) were performed at a constant flow rate of 50 mL/s.

Cut-off: >41 ppb (optimal threshold)

Reference standard
Diagnosis of asthma was made based on a positive bronchodilation test result. Study also diagnosed asthma using bronchoprovocation tests, however for the present review only results for participants diagnosed using the bronchodilation test have been extracted as the FeNO cut-off used for those diagnosed using the bronchoprovocation test did not meet the protocol.

Bronchodilator reversibility
To determine the bronchodilation test, baseline spirometry was performed according to ATS guidelines. Bronchodilation test was made for patients whose baseline FEV_1 was less than 70% of predicted. Patients were asked to inhale 400 µg albuterol. After 15-20 minutes rest, spirometry was repeated. Bronchodilation test result was considered as positive if patient's FEV_1 after albuterol inhalation was 15% greater than baseline value and the absolute value of FEV_1 was increased more than 200 ml.

Time between measurement of index test and reference standard: not specified</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td>Prevalence= 35.9%</td></tr>
<tr><td></td><td>Index test +</td><td>134</td><td>83</td><td>217</td><td></td></tr>
<tr><td></td><td>Index test −</td><td>51</td><td>247</td><td>298</td><td></td></tr>
<tr><td></td><td>Total</td><td>185</td><td>330</td><td>515</td><td></td></tr>
<tr><td>Statistical measures</td><td colspan="5">Sensitivity: 0.72 (95%CI 0.65-0.79)
Specificity: 0.75 (95%CI 0.70-0.79)
PPV: 62%
NPV: 83%</td></tr>
<tr><td>Source of funding</td><td colspan="5">Not specified</td></tr>
<tr><td>Limitations</td><td colspan="5">Risk of bias: Downgraded by one increment due to concerns arising from the interpretation of the index test and reference standard (unclear if blinded)</td></tr>
</table>

Reference	**Wang 2015 (Wang et al., 2015)**
	Indirectness: Downgraded by two increments due to population (mixed children/young people and adults, mixed smoking and non-smoking participants and participants were excluded if they used inhaled corticosteroids in the 4 weeks before FeNO measurement but for systemic steroids the cut-off was 2 days before FeNO measurement) indirectness
Comments	2x2 data calculated from sensitivity, specificity and prevalence (35.9%) data reported in paper

Reference	**Woo 2012 (Woo et al., 2012)**
Study type	Prospective study
Study methodology	Data source: Collected for this study Recruitment: Consecutive
Number of patients	n = 245
Patient characteristics	Age, mean (SD): Atopic asthma: 11.7 (2.4) years; atopic non-asthma: 12.6 (2.6) years; non-atopic asthma: 11.6 (2.7) years; non-atopic non-asthma 11.4 (2.0) years Gender (male to female ratio): Overall: 163:82; atopic asthma: 92:37; atopic non-asthma: 42:18; non-atopic asthma: 20:18; non-atopic non-asthma: 9:9 Ethnicity: Not reported Setting: Paediatric department Country: Korea Inclusion criteria: Children aged 8-16 years, presenting with non-specific respiratory symptoms e.g., cough, wheezing, shortness of breath, referred to paediatric outpatient department for evaluation of asthma Exclusion criteria: Receiving inhaled short-acting β2 agonist in previous 8 hours; receiving regular treatment with controller medications for 3 month or more before enrolment
Target condition(s)	Asthma vs. non-asthma (not airway hyper-responsiveness (cut off for methacholine PC20 of 8mg/mL) or reversible airflow obstruction (12% improvement in FEV1 with inhaled β-agonist); final diagnoses not stated. Asthma and non-asthma groups also sub-divided by atopic vs. nonatopic
Index test(s) and reference standard	Index test FeNO was measured by chemoluminescence using an online nitric oxide monitor, according to ERS/ATS guidelines. Participants were instructed to avoid eating, drinking, and strenuous exercise 2 h before FeNO measurements. After inhalation of ambient air through a nitric

Reference	Woo 2012 (Woo et al., 2012)				
	oxide scrubber to total lung capacity, participants then exhaled against expiratory resistance to exclude nasal air. Exhalation times were 10 s with a 2-min analysis period. Repeated exhalations (two values that agree within 5% or 3 that agree within 10%) were performed without a nose clip at a constant flow rate of 50 mL/s. Cut-off: >22 ppb (optimal threshold) Reference standard History plus reversible airflow obstruction (≥12% improvement in FEV_1 with inhaled β-agonist) and/or airway hyper-responsiveness (methacholine PC20 ≤8mg/mL) **Spirometry** Lung function tests were performed in accordance with ATS/ERS recommendations. FVC, FEV_1, FEF 25-75, and FEV_1 /FVC ratio were obtained from the best of 3 reproducible forced expiratory manoeuvres. **Methacholine challenge and bronchodilator reversibility** Methacholine PC20 and maximum bronchodilator responses to salbutamol (400 mg) were measured in all study participants according to ATS/ERS guidelines. Methacholine was inhaled in doubling concentrations ranging from 0.05 to 16 mg/mL at 5-min intervals. FEV_1 was measured after 2- min tidal breathing through a calibrated nebulizer. The challenge with inhaled methacholine was performed until FEV_1 decreased by at least 20% from baseline FEV_1 to determine methacholine PC20. **Skin prick testing** Skin prick testing was performed with common aeroallergens including house dust mite, Alternaria, *Cladosporium, Aspergillus, Mucor*, Penicillium, dog, cat, cockroach, mugwort, timothy, ragweed, birch, alder, Hazel, plane tree, and oak. Those with a mean wheal of at least 3 mm were considered positive. Time between measurement of index test and reference standard: same time				
2×2 table FeNO >20 ppb		Reference standard +	Reference standard −	Total	Prevalence= 68.2%
	Index test +	101	15	116	
	Index test −	66	63	129	
	Total	167	78	245	
2×2 table FeNO >21 ppb		Reference standard +	Reference standard −	Total	
	Index test +	95	10	105	
	Index test −	72	68	140	
	Total	167	78	245	

Reference	Woo 2012 (Woo et al., 2012)			
2×2 table FeNO >22 ppb		Reference standard +	Reference standard −	Total
	Index test +	95	10	105
	Index test −	72	68	140
	Total	167	78	245
2×2 table FeNO >23 ppb		Reference standard +	Reference standard −	Total
	Index test +	86	7	93
	Index test −	81	71	152
	Total	167	78	245
2×2 table FeNO >24 ppb		Reference standard +	Reference standard −	Total
	Index test +	84	7	91
	Index test −	83	71	154
	Total	167	78	245
2×2 table FeNO >25 ppb		Reference standard +	Reference standard −	Total
	Index test +	83	6	89
	Index test −	84	72	156
	Total	167	78	245
2×2 table FeNO >30 ppb		Reference standard +	Reference standard −	Total
	Index test +	71	6	77
	Index test −	96	72	168
	Total	167	78	245
2×2 table FeNO >35 ppb		Reference standard +	Reference standard −	Total
	Index test +	54	1	55
	Index test −	113	77	190
	Total	167	78	245
2×2 table FeNO >40 ppb		Reference standard +	Reference standard −	Total
	Index test +	41	1	42
	Index test −	126	77	203
	Total	167	78	245

Reference	**Woo 2012 (Woo et al., 2012)**				
2×2 table FeNO >45 ppb		Reference standard +	Reference standard −	Total	
	Index test +	29	0	29	
	Index test −	138	78	216	
	Total	167	78	245	
2×2 table FeNO >50 ppb		Reference standard +	Reference standard −	Total	
	Index test +	24	0	24	
	Index test −	143	78	221	
	Total	167	78	245	
Statistical measures	FeNO >20 ppb Sensitivity: 0.60 (95%CI 0.53-0.68) Specificity: 0.81 (95%CI 0.70-0.89) PPV: 87% NPV: 49% FeNO >21 ppb Sensitivity: 0.57 (95%CI 0.49-0.65) Specificity: 0.87 (95%CI 0.78-0.94) PPV: 90% NPV: 49% FeNO >22 ppb Sensitivity: 0.57 (95%CI 0.49-0.65) Specificity: 0.87 (95%CI 0.78-0.94) PPV: 90.5% NPV: 48.6% FeNO >23 ppb Sensitivity: 0.51 (95%CI 0.44-0.59) Specificity: 0.91 (95%CI 0.82-0.96) PPV: 92% NPV: 47% FeNO >24 ppb				

Reference	Woo 2012 (Woo et al., 2012)
	Sensitivity: 0.50 (95%CI 0.42-0.58) Specificity: 0.91 (95%CI 0.82-0.96) PPV: 92% NPV: 46% <u>FeNO >25 ppb</u> Sensitivity: 0.50 (95%CI 0.42-0.58) Specificity: 0.92 (95%CI 0.84-0.97) PPV: 93% NPV: 46% <u>FeNO >30 ppb</u> Sensitivity: 0.43 (95%CI 0.35-0.50) Specificity: 0.92 (95%CI 0.84-0.97) PPV: 92% NPV: 43% <u>FeNO >35 ppb</u> Sensitivity: 0.32 (95%CI 0.25-0.40) Specificity: 0.99 (95%CI 0.93-1.00) PPV: 98% NPV: 41% <u>FeNO >40 ppb</u> Sensitivity: 0.25 (95%CI 0.18-0.32) Specificity: 0.99 (95%CI 0.93-1.00) PPV: 98% NPV: 38% <u>FeNO >45 ppb</u> Sensitivity: 0.17 (95%CI 0.12-0.24) Specificity: 1.00 (95%CI 0.95-1.00) PPV: 100% NPV: 36% <u>FeNO >50 ppb</u>

Reference	Woo 2012 (Woo et al., 2012)
	Sensitivity: 0.14 (95%CI 0.09-0.21) Specificity: 1.00 (95%CI 0.95-1.00) PPV: 100% NPV: 35%
Source of funding	Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology
Limitations	Risk of bias: No concerns Indirectness: No concerns

Reference	Yang 2018 (Yang et al., 2018)
Study type	Retrospective cohort
Study methodology	Data source: Retrospective review of electronic medical records of adult outpatients aged ≥18 years who visited the Respiratory Medicine Department of Gangnam Severance Hospital, Seoul, Korea. The patients were referred for measurement of FeNO between June 2016 and July 2017 to diagnose suspected asthma Recruitment: Respiratory Medicine Department of Gangnam Severance Hospital, Seoul, Korea
Number of patients	n = 132
Patient characteristics	Age, mean (SD): 42.8 (16.0) years Gender (male to female ratio): 66/66 Height, mean (SD): 165.7 (9.2) cm Smoking history: not specified Ethnicity: not specified Asthma: 59.8% Setting: Respiratory Medicine Department of Gangnam Severance Hospital, Seoul, Korea Country: Korea Inclusion criteria: None specified

Reference	**Yang 2018 (Yang et al., 2018)**				
	Exclusion criteria: None specified				
Target condition	Asthma				
Index test and reference standard	Index test: FeNO To measure FeNO, a handheld device was used during scheduled study visits according to ATS/ERS guidelines. Patients exhaled fully while seated, then inhaled over 2 to 3 seconds to total lung capacity through a filter, and finally exhaled with an upper airway pressure of 5 to 20 cmH2O. Two successive FeNO measurements were performed with an interval of 4-5 minutes between them. All patients exhaled against an airflow resistor for 10 seconds at a flow rate of 50 mL/s. Measurements were taken before performing spirometry. Cut-offs: >28 and 29 ppb (pre-specified) Reference standard Asthma was diagnosed by clinicians based on the symptoms, physical examination, and the results of the bronchodilator test and methacholine test in all patients according to the Global Initiative for Asthma standard. **Spirometry and bronchodilator response** Spirometry was carried out on the first study day after the FeNO measurements. Lung function tests were performed with a spirometer in accordance with ATS/ERS recommendations. FEV1, FVC, and the FEV1/FVC ratio were obtained from the best reproducible forced expiratory manoeuvres. A significant improvement in lung function resulting from bronchodilator use was defined as an improvement in prebronchodilator FEV1 of ≥12% and 200 mL after administration of salbutamol. **Methacholine challenge** Methacholine challenge test was carried out using the standard 5-breath dosimeter method. Methacholine dilutions of 1, 4, 8, and 16 mg/mL were used. Spirometry was performed 30 seconds and 90 seconds after each inhalation. The test was finished when the FEV1 value decreased by more than 20% from baseline. Time between measurement of index test and reference standard: not specified				
2×2 table FeNO >29 ppb		Reference standard +	Reference standard −	Total	Prevalence= 59.8%
	Index test +	64	8	71	
	Index test −	15	45	61	
	Total	79	53	132	
2×2 table FeNO >28 ppb		Reference standard +	Reference standard −	Total	
	Index test +	60	9	69	

	Index test −	18	44	63	
	Total	79	53	132	
Statistical measures	First measurement (cut-off >29 ppb) Sensitivity: 0.81 (95%CI 0.71-0.89) Specificity: 0.85 (95%CI 0.72-0.93) PPV: 89% NPV: 75% Second measurement (cut-off >28 ppb) Sensitivity: 0.77 (95%CI 0.66-0.86) Specificity: 0.83 (95%CI 0.70-0.92) PPV: 87% NPV: 71%				
Source of funding	No funding was obtained for the study.				
Limitations	Risk of bias: Downgraded by one increment due to concerns arising from the method of participant selection (method not reported) Indirectness: Downgraded by two increments due to population (ICS use not reported and smoking status not reported) indirectness				
Comments	2x2 data calculated from sensitivity, specificity and prevalence (59.8%) data reported in paper				

Reference	**Zhou 2018 (Zhou et al., 2018)**
Study type	Prospective cohort study
Study methodology	Data source: tertiary hospital providing services for children in Suzhou, China Recruitment: not specified
Number of patients	n = 115; n=25 healthy controls
Patient characteristics	Age, mean (SD): CVA group: 7(1); CVA+ UACS group 7(1); UACS group 8(1); other causes 8(1); control group 8(2) Gender (male to female ratio): 71/44 Ethnicity: not specified Setting: (tertiary) Children's Hospital of Soochow University

Reference	Zhou 2018 (Zhou et al., 2018)
	Country: China Inclusion criteria: Children aged 6–14 years with a cough of duration >4 weeks; cough was the main symptom; lesions were not observed upon chest radiography; use of drugs that could affect the FeNO value had been stopped for >2 weeks. Healthy school children with normal indices of lung function and without acute respiratory infection within the previous 4 weeks were enrolled as controls. Exclusion criteria: patients: who were reluctant to undergo FeNO measurement and pulmonary function tests; diagnosed with bronchopulmonary dysplasia, immotile cilia syndrome, tuberculosis, asthma, lung cancer, or other serious systemic diseases. Other Characteristics: n=23 had cough-variant asthma (CVA), 12 (52.2%) of which had atopy; n=30 had CVA + upper airway cough syndrome (UACS) 16 (53.3%) of which had atopy; n=45 had UACS, 19(42.2%) of which had atopy; n=17 had other causes, 6(35.3%) of which had atopy. Height (cm (SD)): CVA group 132 (11); CVA+ UACS group 130 (10); UACS group 136(10); other causes 134 (13); control 137 (12)
Target condition	Cough-variant asthma
Index test(s) and reference standard	Index test: FeNO FeNO was measured prior to spirometry and sputum induction, following ATS/ERS guidelines using an exhaled nitric oxide analyser Cut-off: >25 ppb (pre-specified) Reference standard Diagnostic criteria were based on clinical guidelines set by the American College of Chest Physicians for evaluating chronic cough in children. A questionnaire on drug treatment was completed. FeNO measurement was done in patients with no lesion shown on chest radiographs. Furthermore, patients underwent spirometry, sputum induction, complete blood count, differential diagnosis of common pathogens for cough. Cough score was recorded by physician based on inhibition of daytime activities and nighttime disturbances due to cough. **Spirometry** Vital capacity was measured in accordance with the standards set by the ERS. **Histamine challenge** Bronchial provocation was assessed in participants with FEV1 >70% of predicted, with histamine as the excitatory drug. A bronchial provocation test was deemed positive if FEV1 decreased by 20% before the final step. The test was defined to be negative if FEV1 decreased by <15% when the maximum amount of histamine was inhaled. **Skin prick tests**

Reference	**Zhou 2018 (Zhou et al., 2018)**				
	Six groups of common aeroallergens were tested, including mites, cockroaches, pollens, cats, dogs and moulds. Atopy was defined as the presence of at least one positive skin reaction to any allergen. Time between measurement of index test and reference standard: not specified				
2×2 table		Reference standard +	Reference standard −	Total	Prevalence= 20%
	Index test +	19	3	22	
	Index test −	4	89	93	
	Total	23	92	115	
Statistical measures	Sensitivity: 0.83 (95%CI 0.61-0.95) Specificity: 0.97 (95%CI 0.91-0.99) PPV: 97.5% NPV: 81.4%				
Source of funding	Social Development Projects of Jiangsu Province, Key Lab of Respiratory Disease of Suzhou, Research Project of Provincial Health and Family Planning Commission, the Science and Technology Program of Suzhou, Beijing Natural Science Foundation and the Priming Scientific Research Foundation for the Junior Researcher in Beijing Tongren Hospital, Capital Medical University				
Limitations	Risk of bias: Downgraded by one increment due to concerns arising from the method of participant selection (method not reported) Indirectness: Downgraded by one increment due to population (unclear ICS use) indirectness				
Comments	2x2 data calculated from sensitivity, specificity and prevalence (20%) data reported in paper				

FeNO Test and Treat Effectiveness evidence

No evidence is identified.

Appendix E – Forest plots

Accuracy of FeNO measures: Coupled sensitivity and specificity forest plots

Children and Young People

Figure 3: FeNO (cut-off: >19.6 ppb) vs clinician diagnosis with bronchodilator reversibility test

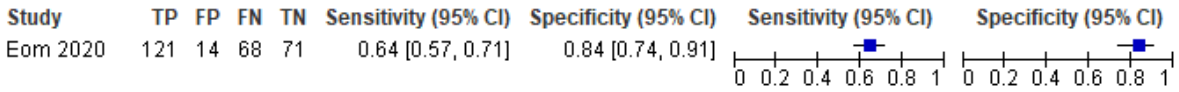


Figure 4: FeNO (cut-off >20 ppb) vs clinician diagnosis with methacholine bronchial challenge or bronchodilator reversibility tests

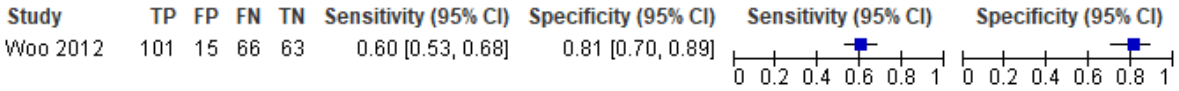


Figure 5: FeNO (cut-off >21 ppb) vs clinician diagnosis with methacholine bronchial challenge or bronchodilator reversibility tests

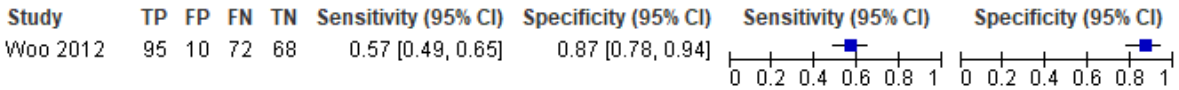


Figure 6: FeNO (cut-off: >22 ppb) vs clinician diagnosis with bronchodilator reversibility and/or methacholine bronchial challenge tests

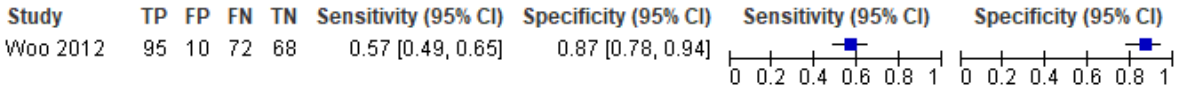


Figure 7: FeNO (cut-off: >23 ppb) vs diagnosis with methacholine bronchial challenge test or clinician diagnosis with methacholine bronchial challenge or bronchodilator reversibility tests

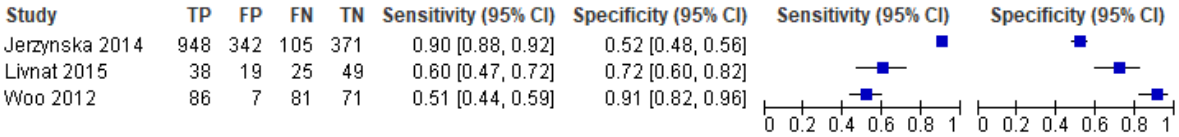


Figure 8: FeNO (cut-off >24 ppb) vs diagnosis with/without clinician decision with methacholine bronchial challenge tests

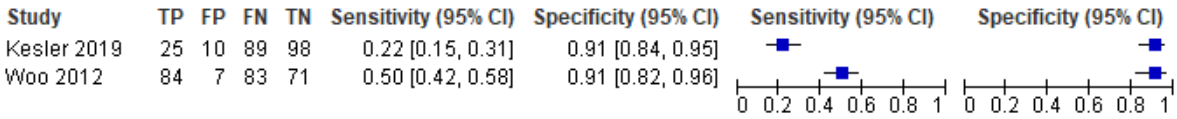


Figure 9: FeNO (cut-off: >25 ppb) vs clinician diagnosis with bronchodilator reversibility and/or methacholine bronchial challenge tests, or diagnosis with methacholine bronchial challenge and skin prick tests

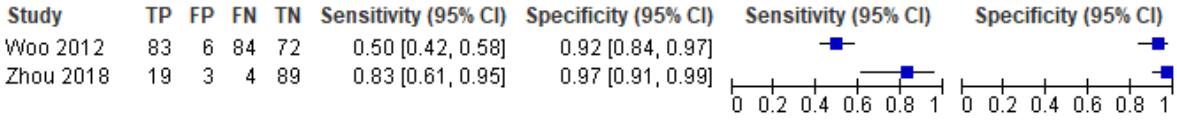


Figure 10: FeNO (cut-off >30 ppb) vs clinician diagnosis with methacholine bronchial challenge or bronchodilator reversibility tests

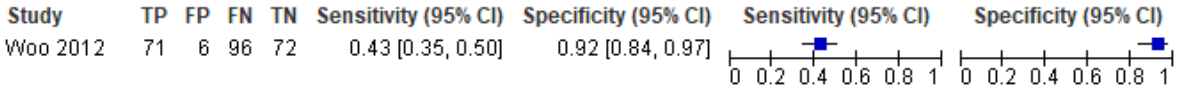


Figure 11: FeNO (cut-off >34 ppb) vs diagnosis with methacholine bronchial challenge test

Figure 12: FeNO (cut-off >35 ppb) vs clinician diagnosis with methacholine bronchial challenge or bronchodilator reversibility tests

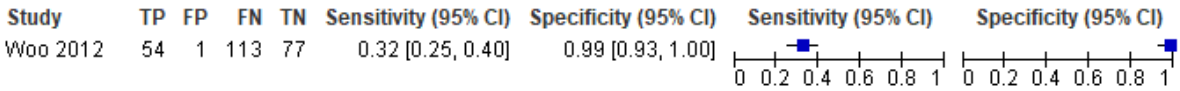


Figure 13: FeNO (cut-off >40 ppb) vs clinician diagnosis with methacholine bronchial challenge or bronchodilator reversibility tests

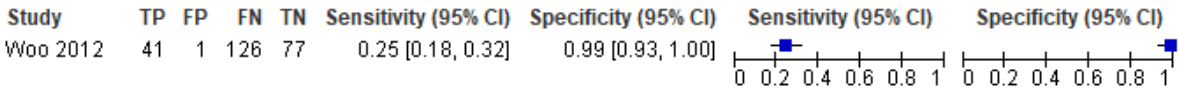


Figure 14: FeNO (cut-off >45 ppb) vs clinician diagnosis with methacholine bronchial challenge or bronchodilator reversibility tests

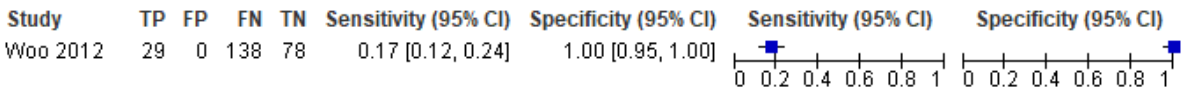
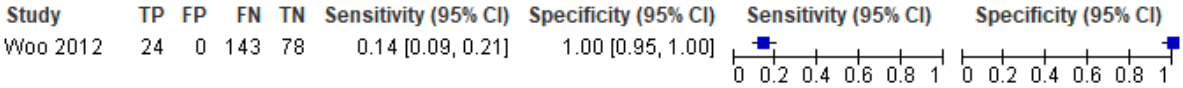


Figure 15: FeNO (cut-off >50 ppb) vs clinician diagnosis with methacholine bronchial challenge or bronchodilator reversibility tests



Smoking Adults

Figure 16: FeNO (cut-off: >20 ppb) vs diagnosis with methacholine bronchial challenge test

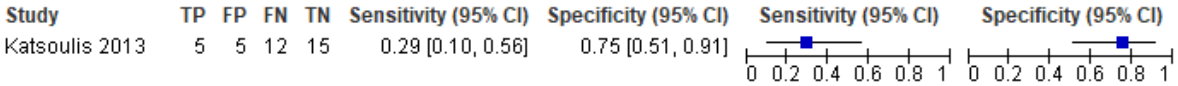


Figure 17: FeNO (cut-off: >25 ppb) vs diagnosis with methacholine bronchial challenge test

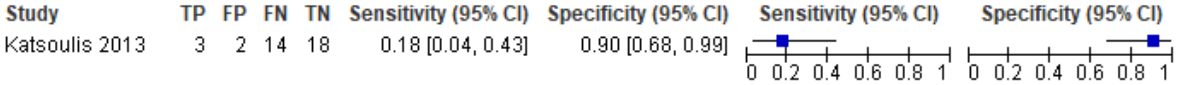
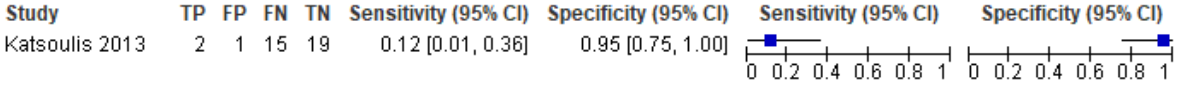


Figure 18: FeNO (cut-off: >30 ppb) vs diagnosis with methacholine bronchial challenge test



Non-smoking Adults

Figure 19: FeNO (cut-off: >20 ppb) vs diagnosis with peak flow variability or bronchodilator reversibility, or clinician diagnosis with bronchodilator reversibility or methacholine bronchial challenge tests

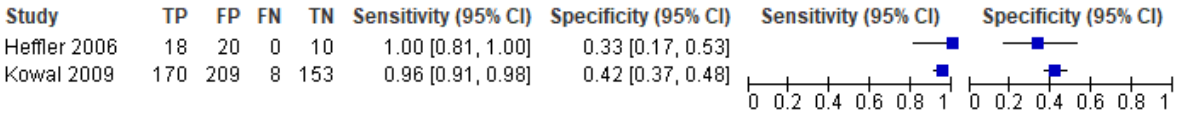


Figure 20: FeNO (cut-off: >20.5 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

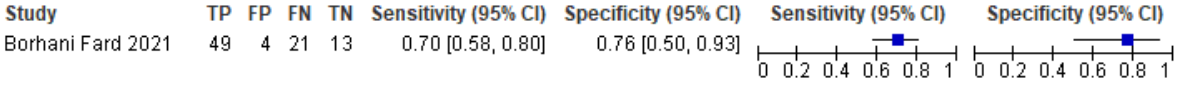


Figure 21: FeNO (cut-off: >25 ppb) vs clinician diagnosis with bronchodilator reversibility or methacholine bronchial challenge tests

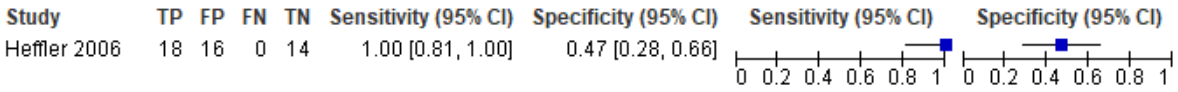


Figure 22: FeNO (cut-off: >27 ppb) vs clinician diagnosis with methacholine bronchial challenge test

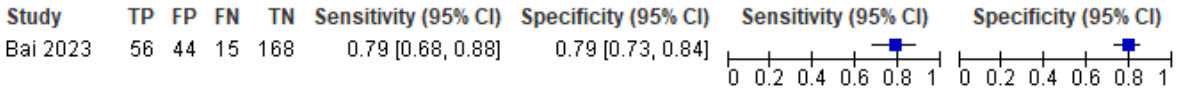


Figure 23: FeNO (cut-off: >29 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

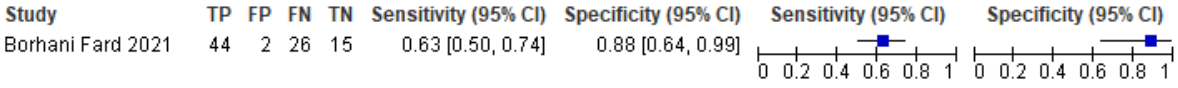


Figure 24: FeNO (cut-off: >30 ppb) vs diagnosis with peak flow variability or bronchodilator reversibility, or clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

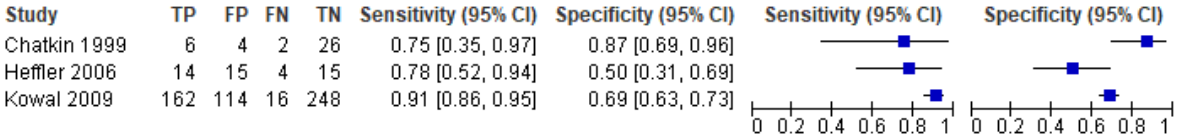


Figure 25: FeNO (cut-off: >34 ppb) vs clinician diagnosis with bronchodilator reversibility or methacholine bronchial challenge tests

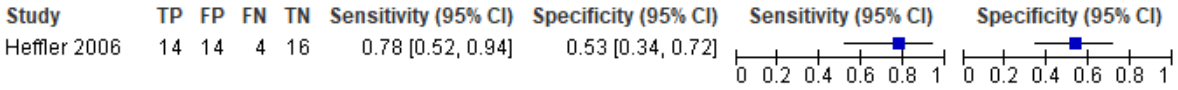


Figure 26: FeNO (cut-off: >36 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

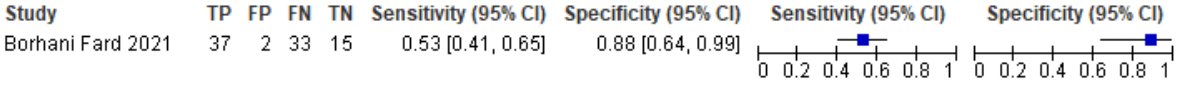


Figure 27: FeNO (cut-off: >37.5 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

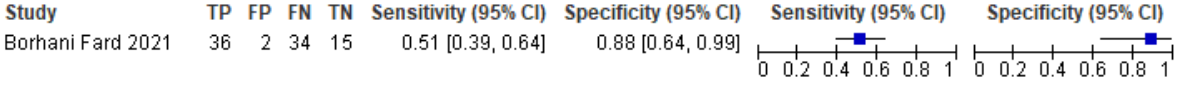


Figure 28: FeNO (cut-off: >39.5 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

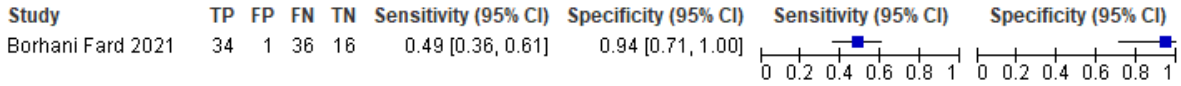


Figure 29: FeNO (cut-off: >40 ppb) vs diagnosis with peak flow variability or bronchodilator reversibility tests, or clinician diagnosis with bronchodilator reversibility or methacholine bronchial challenge tests

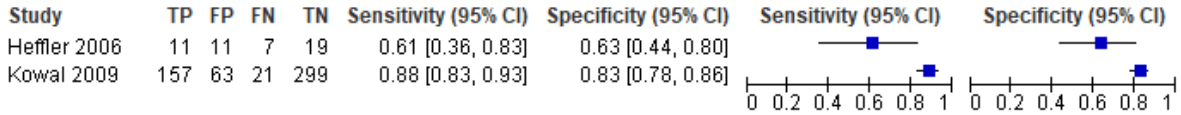


Figure 30: FeNO (cut-off: >40.5 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

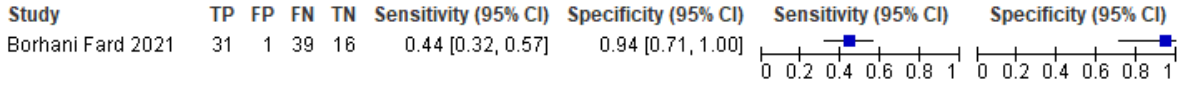


Figure 31: FeNO (cut-off: >41 ppb) vs diagnosis with methacholine bronchial challenge test

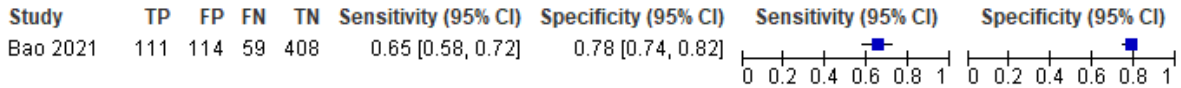


Figure 32: FeNO (cut-off: >41.5 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

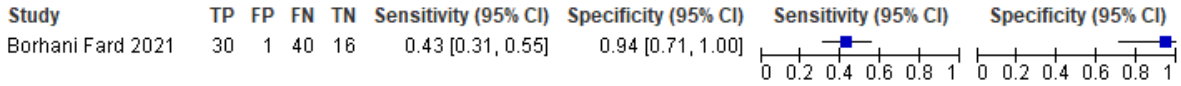


Figure 33: FeNO (cut-off: >42.5 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

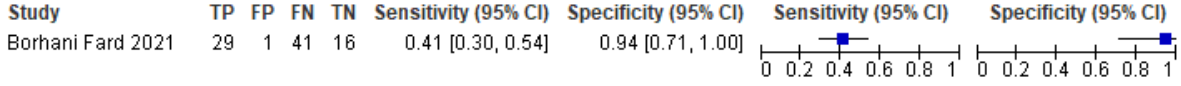


Figure 34: FeNO (cut-off: >45 ppb) vs clinician diagnosis with bronchodilator reversibility or methacholine bronchial challenge tests

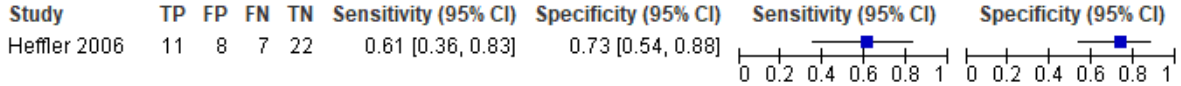


Figure 35: FeNO (cut-off: >48.5 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

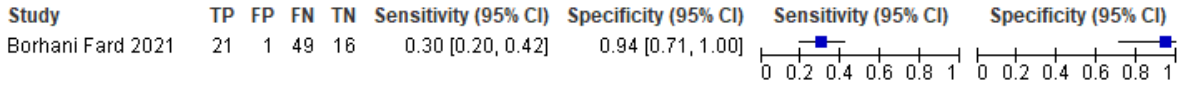
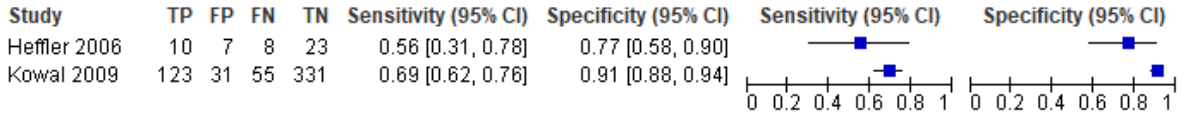


Figure 36: FeNO (cut-off: >50 ppb) vs diagnosis with peak flow variability or bronchodilator reversibility, or clinician diagnosis with bronchodilator reversibility or methacholine bronchial challenge tests



Adults with Mixed/Not Reported Smoking Status

Figure 37: FeNO (cut-off: >19 ppb) vs clinician diagnosis with methacholine bronchial challenge test

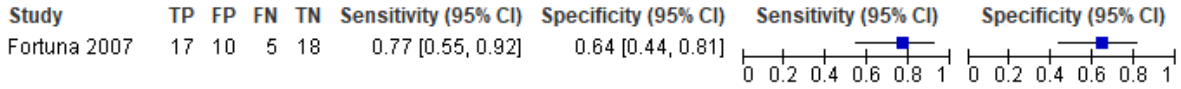


Figure 38: FeNO (cut-off: >20 ppb) vs clinician diagnosis with bronchodilator reversibility and/or methacholine/saline bronchial challenge tests or diagnosis with methacholine bronchial challenge test

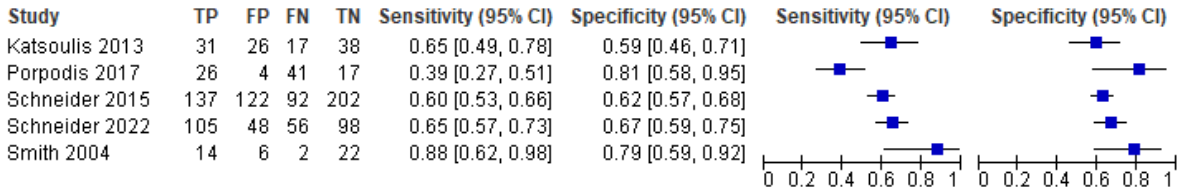


Figure 39: FeNO (cut-off: >21 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

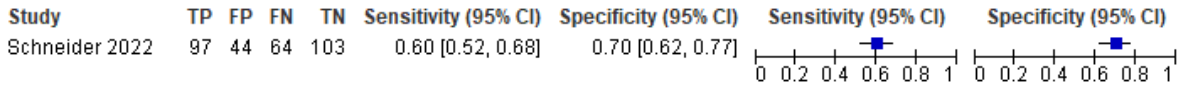


Figure 40: FeNO (cut-off: >22 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

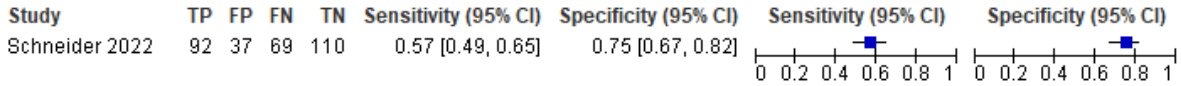


Figure 41: FeNO (cut-off: >23.5 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

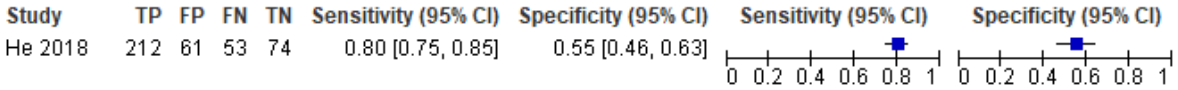


Figure 42: FeNO (cut-off: >25 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests or diagnosis with methacholine bronchial challenge test

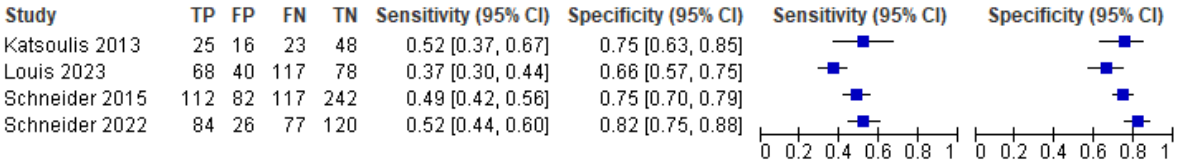


Figure 43: FeNO (cut-off: >27 ppb) vs clinician diagnosis with bronchodilator reversibility and histamine bronchial challenge tests

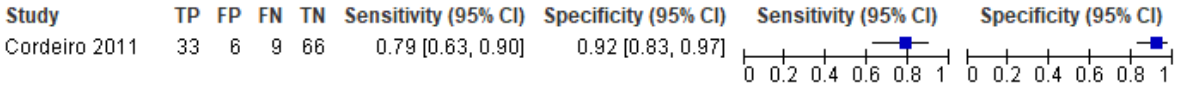


Figure 44: FeNO (cut-off: >28 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

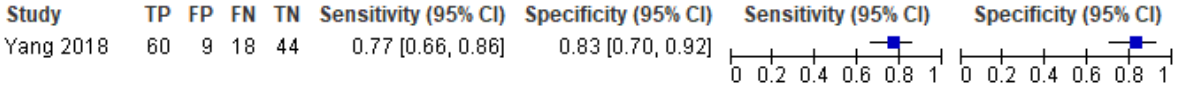


Figure 45: FeNO (cut-off: >29 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

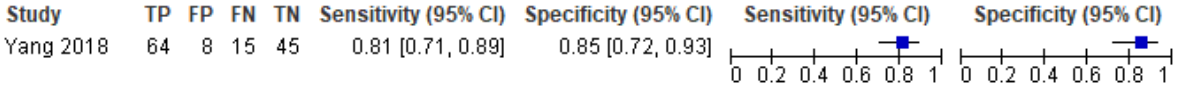


Figure 46: FeNO (cut-off: >30 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests or diagnosis with methacholine bronchial challenge test

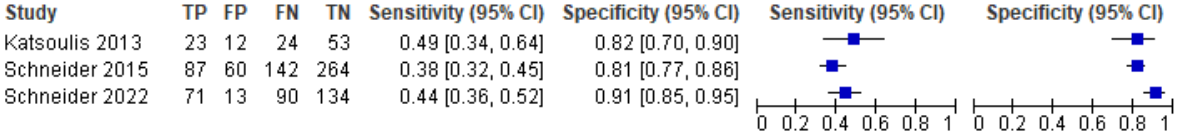


Figure 47: FeNO (cut-off: >31 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

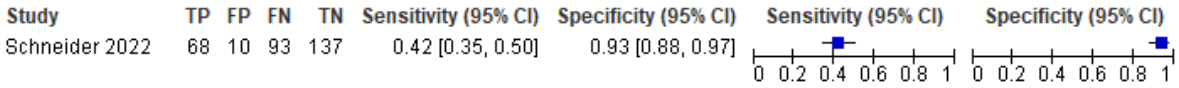


Figure 48: FeNO (cut-off: >32 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests or diagnosis with methacholine bronchial challenge test

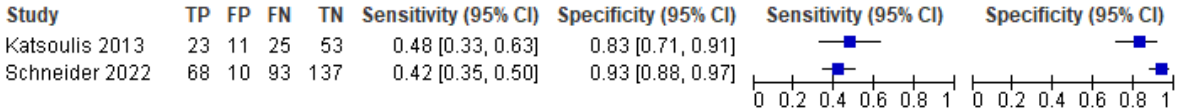


Figure 49: FeNO (cut-off: >33 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

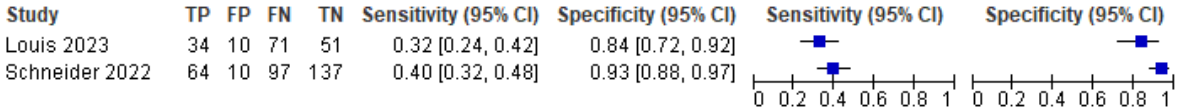


Figure 50: FeNO (cut-off: >34 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

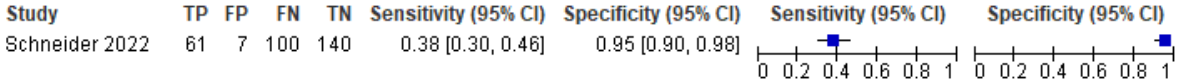


Figure 51: FeNO (cut-off: >35 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

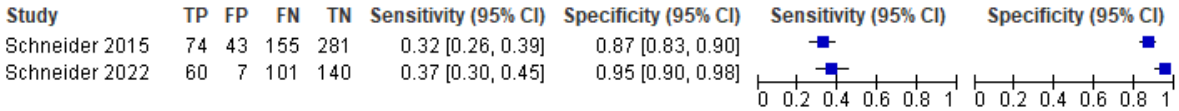


Figure 52: FeNO (cut-off: >36 ppb) vs diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

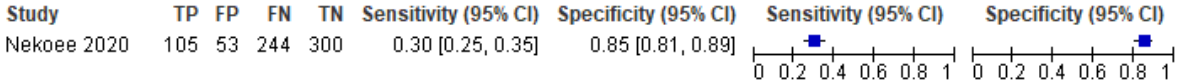


Figure 53: FeNO (cut-off: >37 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

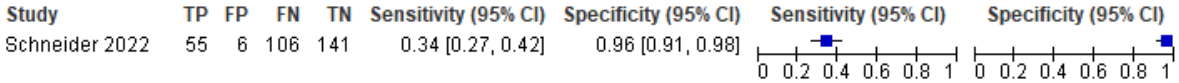


Figure 54: FeNO (cut-off: >38.8 ppb) vs clinician diagnosis with methacholine bronchial challenge, bronchodilator reversibility and sputum eosinophil tests

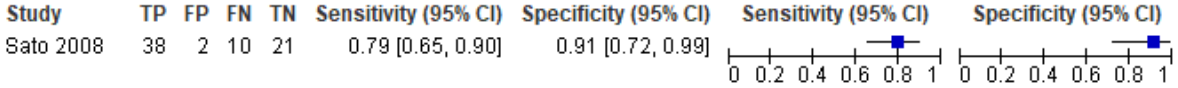


Figure 55: FeNO (cut-off: >39 ppb) vs clinician diagnosis with methacholine bronchial challenge, bronchodilator reversibility and sputum eosinophil tests or expert panel diagnosis with multiple diagnostic tests

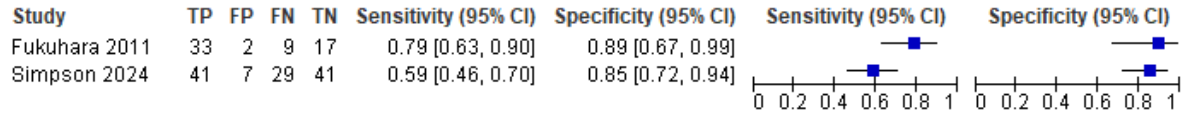


Figure 56: FeNO (cut-off: >40 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

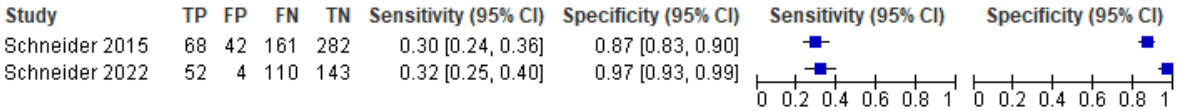


Figure 57: FeNO (cut-off: >41 ppb) vs diagnosis with bronchodilator reversibility test

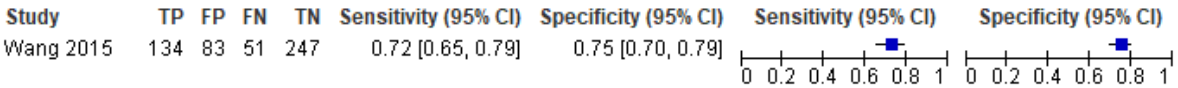


Figure 58: FeNO (cut-off: >46 ppb) vs diagnosis with bronchodilator reversibility or methacholine bronchial challenge tests

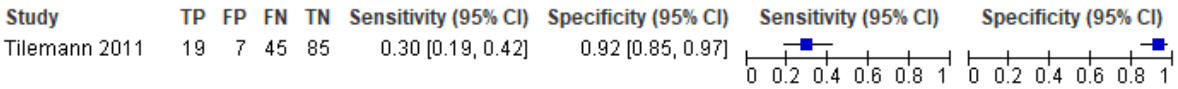


Figure 59: FeNO (cut-off: >47 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests

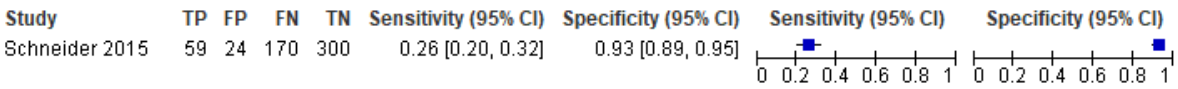
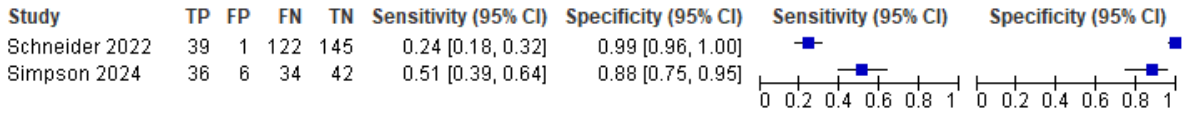


Figure 60: FeNO (cut-off: >50 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests or expert panel diagnosis with multiple diagnostic tests



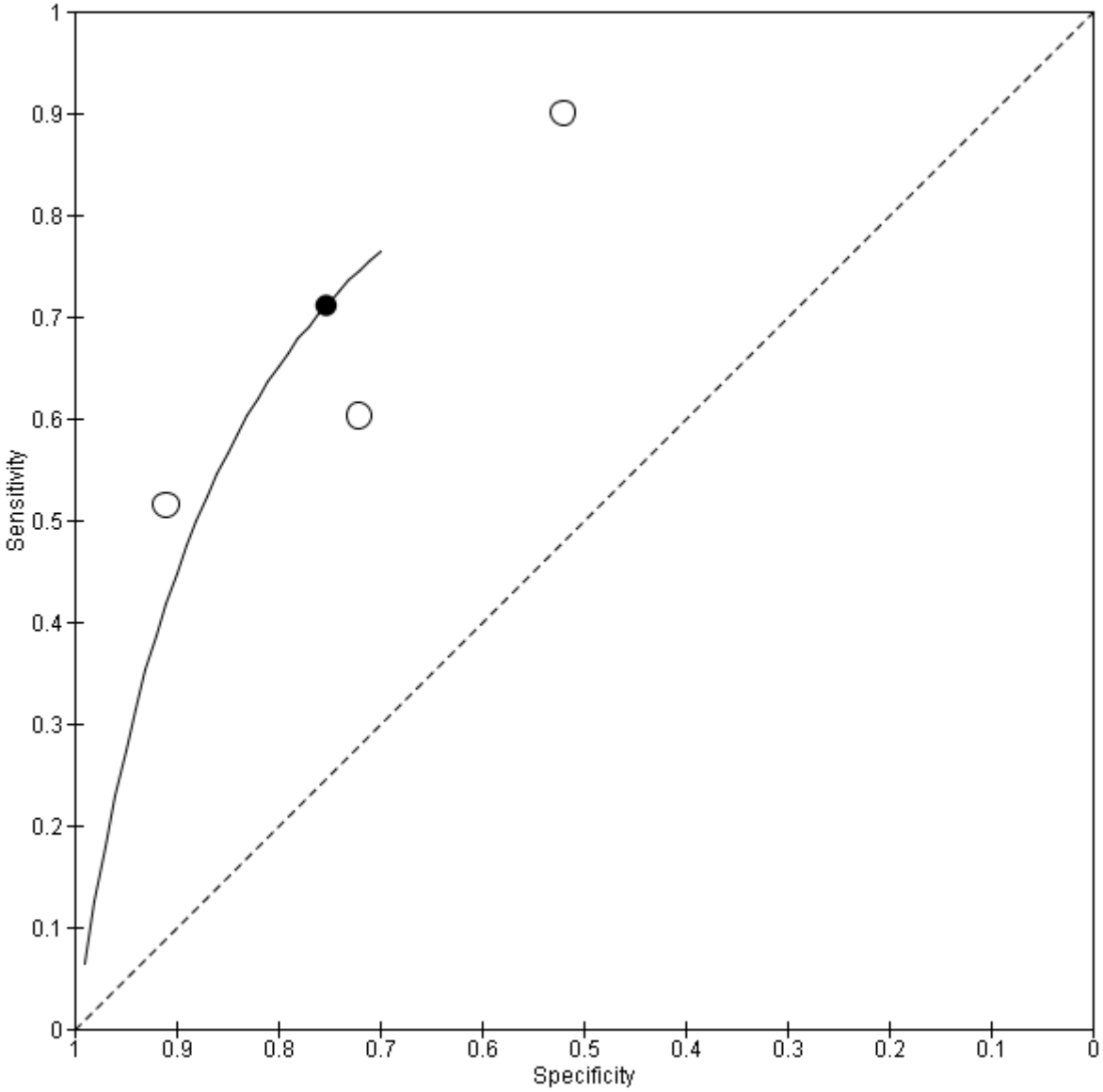
FeNO Test and treat: Forest plots

No evidence identified.

ROC Curves

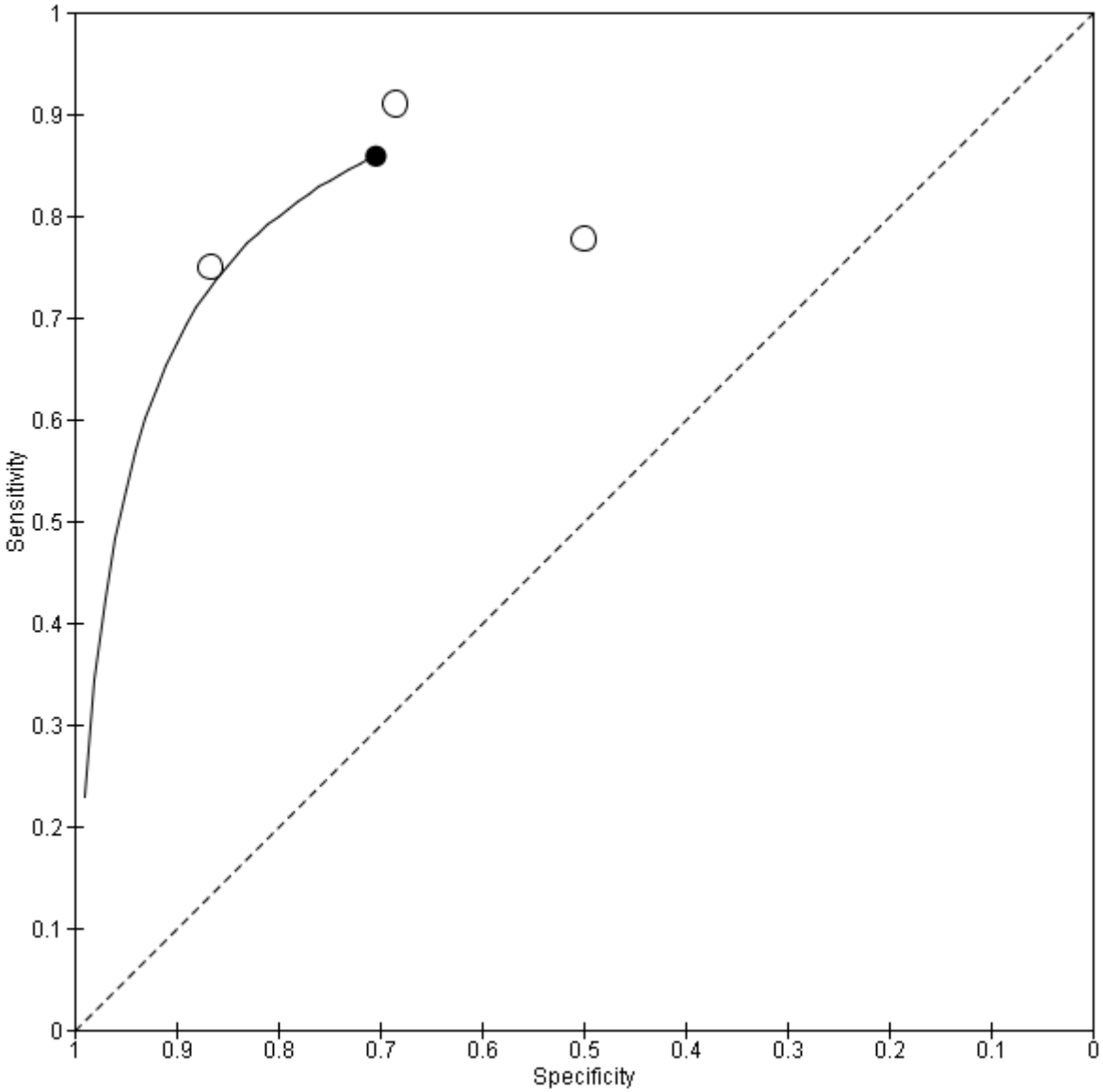
Children and Young People

FeNO (cut-off: >23 ppb) vs diagnosis with methacholine bronchial challenge test or clinician diagnosis with methacholine bronchial challenge or bronchodilator reversibility tests



Non-Smoking Adults

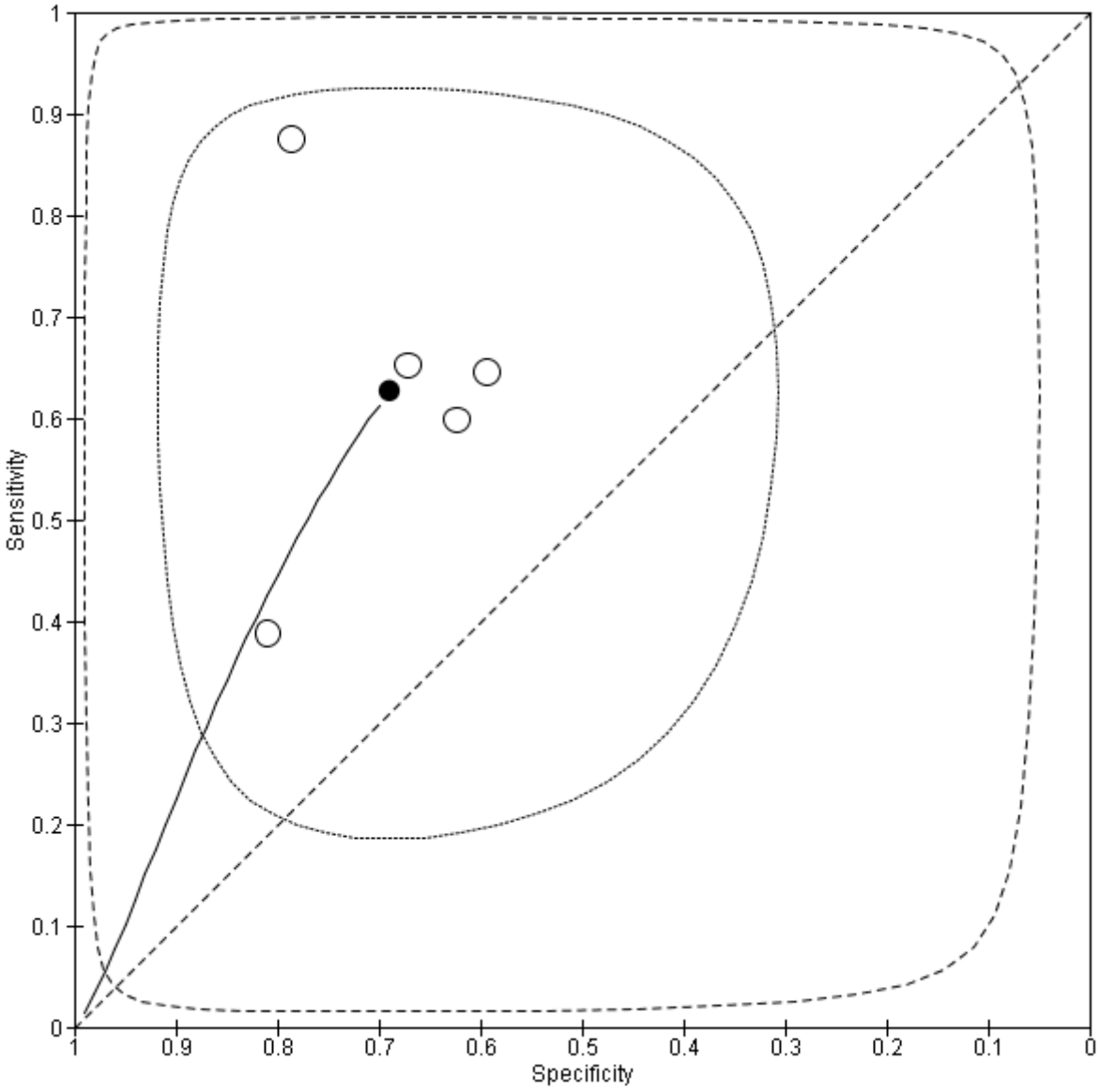
FeNO (cut-off: >30 ppb) vs diagnosis with peak flow variability or bronchodilator reversibility, or clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests



Adults with Mixed/Not Reported Smoking Status

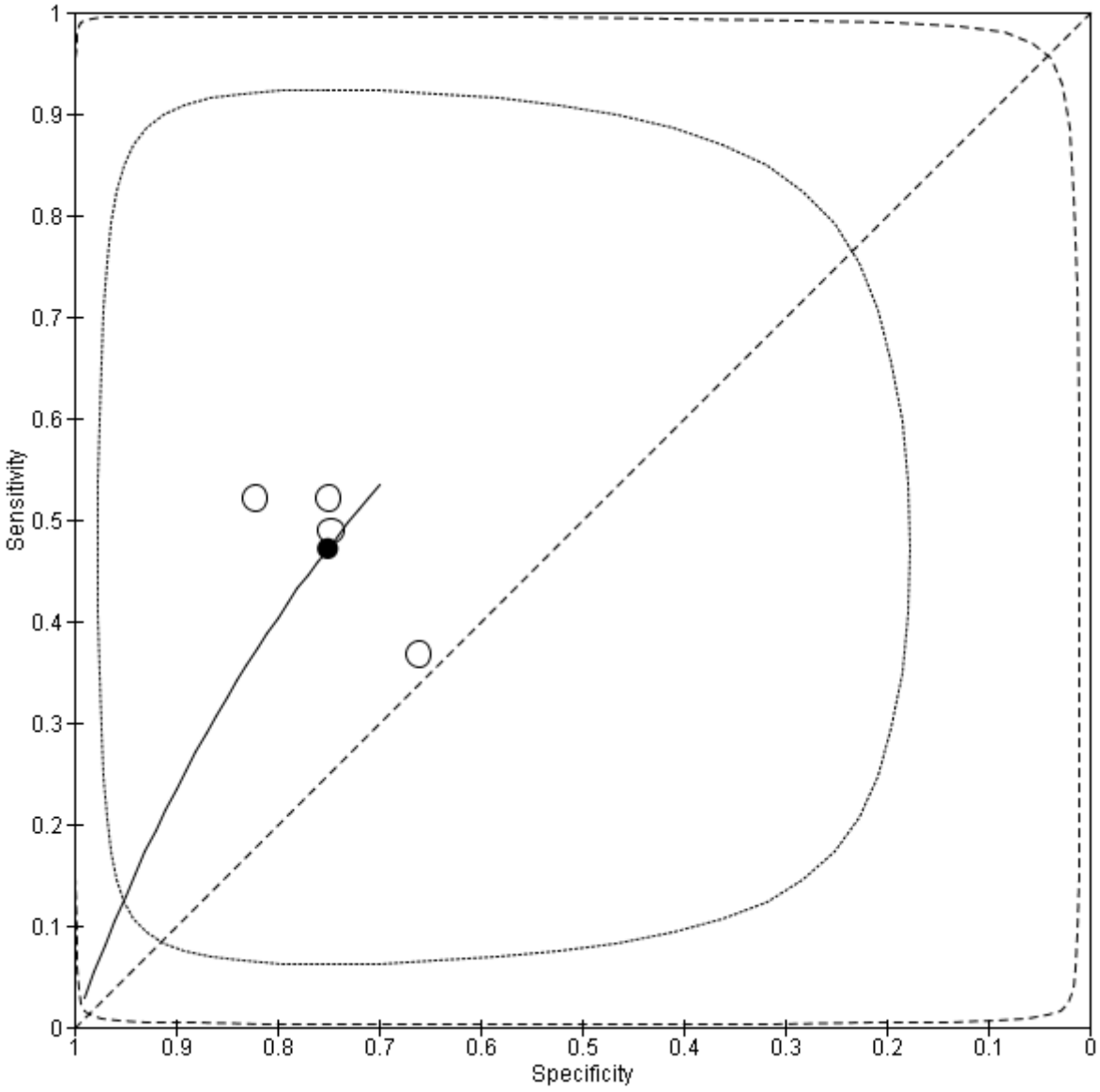
FeNO (cut-off: >20 ppb) vs clinician diagnosis with bronchodilator reversibility and/or methacholine/saline bronchial challenge tests or diagnosis with methacholine

bronchial challenge test



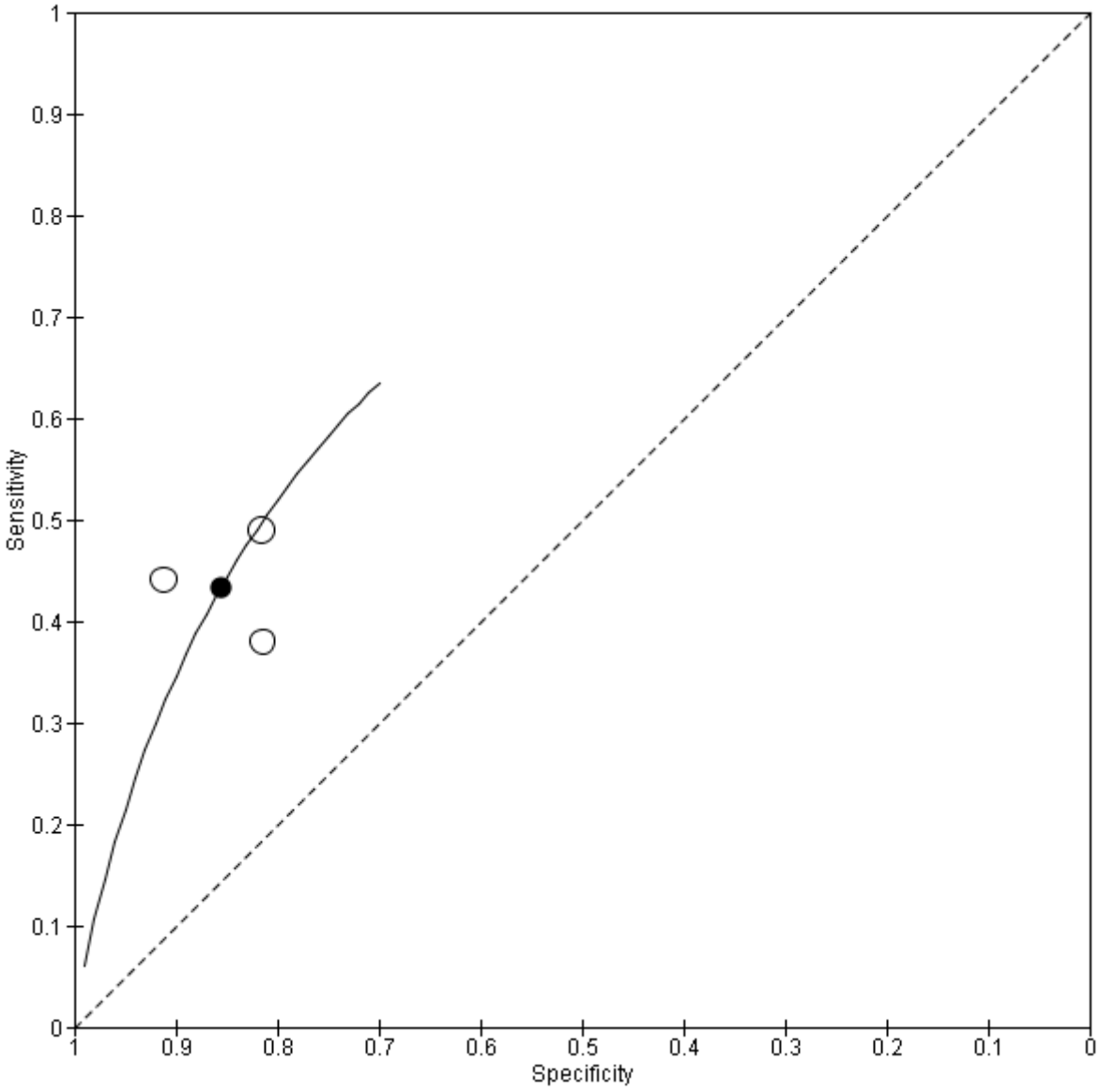
FeNO (cut-off: >25 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests or diagnosis with methacholine bronchial

challenge test



FeNO (cut-off: >30 ppb) vs clinician diagnosis with bronchodilator reversibility and methacholine bronchial challenge tests or diagnosis with methacholine bronchial

challenge test



Appendix F – GRADE tables

Accuracy of FeNO measures

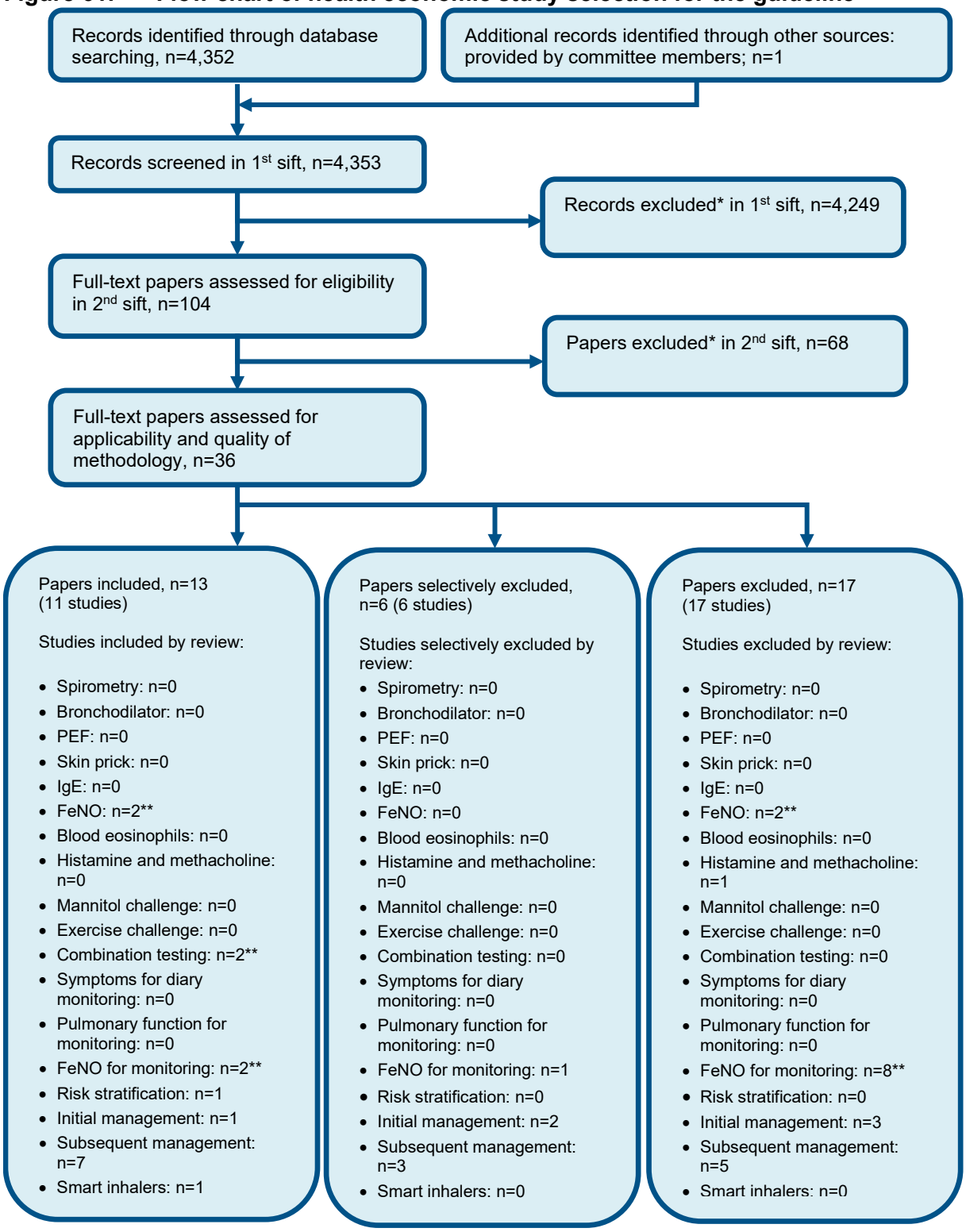
Not applicable to this evidence review.

FeNO Test and treat: GRADE tables.

No evidence identified.

Appendix G – Economic evidence study selection

Figure 61: 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 H – Economic evidence tables

<table>
<tr><th>Study</th><th colspan="4">Harnan 2015(Harnan et al., 2015)</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)

Study design:
Decision tree

Approach to analysis:

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</td>
<td>Population:

People with symptoms of asthma as seen in primary and secondary care in England and Wales.

Cohort settings:

Start age: NR

Male: NR

Intervention
1. Bronchial challenge test with methacholine (MCT)
2. FeNO + bronchodilator reversibility (NObreath)
3. FeNO + bronchodilator</td>
<td>Total costs (mean per patient):

Intervention (£)
1. 1226
2. 686.08
3. 687.61
4. 688.33
5. 1265.78
6. 1267.32
7. 1268.03
8. 810.14
9. 811.67
10. 812.38
11. 1328.28
12. 819.94
13. 821.47
14. 822.18
15. 877.91
16. 886.27
17. 907.71

For incremental analysis see</td>
<td>Total QALYs

Intervention
1. 4.2834
2. 4.2829
3. 4.2829
4. 4.2829
5. 4.2812
6. 4.2812
7. 4.2812
8. 4.2783
9. 4.2783
10. 4.2783
11. 4.2774
12. 4.2771
13. 4.2771
14. 4.2771
15. 4.2719
16. 4.2710
17. 4.2686</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>
</table>
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</table>

<table>
<tr><th>Study</th><th colspan="4">Harnan 2015(Harnan et al., 2015)</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>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. 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%</td>
<td>reversibility (NIOX VERO)
4. FeNO + bronchodilator reversibility (NIOX MINO)
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)</td>
<td>cost effectiveness column
Currency & cost year:

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</td>
<td>For incremental analysis see cost effectiveness column</td>
<td>
<table>
<tr><td>10</td><td>812.38</td><td>4.2783</td><td>Dominated by 2</td><td>0%/0%</td></tr>
<tr><td>9</td><td>811.67</td><td>4.2783</td><td>Dominated by 2</td><td>0%/0%</td></tr>
<tr><td>8</td><td>810.14</td><td>4.2783</td><td>Dominated by 2</td><td>2%</td></tr>
<tr><td>7</td><td>1268.03</td><td>4.2812</td><td>Dominated by 2</td><td>0%/0%</td></tr>
<tr><td>6</td><td>1267.32</td><td>4.2812</td><td>Dominated by 2</td><td>0%/0%</td></tr>
<tr><td>5</td><td>1265.78</td><td>4.2812</td><td>Dominated by 2</td><td>0%/0%</td></tr>
<tr><td>4</td><td>688.33</td><td>4.2829</td><td>Dominated by 2</td><td>0%/0%</td></tr>
<tr><td>3</td><td>687.61</td><td>4.2829</td><td>Dominated by 2</td><td>98%/95%</td></tr>
<tr><td>2</td><td>686.08</td><td>4.2829</td><td>Baseline</td><td>0%/0%</td></tr>
</table>
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</table>

<table>
<tr><th>Study</th><th colspan="4">Harnan 2015(Harnan et al., 2015)</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></td>
<td>13. FeNO (NIOX VERO)
14. FeNO (NIOX MINO)
15. PEF
16. Bronchodilator reversibility
17. FEV1/FVC</td>
<td>methacholine 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 and 1 laboratory visit).

Costs associated with loss of control for FN patients, (1 exacerbation per year)</td>
<td></td>
<td>
<table>
<tr><td>1</td><td>1226</td><td>4.2834</td><td>539.92</td><td>0.005</td><td>£1,125,074 per QALY</td><td>0%/0%</td></tr>
</table>

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]
<table>
<tr><th>Int</th><th>Cost (£)</th><th>QALY</th><th>Inc cost</th><th>Inc QALY</th><th>ICER</th></tr>
<tr><td>17</td><td>907.71</td><td>4.2686</td><td colspan="3">Dominated by 12</td></tr>
<tr><td>16</td><td>886.27</td><td>4.2710</td><td colspan="3">Dominated by 12</td></tr>
<tr><td>15</td><td>877.91</td><td>4.2719</td><td colspan="3">Dominated by 12</td></tr>
<tr><td>14</td><td>822.18</td><td>4.2771</td><td colspan="3">Dominated by 12</td></tr>
<tr><td>13</td><td>821.47</td><td>4.2771</td><td colspan="3">Dominated by 12</td></tr>
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<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>12</td><td>819.94</td><td>4.2771</td><td colspan="3">Baseline</td></tr>
<tr><td>11</td><td>1328.28</td><td>4.2774</td><td colspan="3">Dominated by 1</td></tr>
<tr><td>1</td><td>1226</td><td>4.2834</td><td>406.06</td><td>0.0063</td><td>£64,454 per QALY</td></tr>
</table>
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.
</td></tr>
</table>

Study	Harnan 2015(Harnan et al., 2015)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
				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. Unclear if FeNO prices are VAT exclusive or inclusive. 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.

Study	Harnan 2015(Harnan et al., 2015)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
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= methacholine 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 I – Health economic model

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

Appendix J – Excluded studies

Accuracy of FeNO measures: Studies excluded from the diagnostic review

Table 14: Studies excluded from the review

Study	Code [Reason]
Abbas, A. H., Rasheed, M. A., Al-Hindy, H. A. A. et al. (2021) The role of serum IL-1beta in combination with fractional exhaled nitric oxide in the diagnosis of adult bronchial asthma. NeuroQuantology 19(8): 13-19	- Reference standard used in study was unclear or not relevant to this review protocol
Alvarez-Puebla, M. J., Olaguibel Rivera, J. M., Almudevar, E. et al. (2015) Cutoff point for exhaled nitric oxide corresponding to 3% sputum eosinophils. Journal of investigational allergology & clinical immunology 25(2): 107-11	- ICS treatment washout period not suitable for index test
Asano, Takamitsu, Takemura, Masaya, Fukumitsu, Kensuke et al. (2017) Diagnostic utility of fractional exhaled nitric oxide in prolonged and chronic cough according to atopic status. Allergology international : official journal of the Japanese Society of Allergology 66(2): 344-350	- Study aiming to diagnose a disease not relevant to this review protocol *cough-variant asthma and cough-predominant asthma and results not reported in an extractable format.*
Backer, Vibeke; Sverrild, Asger; Porsbjerg, Celeste (2014) FENO and AHR mannitol in patients referred to an out-of-hospital asthma clinic: a real-life study. The Journal of asthma : official journal of the Association for the Care of Asthma 51(4): 411-6	- Reference standard used in study was unclear or not relevant to this review protocol
Baranski, Kamil and Schlunssen, Vivi (2022) The Accuracy of a Screening Tool in Epidemiological Studies-An Example of Exhaled Nitric Oxide in Paediatric Asthma. International journal of environmental research and public health 19(22)	- Population not relevant to this review protocol *Epidemiological study considering screening in healthy participants*
Bougard, N., Nekoee, H., Schleich, F. et al. (2020) Assessment of diagnostic accuracy of lung function indices and FeNO for a positive methacholine challenge. Biochemical pharmacology 179: 113981	- ICS treatment washout period not suitable for index test
Boulet, Louis-Philippe, Boulay, Marie-Eve, Cote, Andreanne et al. (2023) Airway inflammation and hyperresponsiveness in subjects with	- Reference standard used in study was unclear or not relevant to this review protocol

Study	Code [Reason]
respiratory symptoms and normal spirometry. The European respiratory journal 61(3)	*case finding study but not physician diagnosis of asthma as an outcome*
Brindisi, Giulia, De Vittori, Valentina, De Nola, Rosalba et al. (2021) The Role of Nasal Nitric Oxide and Anterior Active Rhinomanometry in the Diagnosis of Allergic Rhinitis and Asthma: A Message for Pediatric Clinical Practice. Journal of asthma and allergy 14: 265-274	- ICS treatment washout period not suitable for index test
Brooks, Elizabeth A. and Massanari, Marc (2018) Cost-Effectiveness Analysis of Monitoring Fractional Exhaled Nitric Oxide (FeNO) in the Management of Asthma. Managed care (Langhorne, Pa.) 27(7): 42-48	- Study design not relevant to this review protocol
Brunn, Benjamin, Hapfelmeier, Alexander, Jorres, Rudolf A et al. (2023) Development of a diagnostic score using FeNO and symptoms to predict asthma. Respiratory medicine 215: 107299	- ICS treatment washout period not suitable for index test *no evidence of wash-out period* - Population not relevant to this review protocol *16.9% of participants on inhaled meds. 12% inhaled steroids and no evidence of wash-out period*
Chen, Feng-Jia, Liao, Huai, Huang, Xin-Yan et al. (2016) Importance of fractional exhaled nitric oxide in diagnosis of bronchiectasis accompanied with bronchial asthma. Journal of thoracic disease 8(5): 992-9	- Reference standard used in study was unclear or not relevant to this review protocol
Chen, Hao, Zhang, Xinyu, Zhu, Li et al. (2022) Clinical and immunological characteristics of Aspergillus fumigatus-sensitized asthma and allergic bronchopulmonary aspergillosis. Frontiers in immunology 13: 939127	- Population not relevant to this review protocol *Majority of participants had asthma before testing*
Chen, Li-Chang, Zeng, Guan-Sheng, Wu, Ling-Ling et al. (2021) Diagnostic value of FeNO and MMEF for predicting cough variant asthma in chronic cough patients with or without allergic rhinitis. The Journal of asthma : official journal of the Association for the Care of Asthma 58(3): 326-333	- Study aiming to diagnose a disease not relevant to this review protocol *distinguishing cough-variant asthma from non-cough variant asthma*
Darba, Josep, Ascanio, Meritxell, Syk, Jorgen et al. (2021) Economic Evaluation of the Use of FeNO for the Diagnosis and Management of Asthma Patients in Primary Care in Sweden.	- Study design not relevant to this review protocol

Study	Code [Reason]
ClinicoEconomics and outcomes research : CEOR 13: 289-297	
de Jong, Carmen C. M., Pedersen, Eva S. L., Mozun, Rebeca et al. (2020) Diagnosis of asthma in children: findings from the Swiss Paediatric Airway Cohort. The European respiratory journal 56(5)	- ICS treatment washout period not suitable for index test
Duong-Quy, Sy, Vu-Minh, Thuc, Hua-Huy, Thong et al. (2017) Study of nasal exhaled nitric oxide levels in diagnosis of allergic rhinitis in subjects with and without asthma. Journal of asthma and allergy 10: 75-82	- Study aiming to diagnose a disease not relevant to this review protocol
Elenius, V., Jartti, T., Adamiec, A. et al. (2020) FeNO, forced oscillation, or spirometry? Lung function testing in wheezy pre-schoolers and the prediction of asthma, a systematic review. Allergy Eur. J. Allergy Clin. Immunol. 75(suppl109): 68-None	- Conference abstract
Engel, Julia, van Kampen, Vera, Gering, Vitali et al. (2019) Non-invasive tools beyond lung function before and after specific inhalation challenges for diagnosing occupational asthma. International archives of occupational and environmental health 92(7): 1067-1076	- ICS treatment washout period not suitable for index test
Feng, Yong, Zhang, Shiyao, Shang, Yunxiao 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: 1-8	- Reference standard used in study was unclear or not relevant to this review protocol
Feng-Jia, Chen, Xin-Yan, Huang, Geng-Peng, Lin et al. (2018) Validity of fractional exhaled nitric oxide and small airway function indices in diagnosis of cough-variant asthma. The Journal of asthma : official journal of the Association for the Care of Asthma 55(7): 750-755	- Study aiming to diagnose a disease not relevant to this review protocol *accuracy for distinguishing between cough-variant and non-cough variant asthma*
Florentin, A., Acouetey, D. S., Remen, T. et al. (2014) Exhaled nitric oxide and screening for occupational asthma in two at-risk sectors: bakery and hairdressing. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease 18(6): 744-50	- Reference standard used in study was unclear or not relevant to this review protocol

Study	Code [Reason]
Giovannelli, J., Cherot-Kornobis, N., Hulo, S. et al. (2016) Both exhaled nitric oxide and blood eosinophil count were associated with mild allergic asthma only in non-smokers. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 46(4): 543-54	- ICS treatment washout period not suitable for index test
Giovannini, M., Valli, M., Ribuffo, V. et al. (2014) Relationship between Methacholine Challenge Testing and exhaled nitric oxide in adult patients with suspected bronchial asthma. European annals of allergy and clinical immunology 46(3): 109-13	- Study does not contain any diagnostic accuracy outcomes
Grzelewski, Tomasz, Witkowski, Konrad, Makandjou-Ola, Eusebio et al. (2014) Diagnostic value of lung function parameters and FeNO for asthma in schoolchildren in large, real-life population. Pediatric pulmonology 49(7): 632-40	- Study does not contain any relevant index tests *cut-off used in the study does not match protocol*
Guida, Giuseppe, Carriero, Vitina, Bertolini, Francesca et al. (2023) Exhaled nitric oxide in asthma: from diagnosis to management. Current opinion in allergy and clinical immunology 23(1): 29-35	- Review article but not a systematic review
Hao, Huijuan, Bao, Wuping, Xue, Yishu 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 and clinical immunology. In practice 9(8): 3098-3108.e4	- No relevant outcomes *study does not report relevant data on sensitivity and specificity*
Harnan, S. E., Essat, M., Gomersall, T. et al. (2017) Exhaled nitric oxide in the diagnosis of asthma in adults: a systematic review. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 47(3): 410-429	- Systematic review used as source of primary studies
Harnan, S, Essat, M, Gomersall, T et al. (2015) Exhaled Nitric Oxide For The Diagnosis Of Asthma In Adults And Children: A Systematic Review. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 18(7): a345	- Systematic review used as source of primary studies
Jo, Eun-Jung, Song, Woo-Jung, Kim, Tae-Wan et al. (2014) Reference ranges and determinant	- Population not relevant to this review protocol

Study	Code [Reason]
factors for exhaled nitric oxide in a healthy korean elderly population. Allergy, asthma & immunology research 6(6): 504-10	*Participants were not suspected of having asthma*
Kanemitsu, Yoshihiro, Matsumoto, Hisako, Osman, Nuriamina et al. (2016) "Cold air" and/or "talking" as cough triggers, a sign for the diagnosis of cough variant asthma. Respiratory investigation 54(6): 413-418	- Population not relevant to this review protocol *15% had received corticosteroids treatment in the four weeks before the study*
Kellerer, Christina, Hapfelmeier, Alexander, Jorres, Rudolf A. et al. (2021) Evaluation of the diagnostic accuracy of fractional exhaled nitric oxide (FeNO) in patients with suspected asthma: study protocol for a prospective diagnostic study. BMJ open 11(2): e045420	- study protocol
Kellerer, Christina, Wagenpfeil, Stefan, Daines, Luke 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	- Reference standard used in study was unclear or not relevant to this review protocol *reports the sensitivity of FeNo compared with reference standards not meeting protocol: whole-body plethysmography (WBP) and spirometry*
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
Liu, Yalan, Chang, Xiaohong, Liang, Lirong et al. (2021) A comparative study of the RuiBreath and NIOX VERO analyzers for detecting fractional exhaled nitric oxide. Journal of thoracic disease 13(7): 4418-4426	- Population not relevant to this review protocol *only included people with confirmed Asthma*
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	- Study does not contain any diagnostic accuracy outcomes
Maniscalco, Mauro, Faraone, Stanislao, Sofia, Matteo et al. (2015) Extended analysis of exhaled and nasal nitric oxide for the evaluation of chronic cough. Respiratory medicine 109(8): 970-4	- No relevant outcomes *reports sensitivity and specificity data for differentiating between cough variant asthma, and non-asthmatic eosinophilic bronchitis vs upper airway cough syndrome and gastroesophageal reflux disease.*
Marshall, Helen, Wild, Jim M, Smith, Laurie J et al. (2023) Functional imaging in asthma and	- study protocol

Study	Code [Reason]
COPD: design of the NOVELTY ADPro substudy. ERJ open research 9(2)	
Martin, M. J., Wilson, E., Gerrard-Tarpey, W. et al. (2016) The utility of exhaled nitric oxide in patients with suspected asthma. Thorax 71(6): 562-564	- Data not reported in an extractable format or a format that can be analysed
Martins, C., Silva, D., Pinto, M. et al. (2016) Exhaled NO is not a useful tool to identify childhood asthma in epidemiological studies. Allergy: European Journal of Allergy and Clinical Immunology 71(supplement102): 357-358	- Conference abstract
Mikeladze, T., Zhorzholiani, L., Saginadze, L. et al. (2018) ASTHMA PREDICTIVE INDEX AND NITRIC OXIDE PROGNOSTIC VALUE IN YOUNG CHILDREN WITH RECURRENT WHEEZING. Georgian medical news: 104-107	- Reference standard used in study was unclear or not relevant to this review protocol
Miskoff, Jeffrey A.; Dewan, Asa; Chaudhri, Moiuz (2019) Fractional Exhaled Nitric Oxide Testing: Diagnostic Utility in Asthma, Chronic Obstructive Pulmonary Disease, or Asthma-chronic Obstructive Pulmonary Disease Overlap Syndrome. Cureus 11(6): e4864	- Study design not relevant to this review protocol
Murray, Clare, Foden, Philip, Lowe, Lesley 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	- Population not relevant to this review protocol
Perez, M. P., Falcon, A. R., Galvan, M. F. et al. (2015) Comparative study of bronchial provocation tests using methacholine or mannitol in bronchial asthma. European Respiratory Journal 46(suppl59)	- Study does not contain any relevant index tests
Sabatelli, L., Seppala, U., Sastre, J. et al. (2017) Cost-effectiveness and Budget Impact of Routine Use of Fractional Exhaled Nitric Oxide Monitoring for the Management of Adult Asthma Patients in Spain. Journal of investigational allergology & clinical immunology 27(2): 89-97	- Study design not relevant to this review protocol
Schneider, Antonius, Faderl, Bernhard, Schwarzbach, Johannes et al. (2014) Prognostic value of bronchial provocation and FENO measurement for asthma diagnosis--	- ICS treatment washout period not suitable for index test

Study	Code [Reason]
results of a delayed type of diagnostic study. Respiratory medicine 108(1): 34-40	
Song, Woo-Jung, Kim, Hyun Jung, Shim, Ji-Su et al. (2017) Diagnostic accuracy of fractional exhaled nitric oxide measurement in predicting cough-variant asthma and eosinophilic bronchitis in adults with chronic cough: A systematic review and meta-analysis. The Journal of allergy and clinical immunology 140(3): 701-709	- Systematic review used as source of primary studies
Tang, Songqi, Xie, Yiqiang, Yuan, Conghu et al. (2019) Fractional Exhaled Nitric Oxide for the Diagnosis of Childhood Asthma: a Systematic Review and Meta-analysis. Clinical reviews in allergy & immunology 56(2): 129-138	- Systematic review used as source of primary studies
Urbankowski, T. and Przybylowski, T. (2022) Blood eosinophils, FeNO and small airways dysfunction in predicting airway hyperresponsiveness in patients with asthma-like symptoms. Journal of Asthma 59(7): 1376-1386	- Reference standard used in study was unclear or not relevant to this review protocol *reference standard is for airway hyperresponsiveness (MCT); no physician involvement for asthma diagnosis*
Voutilainen, Mikko, Malmberg, Leo Pekka, Vasankari, Tommi et al. (2013) Exhaled nitric oxide indicates poorly athlete's asthma. Clinical Respiratory Journal 7(4): 347-353	- Population not relevant to this review protocol *Participants were not presenting with symptoms of asthma - not considered to be representative of typical presentation in the NHS*
Wagener, A. H., de Nijs, S. B., Lutter, R. et al. (2015) External validation of blood eosinophils, FE(NO) and serum periostin as surrogates for sputum eosinophils in asthma. Thorax 70(2): 115-20	- Population not relevant to this review protocol *two separate cohorts of people with confirmed asthma*
Wang, Yanqi, Zhao, Lixuan, Chen, Fang et al. (2021) Diagnostic Value of Fractional Exhaled Nitric Oxide and Small Airway Function in Differentiating Cough-Variant Asthma from Typical Asthma. Canadian respiratory journal 2021: 9954411	- Study design not relevant to this review protocol
Yune, Sehyo, Lee, Jin Young, Choi, Dong Chull et al. (2015) Fractional exhaled nitric oxide: comparison between portable devices and correlation with sputum eosinophils. Allergy, asthma & immunology research 7(4): 404-8	- No relevant outcomes *reports on the correlation between FeNO and induced sputum eosinophil count (ISE) >3% rather than asthma diagnosis*
Zhang, Li, Liu, Shuang, Li, Mei et al. (2020) Diagnostic value of fractional exhaled nitric	- Systematic review used as source of primary studies

Study	Code [Reason]
oxide in cough-variant asthma: an updated meta-analysis. The Journal of asthma : official journal of the Association for the Care of Asthma 57(3): 335-342	
Zhang, Xue, Xu, Zichong, Lin, Jingwang et al. (2023) Sex differences of small airway function and fractional exhaled nitric oxide in patients with mild asthma. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 130(2): 187-198e3	- Reference standard used in study was unclear or not relevant to this review protocol *reference std is MCT alone, no physician assessment*
Zhu, H. Y., Wu, J. S., Zhang, Z. et al. (2016) Fractional exhaled nitric oxide: A comparative study in patients with acute exacerbation of chronic obstructive pulmonary disease and bronchial asthma. International Journal of Clinical and Experimental Medicine 9(6): 10565-10571	- Population not relevant to this review protocol *mixed population of people already diagnosed with Asthma and people with COPD*
Zhu, Haiyan, Zhang, Rongrong, Hao, Chuangli 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 Children. Medical science monitor : international medical journal of experimental and clinical research 25: 3832-3838	- Population not relevant to this review protocol *children with confirmed asthma at baseline; incorrect outcome: detecting cough-variant vs non-cough variant asthma*

FeNO Test and treat: Excluded studies

No evidence was identified for this review.

Health Economic: Excluded 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.

Table 15: Studies excluded from the health economic review

Reference	Reason for exclusion
Berg 2008(Berg et al., 2008)	Excluded as rated partially applicable with potentially serious limitation. The analysis compares only costs and a most applicable cost-utility analysis was identified(Harnan et al., 2015). Sources for unit costs are outdates and on cusp of the exclusion cut-off. The perspective is not UK NHS.
Price 2009(Price et al., 2009)	Excluded as rated partially applicable with potentially serious limitation. The analysis compares only costs and a most applicable cost-utility analysis was identified(Harnan et al., 2015). Sources for unit costs are outdates and on cusp of the exclusion cut-off.