EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Task force report

European Respiratory Society Guidelines for the Diagnosis of Asthma in Adults

Renaud Louis, Imran Satia, Inigo Ojanguren, Florence Schleich, Matteo Bonini, Thomy Tonia, David Rigau, Anne ten Brinke, Roland Buhl, Stelios Loukides, Janwillem W. H. Kocks, Louis-Philippe Boulet, Arnaud Bourdin, Courtney Coleman, Karen Needham, Mike Thomas, Marco Idzko, Alberto Papi, Celeste Porsbjerg, Daniel Schuermans, Joan B. Soriano, Omar S. Usmani

Please cite this article as: Louis R, Satia I, Ojanguren I, *et al*. European Respiratory Society Guidelines for the Diagnosis of Asthma in Adults. *Eur Respir J* 2022; in press (https://doi.org/10.1183/13993003.01585-2021).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

European Respiratory Society Guidelines for the Diagnosis of Asthma in Adults

[#]Renaud Louis, *Imran Satia, *Inigo Ojanguren, *Florence Schleich, *Matteo Bonini, Thomy Tonia, David Rigau, Anne ten Brinke, Roland Buhl, Stelios Loukides, Janwillem WH Kocks, Louis-Philippe Boulet, Arnaud Bourdin, Courtney Coleman, Karen Needham, Mike Thomas, Marco Idzko, Alberto Papi, Celeste Porsbjerg, Daniel Schuermans, Joan B. Soriano, [$]Omar S. Usmani

* All authors contributed equally

[#] First author, Task force chair

[$] Corresponding author, Task force co-chair

Corresponding author:

Dr. Omar S. Usmani

National Heart and Lung Institute, Imperial College London and Royal Brompton Hospital, London, United Kingdom

Email: o.usmani@imperial.ac.uk

Word Count: 8872

Key words: Lung function, Bronchodilator reversibility, Bronchial challenge, Spirometry, Nitric oxide, Blood eosinophil, Serum IgE

ABBREVIATIONS

AUC-ROC	Area under the receiver operating characteristic curve
BdR	Bronchodilator reversibility
BEC	Blood eosinophil count
BHR	Bronchial hyperresponsiveness
CI	Confidence intervals
COPD	Chronic obstructive pulmonary disease
EtD	Evidence to decision framework
FeNO	Forced exhaled nitric oxide
FEV_1	Forced expiratory volume in one second
FRC	Functional residual capacity
GINA	Global Initiative for Asthma
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HRCT	High resolution computed tomogram
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
IL	Interleukin
NPV	Negative predictive value

OCS	Oral corticosteroid
PC20-H	Provocation concentration causing 20% fall in FEV_1 with histamine
PC20-M	Provocation concentration causing 20% fall in FEV_1 with methacholine
PD15	Provocation dose causing a 15% fall in FEV_1
PEF	Peak expiratory flow
PICO	Population, Index (Test), Comparison and Outcome
PPV	Positive predictive value
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
ROC	Receiver operating characteristic
RV	Residual volume
SABA	Short-acting beta-2 agonist
sGAW	Specific airway conductance
TF	Task force
TLC	Total lung capacity

ABSTRACT

Although asthma is very common affecting 5-10% of the population, the diagnosis of asthma in adults remains a challenge in the real world that results in both over- and under-diagnosis. A task force (TF) was set up by the European Respiratory Society to systematically review the literature on the diagnostic accuracy of tests used to diagnose asthma in adult patients and provide recommendation for clinical practice.

The TF defined eight PICO (Population, Index, Comparator, and Outcome) questions that were assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach, The TF utilised the outcomes to develop an evidenced-based diagnostic algorithm, with recommendations for a pragmatic guideline for everyday practice that was directed by real-life patient experiences.

The TF support the initial use of spirometry followed, and if airway obstruction is present, by bronchodilator reversibility testing. If initial spirometry fails to show obstruction, further tests should be performed in the following order: FeNO, PEF variability or in secondary care, bronchial challenge. We present the thresholds for each test that are compatible with a diagnosis of asthma in the presence of current symptoms.

The TF reinforce the priority to undertake spirometry and recognise the value of measuring blood eosinophils and serum IgE to phenotype the patient. Measuring gas trapping by body plethysmography in patients with preserved FEV_1/FVC ratio deserves

further attention. The TF draw attention on the difficulty of making a correct diagnosis in patients already receiving inhaled corticosteroids, the comorbidities that may obscure the diagnosis, the importance of phenotyping, and the necessity to consider the patient experience in the diagnostic process.

INTRODUCTION

Asthma is the most frequent chronic inflammatory airway disease globally with a prevalence reaching 5-10%(1), affecting 339 million people worldwide.(2) Asthma is defined by the cardinal symptoms of breathlessness, wheeze, chest tightness and cough, together with the presence of exaggerated expiratory airflow fluctuation that varies over time. This airways instability is usually ascertained by peak flow variability, reversibility to fast-acting bronchodilator drug, or by bronchoconstriction following bronchial challenge.(3) However, population data consistently show asthma is both under- and over-diagnosed; a phenomenon which may approach a false positive diagnosis of 30%,(4) where the insufficient use of spirometry is fundamentally recognized to cause misdiagnosis, as the diagnosis is based primarily on symptoms alone. Misdiagnosis also occurs in specialist care, where patients labelled and treated with severe asthma do not satisfy the classic criteria of asthma when thoroughly investigated and monitored overtime.(5) Although there is no unanimous agreement upon an acceptable false positive rate, a 10% threshold represents a significant improvement in diagnostic accuracy.

When faced with the clinical challenge of diagnosing asthma, we must not forget that, at the centre, there is an individual patient struggling to manage their health. Patients describe feeling upset and frustrated when going through a series of tests which do not provide a definitive diagnosis, describing the process as “trial and error”.(6) Combining tests into a single appointment can make the process easier by reducing travel time, childcare costs, and time off work.(7) However, patients do find certain diagnostic tests difficult to complete and may experience side-effects such as breathlessness and anxiety.(8;9) The requirement to stop asthma medications prior to a diagnostic test can cause anxiety,(10) with lack of clear advance information on which medications to stop and for how long.(8)

Although there are many asthma guidelines recommending objective testing to confirm the diagnosis in symptomatic patients, there is considerable variation between them with lack of consensus on the tests and their sequence. Yet, reports consistently reiterate the need to better diagnose asthma and the need to determine which of the commonly used tests are most helpful.(11) It is well-recognized that adherence by healthcare professionals to guidelines is suboptimal,(12) and this may reflect difficulty in access to the recommended tests or incorporating them in their everyday practice in diagnosing asthma within local patient pathways. Importantly, the patients’ perspective is often not taken into account at the planning stage when developing guidelines.(13)

In 2018, the European Respiratory Society (ERS) set up a task force (TF) to systematically review the literature on the diagnostic accuracy of tests used to diagnose asthma in adult patients using the GRADE methodology and provide recommendations for clinical practice. The TF specifically focused to develop an evidence-based pragmatic clinical guideline for everyday practice that was directed by patients' real-life experiences in their diagnosis of asthma (a patient-driven guideline), with a physician-centric practical approach to; (i) determine which tests to use to diagnose asthma in primary care, (ii) the transition point of referral to specialist care and, (iii) which tests to undertake in the specialist setting.

METHODS

The methods are described in detail in the supplementary material. The purpose of the TF was to assess the accuracy of tests used to diagnose asthma in well-resourced health care systems.

Task force composition

The panel consisted of a multidisciplinary group of healthcare professionals with expertise in asthma from both primary and specialist care settings, junior and senior clinicians, and with patient representation (supplementary table 1). The panel did not include respiratory technicians and primary care clinicians from low- or middle-income countries. Methodologists from the ERS provided expertise, overview and guidance on methodology, GRADEing and making recommendations for diagnostic tests.(14) Panel members disclosed potential conflicts of interest according to ERS policies at the start of the TF and prior to publication of this manuscript.

Formulation of the PICO questions

Asthma is characterized by variable respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough, and variable expiratory airflow limitation, and is usually associated with airway inflammation.(3) The TF initially met at the ERS 2018 congress and importantly agreed upon the operating definition of asthma to be used (Table 1), which was close to the definition adopted by the Global Initiative for Asthma (GINA), although the latter mentions the airway inflammatory component as being usually present in asthmatics. In contrast to GINA but similar to NICE and NHLBI we

adopted the PICO framework and GRADE methodology to assess each individual test, but no therapies were evaluated (supplementary table 2).

Several discussions led to finalization of the eight review questions, formulated using the Population, Index (Test), Comparator and Outcome (PICO) format (Table 2). PICO questions were designed to assess tests available in the primary and specialist care setting. Two PICO questions were externally commissioned. A pair of TF members (one senior, one junior) were allocated to address the remaining PICO questions.

Literature search and application of the GRADE approach

An initial systematic literature search was performed by an experienced librarian based at Liege University Public Health Department for each PICO question covering the period from January 1946 to July 2019. Eligible papers had to compare the index test to a reference standard including at least one other objective test. For each question, the outcomes were diagnostic accuracy: sensitivity and specificity. Cross-sectional and retrospective studies were included. Case-control studies were excluded. Manuscripts where tests had been used in the monitoring of asthma or assessment of treatment response were excluded. A final literature review for the eight PICO questions was performed for new publications up until July 2020. Whilst conducting the PICO analysis, we ensured that the index test was only in the index group and not in the gold standard reference group as, in routine clinical care, current clinical symptoms with either peak expiratory flow (PEF) variability, bronchodilator reversibility or bronchial hyper-responsiveness are used to diagnose asthma, so It may seem like the index test is also part of the ‘gold standard reference operational definition.

Junior members performed the initial screening of the outputs (title, abstract, and full manuscript review) from the systematic literature search, coordinated the final selection of research papers, performed the quality of evidence assessment for each selected research paper and undertook a draft GRADE assessment for presentation to the whole TF, supported by their senior member. In addition to the PICO questions, important diagnostic themes were identified by the TF as additional considerations each assigned to a senior member including the patient representative's view about the diagnostic tests they had undergone and their physical, social or psychological impact of the diagnosis,(15) reported as the patient perspective within each PICO.

Recommendation development process and construction of a diagnostic algorithm

All TF members were presented with and discussed the results of the GRADE assessment. Using the Evidence to Decision (EtD) framework, they agreed recommendations for each PICO question and documented the factors taken into account for each of them. Recommendations were described as strong or conditional to highlight the strength which may engage clinicians, patients and policy makers(16;17) (Tables 3 and 4). The algorithm was constructed based on the TF members clinical practice for the diagnosis of asthma in primary and specialist care, identifying when best for a primary care physician to refer to specialist care if persistent doubt in the diagnosis of asthma. All TF members drafted and agreed on the steps in the diagnostic algorithm.

Patient relevant outcomes

The GRADE approach emphasizes the importance of recommendations based on the impact on relevant patient outcomes.(14) Our patient TF member and the European Lung Foundation (ELF) were involved in every meeting of the TF, apart the first one, and contributed to the evidence to decision process for every PICO. The ELF conducted a patient-centred literature review to identify relevant outcomes and patient experience of diagnostic testing. Although diagnostic accuracy studies do not provide direct evidence for the improvement of patient outcomes, the TF discussed each PICO and the EtD framework in the context of patient related outcomes including test acceptability, feasibility, how important a patient may value the test, and the potential for the test to have impact on treatment (Table 5).

RESULTS

PICO 1: Can airway obstruction measured by spirometry help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Recommendation

- The TF recommends performing spirometry to detect airway obstruction as part of the diagnostic work-up of adults aged 18 years with suspected asthma (strong recommendation for the test, low quality of evidence)

Remarks

- An FEV_1/FVC <LLN or <75%, higher than the commonly utilized 70% threshold, should be considered supportive of an asthma diagnosis and should prompt further testing (see Algorithm)
- A normal spirometry does not exclude asthma

Background

Spirometry is a non-invasive physiological test, performed since the 19th Century, that measures the volume and flow of air during inhalation and exhalation. A standardized procedure for performing spirometry has been published by the ERS and the ATS.(8) The ratio of the forced expiratory volume in the first second to the forced vital capacity (FEV_1/FVC) is an index reflecting airway obstruction. The TF assessed the FEV_1/FVC ratio to determine whether it could help in the diagnosis of asthma.

Review of the evidence

Our literature search identified 11 potentially relevant studies of which four were suitable to be included (supplementary tables 3a&b),(18-21) all performed in secondary care that assessed the accuracy of the FEV_1/FVC ratio to predict the probability of asthma ascertained by either BdR of 12% and 200 ml or 15% reversibility, methacholine BHR (PC20-M <8-16 mg/ml), or 20% PEF variability over a two-week period (supplementary table 4).

In their cross-sectional study, Hunter et al., recruited 89 patients (baseline FEV_1 >65% of predicted) from primary care with a prior label of asthma, but 20 patients were found to have an alternative explanation for their asthma.(19) Of those diagnosed as asthma (n=69), 46% were receiving concomitant inhaled corticosteroid (ICS) while undergoing diagnostic testing. Asthma was diagnosed based on symptoms combined with at least one of the following: BdR of 15% after 200 µg salbutamol, PC20-M <8 mg/ml, or PEF variability of 20% over a 15-day period. A predetermined cut-off of the FEV_1/FVC ratio at 77% based on the 95% LLN found in healthy subjects, yielded a sensitivity and specificity of 61% and 60%, respectively.(19) Stanbrook et al., retrospectively analysed lung function tests of 500 patients referred to secondary care and found a FEV_1/FVC cut-off value of <90% predicted had 53% sensitivity and 27% specificity to identify a positive methacholine test (PC20-M <8mg/ml).(21)

Two retrospective studies conducted in secondary care investigated the best threshold by constructing ROC curves. In 270 patients, where half of the patients were treated with ICS, Bougard et al., found an AUC of 0.62 and a FEV_1/FVC cut-off value at 77% in the training cohort and an AUC of 0.68 with a FEV_1/FVC cut-off value of 79% in the validation cohort.(18) Nekoee et al., recruited steroid-naïve patients (n=702) with symptoms suggestive of asthma, including 19% of current smokers and displaying an average baseline FEV_1 of 95% predicted,(20) and found sensitivity ranged from 0.51 to 0.69 with specificity ranging from 0.28 to 0.76 (GRADE table 6, EtD supplementary table 3b)

Justification of the recommendation

Physiological airflow obstruction and fluctuation of airway caliber, that is usually reversible are recognized as hallmarks of asthma. Though the quality of evidence was low, the TF recommends spirometry as the first test to be conducted in the diagnostic work-up. Over-diagnosis, which occurs in approximately 30% of patients with asthma diagnosed in primary care, occurs in part because spirometry in not performed and has a substantial risk of harm due to inappropriate treatment side-effects, costs, and lack of proper diagnosis(4). Therefore, a strong recommendation can be made despite low quality of evidence. Spirometry is readily available both in primary and secondary care, even though it might not be used sufficiently in primary care. Our research found the FEV_1/FVC cut-off providing the best combination of sensitivity and specificity is close to 75%, a threshold well above the 70% threshold generally recognized as a marker of airway obstruction. However, sensitivity at a cut-off of 75% is close to 50% and much too

low to rule out asthma. Likewise, at this cut-off, specificity remains below 80% making spirometry alone insufficient to rule in asthma with confidence.

Patient perspective

Spirometry is non-invasive and generally well-accepted by the patient. The reproducibility of the measure, however, depends on the skill of the operator and the participation of the patient. Indeed, the role of the operator is crucial in putting patients at ease and guiding them through each step,(22) where patients value their role: “a sympathetic, helpful and considerate nurse can do wonders during this test”. Patients are also interested in knowing about their breathing performance and individual test results, and how they relate to averages for their age, height and weight.

Key unanswered questions

We know that FEV_1/FVC ratio declines with age so fixing a threshold is inappropriate to apply across a population with varying ages.(23) We did not find any study that expressed the FEV_1/FVC ratio as <LLN and calculated its prediction value. There is an urgent need for prospective studies in both primary and secondary care that would combine specific symptoms with spirometry indices expressed as LLN to make a diagnosis of asthma.

PICO 2: Can PEF variability testing help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Recommendation

- The TF suggests not recording PEF variability as the primary test to make a diagnosis of asthma diagnosis (conditional recommendation against the test, low quality of evidence)

Remarks

- PEF may be considered if no other lung function test is available including spirometry at rest and bronchial challenge testing
- PEF should be monitored over a two--week period and a variation of >20% considered as supportive of asthma diagnosis
- PEF variability <20% does not rule out asthma
- PEF may be especially useful to support a diagnosis of occupational asthma

Background

Peak expiratory flow (PEF) measurement over a few weeks has been advocated as a test to diagnose asthma for several decades as the tool to evidence airway caliber fluctuation associated with poor asthma control.(24)

Review of the evidence

Our literature search identified 15 potentially relevant studies of which six studies (one retrospective, five prospective) met the inclusion criteria (supplementary tables 5a&b).(19;25-29) Five studies (three in primary care, two in specialist care referred from primary care) addressed symptomatic patients without any prior investigations or

diagnosis, and one study included patients diagnosed with asthma in primary care but referred to secondary care (supplementary table 4).

All the studies assessed the diagnostic performance of pre-specified thresholds of PEF variability with thresholds most often set at 15% or 20% over a two-week period. The way to calculate the PEF variability has a great impact on diagnostic performance with the greatest sensitivity when variability is the difference between the greatest and the lowest value divided by the lowest.(26) Overall, PEF variability provided a highly variable sensitivity ranging from 5% until 93% while the specificity was ranging from 75% to 100% (GRADE table 7, EtD supplementary table 5b). The lower the variability required to define asthma, the greater the sensitivity.

Justification of the recommendation

Results from studies on PEF variability demonstrate a highly variable sensitivity, with lower sensitivities in studies where the prevalence of asthma was low. The most common method used to calculate PEF variability is the average daily amplitude percentage mean with a cut-off of 20%, however, alternatives such as the % amplitude highest PEF may just be as accurate and not require calculating the daily mean PEF.(26;30) Completion of accurate peak flow diaries was poor, with results as low as 50% in one study,(26) challenging the reliability, accuracy and feasibility of home PEF recordings. In addition, reliability of PEF measurement may be even lower in real life than in a research setting. A very recent study has shown that measurement over 5 days compared to 14 days improved diary completion rate from 15% to 94% with no loss of accuracy.(30) In the absence of spirometry defined obstruction and significant BdR, PEF

can be monitored over a two-week period particularly if access to bronchial challenge is limited. In the context of a patient with symptoms suggestive of asthma, a positive PEF variability of >20%, that is reliably performed, has a high positive predictive value. Lowering the cut-off at 15% to 10% would increase the sensitivity at the expense of specificity. Thus, PEF monitoring may be of higher value to diagnose asthma in patients with highly variable day-to-day symptoms, where variable airflow obstruction might be easily detected, or in patients with suspected occupational asthma. However, we caution that lack of PEF variability does not rule out asthma and further objective testing should always be performed. Spontaneous and ICS induced FEV_1 variability over time could also have been considered. However, we decided not to conduct a separate PICO due to the limitation of the ERS framework to eight PICO questions, and the low number of longitudinal studies that have evaluated FEV_1 variability over time. Having said that we mention a recent study looking at between visit FEV_1 variability, that provided similar results to PEF, with a poor sensitivity but a high specificity in the order to diagnose asthma.(31)

Patient perspective

PEF variability testing has advantages of being cheap and easy to perform even in low-resource settings. Although no undesirable effects of PEF testing were documented, the TF recognizes that for some patients performing home PEF twice daily for at least two weeks may become unrewarding and time-consuming, reinforcing the need for proper education and training. Patients may prefer undertaking a one-stop BdR undertaken in 15 mins, which if positive would potentially prevent delay in diagnosis and potential

treatment. Hence, if available, the TF advises BdR testing, particularly in primary care above PEF testing.

Key unanswered questions

PEF variability between 15% to 20% clearly lacks sensitivity to diagnose asthma compared to bronchial challenge and we advocate prospective studies to establish the threshold of variability that best correlates to a positive bronchial challenge test.

PICO 3: **Can measuring fractional exhaled nitric oxide (FeNO) help diagnose asthma in adults with episodic/chronic suggestive symptoms?**

Recommendation

- In patients suspected of asthma, in whom the diagnosis is not established based on the initial spirometry combined with bronchodilator reversibility testing, the TF suggests measuring the fraction of exhaled nitric oxide (FeNO) as part of the diagnostic work-up of adults aged >18 years with suspected asthma (conditional recommendation for the intervention, moderate quality of evidence)

Remarks

- A cut-off value of 40 ppb offers the best compromise between sensitivity and specificity while a cut-off of 50 ppb has a high specificity >90% and is supportive of a diagnosis of asthma
- A FeNO value <40 ppb does not rule out asthma and similarly high FeNO levels themselves do not define asthma

- FeNO values are markedly reduced by smoking, impaired airway calibre, treatment with ICS or anti-IL4/IL13-receptor alpha antibody

Background

Nitric oxide is a gas measurable in exhaled air by chemoluminescence or an electrochemical method, where the measurement has been standardized and endorsed by the ERS/ATS.(32) The fraction of exhaled nitric oxide (FeNO) measures allergic airway inflammation mediated through allergen-driven IL-4 and IL-13 effects on airway epithelial cells and is associated with the extent of airway eosinophilic inflammation.(33) FeNO is dependent on height, gender, atopy and smoking status and airway caliber.(34) FeNO is raised in patients with asthma compared to healthy subjects, and in asthma patients with allergic rhinitis compared to those without rhinitis. FeNO is exquisitely sensitive to ICS, with a sharp decrease in levels a few days after starting treatment.(35) Certain biological treatments, which can be given for other than severe asthma, eg. nasal polyposis, also reduce FeNO.(36)

Review of the evidence

Our literature search identified 31 potentially relevant studies of which 21 studies met the inclusion criteria (supplementary tables 6a&b).(9;20;37-56) We exclusively selected studies that measured FeNO at an expiratory flow of 50 ml/sec (supplementary table 7), thus excluding two studies where FeNO was measured at a higher flow.(57;58) Optimal FeNO cut-off values for a diagnosis of asthma in adults ranged from 15 ppb to 64 ppb, with sensitivity values ranging from 29% to 79% and specificity values ranging from 55% to 95%. The high variability observed across the studies reflected differences in patient

inclusion criteria in demographics such as smoking and atopy status, or concurrent ICS treatment during assessment.

Katsoulis et al., found a FeNO cut-off of 32 ppb for the whole population of patients with symptoms suggestive of asthma (n=112), but a low cut-off of 11 ppb when selecting actively smoking asthma patients.(46) Nekoee et al., (n=720) found a FeNO cut-off value of 36 ppb yielded a sensitivity of 30% and a specificity of 85%.(20) The TF derived the sensitivity and specificity for fixed FeNO cut-offs where it was provided by the study authors. A lower cut-off of 25 ppb provided sensitivity and specificity of 0.53 (95% CI: 0.33 to 0.72) and 0.72 (95% CI: 0.61 to 0.81) respectively (GRADE table 8a), where a higher 50 ppb cut-off value ranged from 0.19 to 0.56 and 0.77 to 0.95, respectively (GRADE table 8c). A cut-off of 40 ppb yielded a sensitivity of 0.61 (95% CI: 0,37-0,81) and a specificity of 0.82 (95% CI:0,75-0,87) (GRADE table 8b).

Justification of the recommendation

Measuring FeNO is a point-of-care method that may be particularly useful in both primary and secondary care,(59) although it is not yet considered for reimbursement in most of European countries. A cut-off value above 40-50 ppb yields a high specificity (between 0.75 to 0.95), to rule in a diagnosis of asthma with confidence. However, the poor sensitivity (between 0.19 to 0.81) does not allow asthma to be ruled out, for values below 40 ppb. Although the TF recommends using FeNO to help in the diagnosis of asthma, we make it clear that high FeNO levels do not define asthma. High FeNO levels may be observed in patients with eosinophilic chronic bronchitis, allergic rhinitis or eczema who may deny any asthma symptoms and do not show bronchial

hyperresponsiveness.(3) Additional factors such as training, cost of device and sensors, and local reimbursement policies may limit use in primary care.

Patient perspective

FeNO is a non-invasive, quick and relatively cheap measurement well accepted by the patient. It is worth noting that some patients are unable to adequately control their expiratory flow to provide a value. Given the strong influence of ICS on FeNO level it is better to measure it when patients have not taken this medication, whenever possible. The cost of paying for FeNO by patients in settings where reimbursement is not available may limit use.

Key unanswered questions

Given the many factors influencing FeNO values, prospective studies are needed defining the best cut-off in different categories of patients taking into account smoking and atopic status.

PICO 4: **Can measuring blood eosinophil count help diagnose asthma in adults with episodic/chronic suggestive symptoms?**

Recommendation

- The TF suggests not measuring blood eosinophil count to make a diagnosis of asthma (conditional recommendation against the test, low quality of evidence)

Remarks

- Blood eosinophil count does not define asthma but rather contributes to phenotyping

Background

Eosinophilic inflammation is a feature often found, but not specific of asthma, irrespective of the status of atopy,(60) that may contribute to asthma exacerbation.(61) Although analysis of the airway compartment by sputum or bronchoalveolar lavage is preferred, measuring the systemic component of eosinophilic inflammation by blood sampling may be a practical alternative. We investigated whether measuring blood eosinophil count (BEC) may help in the diagnosis of asthma.

Review of the evidence

Our search identified 24 potentially relevant studies of which five studies (four prospective, one retrospective) were suitable for analysis (one in primary care, four in specialist care) (supplementary tables 8a&b and 9). Hunter et al., assessed the value of a BEC cut-off of 6.3%, taken as the upper limit of the normal range.(19) Popovic et al., investigated 195 patients with symptoms of dyspnea where asthma was diagnosed in 141 subjects based on a symptom questionnaire and significant BdR (no threshold was provided) and assessed the value of eosinophilia without providing any cut-off.(62) In a prospective observational study, Yurdakul et al., included 123 participants, where 60 had asthma, 40 pseudo-asthma and 23 were healthy. Asthma was diagnosed based on reported symptoms associated with either BdR of 15%, PC20-M <8mg/ml, or PEF diurnal variation of at least 20%. Nearly half (48%) of patients with asthma were receiving ICS before testing. No cut-off for BEC was provided.(63) Two studies

constructed ROC curves to determine the performance of BEC and the best BEC cut-offs. Tilemann et al., prospectively investigated 210 patients recruited in primary care with symptoms suggestive of asthma, where 5% were receiving ICS treatment. Asthma was confirmed in patients with BdR of 12% and 200 ml improvement, or PC20-M <16 mg/ml. The AUC-ROC (95% confidence intervals (CI)) for BEC was 0.60 (0.52 – 0.68) with an optimal cut-off of 4.1% in the Tilemann's study,(54) and 0.58 (0.54 - 0.62) with a cut-off of 4.4% in the Nekoee's study.(20) Overall, sensitivity ranged between 0.15 and 0.59 while specificity was between 0.39 and 1 (GRADE table 9, supplementary EtD table 8b). A 95% specificity was obtained for a BEC cut-off of 5.9% in Nekoee's study.(20)

Justification of the recommendation

BEC lacks sensitivity to diagnose asthma, with sensitivities ranging between 21% to 59% in the reported studies. A BEC does not provide immediate results at the time of the consultation in order to directly help the clinician, although as blood leukocyte differential is a test frequently performed for several indications in routine practice, it may be that a previous test is available at the time of the consultation. BEC cut-offs above 4% and 6% have a specificity greater than 80% and 95% respectively and may help the clinician to be confident in their diagnosis in patients with suggestive symptoms.

Patient perspective

Performing a blood leukocyte differential is relatively cheap, minimally invasive, although some patients may be anxious of venipuncture.

PICO 5: Can measuring total serum IgE help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Recommendation

- The TF suggests not measuring total serum IgE to make to make a diagnosis of asthma (conditional recommendation against the test, low quality of evidence)

Remarks

- Total serum IgE does not define asthma but rather contributes to phenotyping

Background

Immunoglobulin (Ig)-E is a key component in mediating type-1 hyper-sensitivity reaction resulting in degranulation of mast cells and basophils, which can lead to symptoms of asthma.(64) There are non-IgE mediated events that can also trigger symptoms. IgE mediated mechanisms can also occur in non-atopic patients,(65;66) where elevated levels of total serum IgE have been reported.(67) We investigated whether assessing total serum IgE could help in the diagnosis of asthma.

Review of the evidence

Our search identified 26 potentially relevant studies of which four studies were considered suitable for analysis (supplementary tables 10a&b), which have been previously described above (supplementary table 8).(20;54;62;63) Popovic and Yurdakul assessed the value of a predetermined (but not provided) cut-off while Tilemann and Nekoee constructed ROC curves.(63) The AUC-ROC (95% CI) was 0.58 (0.50-0.66) with a cut-off of 90 Ku/L in Tilemann's study,(54) and 0.57 (0.53–0.61) with a cut-off value of 132 KU/L in Nekoee's study.(20) Overall, sensitivity ranged between

0.33 and 0.51 and specificity between 0.72 and 0.85 (GRADE table 10, supplementary EtD table 10b). Using a cut-off of 584 Ku/L, 95% specificity was obtained.(20)

Justification of the recommendation

Total serum IgE should not be used for the diagnosis of asthma because of consistently poor sensitivities across the studies, reaching at best 51%. This is in line with the existence of a significant proportion of non IgE-mediated asthma, also called “intrinsic” asthma. Measuring total serum IgE does not provide immediate results at the time of the consultation. If specificity is better than sensitivity it remains limited at the cut-offs provided by the ROC curves, ranging from 39% to 85%. The value of measuring IgE may vary according to the population of patients investigated, the seasonal manifestations of the symptoms, the coexistence of allergic rhinitis and is likely to be more valid in young patients as IgE levels decline with age.(68-70)

Patient perspective

Measuring total IgE is relatively cheap and minimally invasive, although some patients may be anxious of venipuncture. Patients are often keen to know their possible allergies and, although skin tests are the gold standard to define allergic status, measuring total and specific serum IgE may certainly represent a useful approach to assess allergy in primary care.

PICO 6: Can combining FeNO, blood eosinophils and IgE help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Recommendation

- The TF suggests not combining FeNO, blood eosinophils and serum IgE to make a diagnosis of asthma (conditional recommendation against the combination of tests, moderate quality of evidence)

Background

Total serum IgE, BEC and FeNO represent facets of the T2 asthma phenotype, although the molecular mechanisms behind these biochemical and cellular variables may be different and eosinophils and IgE dissociated.(71;72) We therefore investigated whether the combination of these variables could improve their diagnostic value.

Review of the evidence

Our search identified 10 potentially relevant studies of which only one study was suitable to be included (supplementary tables 11a&b). Combination of the three tests provided an AUC-ROC of 0.6 (95 CI:0.56-0.64) while the AUC for individual tests were 0.58 (0.54-0.62), 0.57 (0.53-0.61) and 0.58 (0.54-0.62) for FeNO, IgE and BEC respectively.(20) Overall, sensitivity of the combination was 0,46 (95% CI: 0,37 to 0,52) while specificity was 0,74 (95% CI: 0,64 to 0,69) (GRADE table 11, supplementary EtD table 11b)

Justification of the recommendation

Although a large study, the only study that met the criteria was a single-centre secondary care assessment. Combining blood eosinophils, total serum IgE and FeNO does not seem to improve diagnostic accuracy as compared to performing one single test. Further studies are needed, particularly those in primary care.

Patient perspective: Although all the tests are easy to undertake, if one test performs equally well than the combination of tests, there is no utility to combine them.

PICO 7: Can bronchial challenge testing help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Recommendation

- The TF suggests bronchial challenge testing should be performed in secondary care to confirm a diagnosis of asthma in adults when the diagnosis was not previously established in primary care (conditional recommendation for the test, low quality of evidence)

Remarks

- A provocative concentration of methacholine (PC20-M) or histamine (PC20-H) <8 mg/ml in steroid-naïve patients and <16 mg/ml in patient receiving regular inhaled corticosteroids supports a diagnosis of asthma
- Indirect challenges such as mannitol or exercise may be considered in patients who remain negative with direct constricting agents

Background

Bronchial challenges demonstrate bronchial hyperresponsiveness (BHR), one of the key pathophysiological feature of asthma, and are divided into direct and indirect challenges on the basis of the mechanism leading to airway constriction.(73-75) Challenges with methacholine or histamine are considered direct tests as these mediators bind directly to airway smooth muscle leading to constriction. Exercise or mannitol challenge are

considered as indirect airway challenges as they involve local release of constricting mediators such as cysteinyl-leukotrienes in the vicinity of smooth muscle. Indirect challenges are better correlated with the extent of airway inflammation than direct challenges.(74;76) We investigated whether bronchial challenge could identify patients with asthma diagnosed by BdR and we compared the performance of both tests to confirm a diagnosis of asthma.

Review of the evidence

Our search identified 18 potentially relevant studies of which six studies were suitable for inclusion (supplementary tables 12a&b) (five prospective cross-sectional,(19;26;29;63;77) one retrospective).(78) Two studies assessed the value of bronchial challenge to identify patients diagnosed as being asthmatic based on both suggestive symptoms and positive BdR test (supplementary table 13). Porpodis et al., prospectively investigated 88 steroid-naive subjects where 67 patients were diagnosed as asthma based on suggestive symptoms and BdR of 12% and 200-ml FEV_1 improvement.(77) Louis et al., assessed 194 steroid-naive patients retrospectively with symptoms suggestive of asthma and baseline FEV_1 >70% predicted, and found 39 patients with a BdR of 12% and 200-ml FEV_1 improvement.(78) Other studies have compared the performance of BdR versus bronchial challenge in patients with symptoms suggestive of asthma (supplementary table 12). Overall, sensitivity ranged between 0.63 and 0.97 while specificity ranged between 0.12 and 1 (GRADE table 12, supplementary EtD table 12b).

Justification of the recommendation

In making a conditional recommendation the TF balanced the desirable effects of making a diagnosis, against any undesirable effects, risks to patients and the resources required to implement and make bronchial challenge testing a feasible test. Although methacholine, histamine and mannitol are very safe, these tests require additional equipment, reagents, time in the laboratory, air source, and trained staff, with access to resuscitation facilities and medical personnel in rare cases of severe bronchoconstriction. This will undoubtedly increase the costs in comparison to BdR testing. Mannitol challenge appeared slightly more specific than methacholine challenge, albeit one study.

Patient perspective

Patients may feel uncomfortable during bronchial challenge testing as using histamine may cause unpleasant facial flushing and headache, and mannitol can induce cough. In addition, prior to bronchial challenge tests, patients on inhaled and oral treatment including anti-histamines (for histamine challenge) will need to be withdrawn in order to reduce the risk of a false negative test. However, some patients, particular those who may been previously diagnosed as moderate or severe asthma, may find treatment withdrawal difficult or unacceptable. Therefore, the TF recommends careful discussion with patients about medication withdrawal for purpose testing.

Key unanswered questions

Several types of bronchial challenge have been validated to confirm the diagnosis of asthma when reversibility of airway obstruction cannot be demonstrated. Whether prognosis, natural evolution and response whilst on treatment are similar irrespective of the method that has been used to make the diagnosis is largely unknown. Prospective trials are needed to answer this important clinical question.

PICO 8: Can measuring of sGaw and RV/TLC help in the diagnosis of asthma with episodic/chronic suggestive symptoms?

Recommendation

- The TF suggests not measuring sGaw and RV/TLC by whole body plethysmography to make to make a diagnosis of asthma (conditional recommendation against the tests, low quality of evidence)

Remarks

- sGaw does not perform better than FEV_1/FVC ratio to predict positive methacholine challenge in patients with normal baseline FEV_1
- RV/TLC >130% predicted has a high specificity (>90%) but poor sensitivity (25%) to predict a positive methacholine challenge in patient with normal FEV_1/FVC

Background

Temporal fluctuation in airway caliber is linked to variation in airways resistance. Specific airway conductance (sGaw) is a sensitive index to measure airway resistance related to

lung volume and does not require the patient to perform a forced effort-dependent maneuver. Topalovic et al., observed 21% of asthma patients may display abnormally low specific airway conductance (<0.63 1/KPas.sec) despite FEV_1/FVC >LLN.(79) Emphasis has been placed on the role of distal airway narrowing and gas trapping in asthma that can be measured by the ratio RV/TLC.(80;81) We undertook to investigate whether sGaw, a sensitive marker of airway obstruction, and the ratio of residual volume/total lung capacity (RV/TLC), an index of lung hyperinflation measured by whole body plethysmography, could help in the diagnosis of asthma when baseline spirometry appears to be normal.

Review of evidence

Our literature search identified 11 potentially relevant studies of which only two were suitable for inclusion (supplementary table 14a). Both were retrospective and performed in secondary care, where only one undertook a direct comparison between FEV_1/FVC, sGaw and RV/TLC (supplementary table 4).(18;21) Stanbrook et al., analysed the lung function results of 500 patients with asthma, chronic obstructive pulmonary disease (COPD), bronchitis and bronchiectasis, where 169 patients had no baseline airway obstruction, defined by FEV_1/FVC >90% of predicted.(21) The authors investigated the relationship between gas trapping, measured by the change in functional residual capacity $(\Delta FRC)_{\text{body plethysmography}}$-(*minus*)-$FRC_{\text{helium}}$) and RV/TLC with a positive PC20-M <8 mg/ml. No details were provided however on the symptom status of the patients, so it is difficult to ascertain if all patients with a positive PC20-M were actually patients with asthma. The authors investigated the diagnostic performance of predetermined values

of $\Delta FRC_{body\ plethysmography}$-(*minus*)-$FRC_{helium}$ and RV/TLC. Bougard et al., assessed the lung function indices of sGaw and RV/TLC to predict a positive bronchial methacholine challenge (PC20-M <16 mg/ml) by constructing ROC curves in 270 patients referred to a secondary care asthma clinic. All patients had whole body plethysmography prior to their visit at the asthma clinic for the methacholine challenge and were divided into a training cohort (n=129, baseline FEV_1 95% predicted) and a validation cohort (n=141, baseline FEV_1 91% predicted), indicating no substantial lung function impairment(18). Among all plethysmography indices measured, RV/TLC provided the best AUC-ROC in both training and validation cohorts with values reaching 0.74 and 0.75, respectively while AUC-ROC reached 0.69 and 0.62 for sGaw in the training and the validation cohorts respectively. A model combining RV/TLC and FeNO provided an AUC that rose up to 0,79. Overall, sensitivity for sGaw ranged from 0.50 to 0.51 and specificity from 0.71 to 0.74 (GRADE table 13, supplementary EtD table 14b). Sensitivity for RV/TLC ranged from 0.28 to 0.71 while specificity was ranged from 0.68 to 0.86 (GRADE table 14, supplementary EtD table 14b). In patients with RV/TLC >135% predicted and an FEV_1/FVC >90%, provided 95% specificity in Stanbrook's study.(21)

Justification of the recommendation

The current evidence with RV/TLC is too limited to recommend using it to ascertain a diagnosis of asthma. The two studies suggest a high RV/TLC might be a useful physiological index to consider asthma diagnosis. Whole body plethysmography can provide sophisticated lung function measurements including the early physiological sign of hyperdistention as a consequence of small airway obstruction, not revealed by spirometry. Where RV/TLC may hold some promise, measuring sGaw does not bring

additional value to the measurement FEV_1/FVC ratio by spirometry. Whole body plethysmography, however, requires technical expertise from laboratory personnel and the cost and relatively limited access even in specialist secondary care may preclude use of this test on a large scale.

Patient perspective: Patients are usually keen to know about their lung function and respiratory performance. Body plethysmography is sophisticated and requires both technical expertise and patient collaboration, and some maneuvers may be unpleasant and possibly induce anxiety when the patient is forced to breathe while airflow is suppressed.

Key unanswered questions

Prospective studies are needed to further assess the value of RV/TLC, potentially combined with FeNO in patients with normal baseline spirometric indices.

Shaping the clinical practice algorithm

Historically asthma is defined by an episode of airway obstruction that reverses either spontaneously or following a treatment, and this is why our algorithm starts with spirometry (Figure 1). However, in clinical practice the majority of patients with symptoms suggestive of asthma do not present with spirometric airway obstruction, thereby limiting a significant response to bronchodilator. We observed the T2 biomarkers

greatly lacked sensitivity to make a diagnosis of asthma, while displaying an acceptable specificity. We decided to recommend FeNO as an aid to diagnose asthma in our algorithm, in contrast to blood eosinophil count and total serum IgE, as FeNO is non-invasive and provides an immediate result at the time of the consultation. Values of FeNO above 50 ppb (*or 40 ppb*) have a low false positive rate (< 10%; < *20% in case 40 ppb*) which gives confidence to rule in asthma. However, where a high FeNO is supportive of a diagnosis of asthma it does not define the disease itself, as high FeNO without asthma is observed in other conditions like allergic rhinitis or chronic eosinophilic bronchitis. With respect to lung function testing in secondary care, our conditional recommendation for bronchial challenge is justified by its high sensitivity to demonstrate excessive airflow variation, which is far superior to BdR or PEF variability over a two-week period. In addition, PEF monitoring requires a two-week observation period that may result in a lack of patient adherence with incomplete recording.

Additional considerations

How to investigate patients already receiving regular maintenance medication to make an asthma diagnosis?

In patients receiving ICS maintenance therapy as monotherapy or in combination with LABA, the demonstration of variable airway obstruction may be challenging. Where the influence of LABA disappears in a few days, long-term ICS use may reduce airway responsiveness and normalise airway calibre for longer.(82;83) For patients established on maintenance therapy, GINA recommends making the diagnosis by the classic criteria of reversibility testing or bronchial challenge testing, being less stringent for the latter and accepting a PC20 <16 mg/ml as valid diagnostic criterion. In patients with a negative BdR, (FEV_1 does not improve by 12% and 200 ml) and a negative methacholine challenge (PC20-M <16 mg/ml), ICS maintenance treatment is gradually tapered, and if symptoms do not worsen nor a significant decline in spirometry or PEF monitoring occurs, a bronchial challenge test can be repeated.(3;82)

Objective testing of airflow variability and airway hyper-responsiveness over 12 months is important to address seasonal and occupational asthma or intermittent increases in airway hyper-responsiveness from infections, and asthma is usually excluded if these are normal.(84) Patients should be encouraged to present to the physician if they experience any worsening of respiratory symptoms during this period, and alternative diagnoses should of course be considered and investigated.

How may *comorbidities obscure the diagnosis of asthma*?

Asthma frequently coexists with co-morbidities that not only affect the control and management of asthma,(85) but need to be considered during the diagnostic phase. Some comorbidities can be supportive in diagnosing asthma. The presence of atopy and atopic conditions such as allergic rhinitis or atopic dermatitis increase the probability of the diagnosis of allergic asthma when patients present with respiratory symptoms.(86) The presence of atopy is not specific for asthma,(87) nor does its absence rule out asthma, since atopy is not present in all asthma phenotypes. It should be noted that the relevance of allergen exposure in relation to symptoms requires a positive test (skin prick test or serum specific IgE) confirmed by a corresponding history.

Chronic rhinosinusitis and nasal polyposis are more often associated with the late-onset eosinophilic asthma subtype, characterised by onset of disease in adulthood, absence of atopy, airway obstruction without a smoking history and eosinophilic inflammation.(88;89) In this respect, the presence of chronic rhinosinusitis or nasal polyposis in patients with respiratory symptoms usually alerts physicians to consider the diagnosis of asthma, with the late-onset phenotype.

COPD is the other most common chronic obstructive airway disease. The diagnosis of asthma and COPD may not be mutually exclusive given that many patients with asthma smoke (90) or are exposed to noxious gases and it is common to observe irreversible airway obstruction in moderate to severe asthmatics.(91) Gastro-oesophageal reflux disease (GERD) can cause laryngeal or pharyngeal irritation, chest tightness, and dry

cough, symptoms that can easily be misinterpreted as asthma,(3) and are often more problematic at night. The diagnosis of GERD may be considered, particularly in patients presenting with non-productive cough as their main symptom, and current consensus suggests an empirical treatment of anti-reflux medication may be used where there is objective evidence of reflux or a history suggestive of reflux symptoms.(44)

A particular challenge is the diagnosis of asthma in people with obesity. Obesity itself can cause shortness of breath, wheezing due to breathing at lower volume and reduced exercise tolerance, and may be accompanied by GERD or obstructive sleep apnoea, which in turn can cause asthma-like symptoms. People with obesity are shown to be at risk of both over- and under-diagnosis of asthma,(92) and need an objective diagnosis of asthma to prevent unwanted over- or under-treatment.

Inducible laryngeal obstruction (ILO), hyperventilation and dysfunctional breathing all may cause asthma-like symptoms and lead to an incorrect asthma diagnosis. Patients with inducible laryngeal obstruction have an inappropriate, transient, reversible narrowing of the larynx in response to diverse triggers,(93) that may result in inspiratory breathing difficulties, sometimes with coarse to high-pitched inspiratory breath sounds, and repetitive attacks of acute dyspnea (mimicking exacerbations of asthma). Dysfunctional breathing is characterized by irregular breathing patterns and patients with this condition often present with dyspnea or "air hunger", together with non-respiratory symptoms such as dizziness and palpitations.(94) Valid, accessible and quantifiable tests for diagnosing dysfunction breathing is missing , making it difficult to distinguish from asthma, although continuous laryngoscopy during exercise (CLE) is considered a

reliable test to diagnose or rule out exercise-induced laryngeal obstruction.(95) In these patients, symptoms do not improve on asthma medicines and it is preferable to consider alternative options, such as breathing exercises, speech therapy, biofeedback strategies or psychological support.

Does lung imaging help in the work up of asthma diagnosis?

Beyond the physiological abnormalities defining asthma, additional investigations may be worthwhile to demonstrate co-morbidities that may be contributing to the symptom burden of the patient. High-resolution computed tomogram (HRCT) of the lungs provides a diagnosis of additional conditions in 40% of cases in patients with severe asthma, including bronchiectasis, emphysema and lung nodules.(96) HRCT can identify classical radio-pathological patterns of airway wall thickening, airway distensibility, bronchiectasis, lung distension and air trapping, where most of these changes can overlap with each other and present in varying proportions. The radiological presence of emphysema (or “pseudo-emphysema”) increases the complexity of differentiating asthma from COPD, and air trapping can be challenging to discriminate from emphysema. Assessing HRCT lung changes before and after treatment (bronchodilation, anti-inflammatory treatment) or airway challenge (bronchoconstriction) are potentially insightful.(97-100) However, it appears that as an increasing number of radiological features are incidentally detected (e.g. interstitial lung abnormalities), which may make the diagnosis of asthma a challenge. Beyond an alternative diagnosis, additional studies are needed to assess whether HRCT is able to identify particular phenotypes and predict treatment response.(98;99) and potentially whether radiological features can predict future risk of disease exacerbation and lung function decline.

Noteworthy, sinus CT can not only identify asthma-related comorbidities such as nasal polyposis, but also has the potential to support phenotypic characterization.

Do we need to phenotype airway and systemic inflammation in the patient with asthma?

Asthma is a heterogeneous disease that encompasses different clinical phenotypes and endotypes that share excessive airflow fluctuation.(101;102) In particular, there is now clear evidence of differing patterns of airways inflammation in people with asthma. Although not applicable in primary care setting the development of the technique of induced sputum has been pivotal to airway inflammatory phenotyping in asthma.(103-105) When available in secondary care, induced sputum may complement the diagnostic work-up in severe patients.(3) Some authors have advocated to classify the patients based on the granulocytic airway content.(106-108) In large cohorts of patients across the whole severity spectrum pauci-granunocytic and eosinophilic asthma were found to be the two most frequently encountered phenotypes where the proportion of eosinophilic asthma increases with disease severity.(106;107;109) In contrast, paucigranulocytic asthma is the most prevalent inflammatory phenotype in mild asthma,(78;106;110) even if sputum analysis suggests that paucigranulocytic asthma are actually low-grade eosinophilic airway inflammation.(111) Although sputum eosinophils were shown to provide acceptable accuracy to diagnose asthma,(19) the main interest of identifying airway cell content is that it may provide valuable information regarding several clinical asthma outcomes beyond the diagnosis.(112) Sputum eosinophilia predicts a good response to ICS or to a course of OCS.(103) The persistently mixed granulocytic profile is associated with lung function decline and relative resistance to ICS in contrast to the pure highly variable eosinophilic pattern,

which shows propensity to exacerbation but generally a good response to corticoids preventing decline in lung function.(113) Biomarkers such as blood eosinophils and FeNO have shown consistent relationship with sputum eosinophil counts and were found to be good predictors of the response to ICS in steroid-naïve patients,(51;114-116) making them suitable tools to phenotype asthma in primary care setting. We currently lack of user-friendly biomarkers to identify neutrophilic asthma, a phenotype found to be associated with signs of innate immunity activation(117;118), often induced by dysbiosis(119;120) and resistant to ICS.(121) Analysis of VOCs has recently shown some promise in this respect.(122)

Categorization of asthma according to the inflammatory profile has proved to be invaluable in the appropriate targeting of expensive biological treatments in difficult asthma, where use of T2 biomarkers differentiates those likely to respond from those unlikely to benefit.(123) Furthermore, the growing recognition of the need for personalized,(124) precision medicine, based on categorization and appropriate response to the variety of drivers of disease at an individual level, has led to the proposal for a 'treatable traits' strategy in airways disease.(125) There is preliminary evidence that this is a successful strategy in hospital-based care,(126) with calls from the ERS for more research into wider clinical implementation of this approach.(127)

What are the patient perspectives of asthma diagnosis in adults?

A review of published and grey literature explored patient experiences of adult asthma diagnosis. Details of the search strategy available in the supplement.

Patients are often uncertain about starting treatment without first having a definitive diagnosis(6). In the absence of a diagnosis, some patients may want to trial treatment to check if they experience any benefit (Table 5). Patients describe the surprise of being diagnosed later in life as an adult. They often considered asthma to be a childhood illness, and thought it was possible to 'grow out of' asthma. Patients express frustration at not knowing why they develop asthma at this point in life (Table 5).

Patients describe the psycho-social impact of diagnosis where for some, getting a diagnosis can be positive, finally pinpointing the underlying cause of their poor health and providing tools to manage it. Depression, feeling scared and having anxiety about how asthma will affect other aspects of their life are common. Patients have complex emotions about how their condition impacts their loved ones, and how their relationships have changed as a result. Overall, patients describe coming to terms with the diagnosis, accepting it as something they have to live with long term, recognising that asthma can be life-threating, and their role in self-management. Professionals have an important role in supporting their patients with the psycho-social impact (Table 5). If a diagnostic test is done in hospital, results need to be communicated to the family doctor and ideally followed up in community care.(128)

Patients would benefit from further research on the actual diagnostic pathways of asthma patients. Professionals have an important role in improving the patient

experience of diagnostic testing and supporting individuals to manage the wider impact of diagnosis. The diagnostic process can be long and confusing for adult patients who would benefit from clear patient-centred information which takes into account variation in access to diagnostic testing across Europe.

CONCLUSION

The remit of this TF was to produce a pragmatic guideline for clinicians focusing on the best current strategy for making a secure diagnosis of asthma. The TF did not select symptoms in the list of PICO questions as it was thought we needed more than symptoms alone to improve diagnostic accuracy, even if we recognize there are currently valuable symptom diaries approved by regulatory authorities to assess the clinical status of the patient with asthma.(129) We believe there is, however, more research to be undertaken on the value of each symptom, and of their combinations, to predict an accurate diagnosis of asthma as key asthma symptoms such as breathlessness, chest tightness, cough and wheeze can be present in other diseases than asthma. The TF emphasizes the need to establish a correct diagnosis of asthma in patients with suggestive symptoms and reinforce performing spirometry on a much larger scale than is currently undertaken in primary care. Whether measuring FeNO or monitoring PEF should be implemented in primary care, in the absence of significant bronchodilator reversibility, depends on the availability and access to bronchial challenge. Both direct and indirect bronchial challenges detect airway hyper-reactivity in patients with symptoms, which make these tests optimal to eventually diagnose asthma in secondary care.

The main advantage of this guideline is that it has been developed with input from patients, the European Lung Foundation, generalists and specialists in both primary and secondary care and respiratory nurse specialist. Unlike GINA, we have adopted a methodological approach using the PICO and GRADE system. In so doing we have generated and evaluated the evidence using strict inclusion and exclusion criteria and

then using a standardised Evidence to Decision framework to make a recommendation. GINA describe their own document as a ‘strategy document’ rather than a guideline because they have not adopted such a rigorous methodological approach.

A consistent problem encountered by the TF in the PICO questions was the paucity of well-designed studies and the difficulties of defining a ‘gold reference standard’ comparator to confirm or refute the binary ‘yes-no’ question of ‘is this asthma?’ There is growing recognition of the heterogeneity and complexity of asthma, and evidence that within the broad diagnostic label, it is possible to further categorize patients into distinct groups that have differing responses to treatment and differing risk profiles. During the literature analysis, the TF found several manuscripts that addressed the issue of phenotyping patients with asthma using the index tests discussed above. A phenotype is defined as the “observable properties of an organism that are produced by the interactions of the genotype and the environment”, which can be identified by biomarkers discussed in this document, and which may have a role in prognosis and therapeutic decision-making.

In less well-resourced health care systems and low- and middle-income countries (LMIC), some of these diagnostics tests may not be available and a pragmatic empirical treatment trials protocol may be used instead. However, we hope that this guideline would be an impetus for change against such practices. Large population-based studies like the Prospective Urban and Rural Epidemiological Study (PURE) involved studying 225,000 participants in detail including spirometry from more than 1,000 urban and rural communities in 27 high, middle and low-income countries,(130) or the Global Burden of

Disease (GBD) study,(131) has demonstrated the feasibility of performing spirometry using cheap handheld devices in countries in LMIC such as Brazil, Tanzania, Kenya, Palestine and India. With salbutamol being freely available, we believe that bronchodilator testing can be performed in most parts of the world.

With this rapidly changing and evolving background, and on the basis of the literature searches performed, the TF highlights that a more nuanced and individualised diagnostic approach may be needed in the near future, to inform accurate prognostic and therapeutic clinical practice. We conclude with the words “Asthma is like love, everybody says that they know what it is, but nobody has the same definition”.(132) We hope the TF has helped clarify some of the mystery .... in the diagnosis of asthma.

REFERENCES

(1) Bloom CI, Saglani S, Feary J, Jarvis D, Quint JK. Changing prevalence of current asthma and inhaled corticosteroid treatment in the UK: population-based cohort 2006-2016. Eur Respir J 2019 Apr;53(4).

(2) Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017 Sep 16;390(10100):1211-59.

(3) Global Initiative of Asthma 2021. Global Strategy for Asthma Management and Prevention. https://ginasthma.org. Ref Type: Generic

(4) Aaron SD, Boulet LP, Reddel HK, Gershon AS. Underdiagnosis and Overdiagnosis of Asthma. Am J Respir Crit Care Med 2018 Oct 15;198(8):1012-20.

(5) Heaney LG, Robinson DS. Severe asthma treatment: need for characterising patients. Lancet 2005 Mar 12;365(9463):974-6.

(6) Health unlocked. Health Unlocked 2020 Dec 15.

(7) National Institute for Health and Care Excellence. Asthma: diagnosis, monitoring of asthma in adults, children, and young people.NICE Guideline NG80. Methods,evidence and recommendations.2017. https://www nice org uk/guidance/ng80/resources/2021 2017.

(8) Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med 2019 Oct 15;200(8):e70-e88.

(9) Pedrosa M, Cancelliere N, Barranco P, Lopez-Carrasco V, Quirce S. Usefulness of exhaled nitric oxide for diagnosing asthma. J Asthma 2010 Sep;47(7):817-21.

(10) Anderson SD, Charlton B, Weiler JM, Nichols S, Spector SL, Pearlman DS. Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. Respir Res 2009 Jan 23;10:4.

(11) Garcia-Marcos L, Edwards J, Kennington E, Aurora P, Baraldi E, Carraro S, et al. Priorities for future research into asthma diagnostic tools: A PAN-EU consensus exercise from the European asthma research innovation partnership (EARIP). Clin Exp Allergy 2018 Feb;48(2):104-20.

(12) Akinbami LJ, Salo PM, Cloutier MM, Wilkerson JC, Elward KS, Mazurek JM, et al. Primary care clinician adherence with asthma guidelines: the National Asthma Survey of Physicians. J Asthma 2020 May;57(5):543-55.

(13) Lingner H, Burger B, Kardos P, Criee CP, Worth H, Hummers-Pradier E. What patients really think about asthma guidelines: barriers to guideline implementation from the patients' perspective. BMC Pulm Med 2017 Jan 11;17(1):13.

(14) Schunemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ 2008 May 17;336(7653):1106-10.

(15) Miravitlles M, Tonia T, Rigau D, Roche N, Genton C, Vaccaro V, et al. New era for European Respiratory Society clinical practice guidelines: joining efficiency and high methodological standards. Eur Respir J 2018 Mar;51(3).

(16) Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013 Jul;66(7):719-25.

(17) Brozek JL, Akl EA, Compalati E, Kreis J, Terracciano L, Fiocchi A, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines part 3 of 3. The GRADE approach to developing recommendations. Allergy 2011 May;66(5):588-95.

(18) Bougard N, Nekoee H, Schleich F, Guissard F, Paulus V, Donneau AF, et al. Assessment of diagnostic accuracy of lung function indices and FeNO for a positive methacholine challenge. Biochem Pharmacol 2020 Sep;179:113981.

(19) Hunter CJ, Brightling CE, Woltmann G, Wardlaw AJ, Pavord ID. A comparison of the validity of different diagnostic tests in adults with asthma. Chest 2002 Apr;121(4):1051-7.

(20) Nekoee H, Graulich E, Schleich F, Guissard F, Paulus V, Henket M, et al. Are type-2 biomarkers of any help in asthma diagnosis? ERJ Open Res 2020 Apr;6(2).

(21) Stanbrook MB, Chapman KR, Kesten S. Gas trapping as a predictor of positive methacholine challenge in patients with normal spirometry results. Chest 1995 Apr;107(4):992-5.

(22) Johnson B, Steenbruggen I, Graham BL, Coleman C. Improving spirometry testing by understanding patient preferences. ERJ Open Res 2021 Jan;7(1).

(23) Swanney MP, Ruppel G, Enright PL, Pedersen OF, Crapo RO, Miller MR, et al. Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction. Thorax 2008 Dec;63(12):1046-51.

(24) Reddel H, Ware S, Marks G, Salome C, Jenkins C, Woolcock A. Differences between asthma exacerbations and poor asthma control. Lancet 1999 Jan 30;353(9150):364-9.

(25) den Otter JJ, Reijnen GM, van den Bosch WJ, van Schayck CP, Molema J, van WC. Testing bronchial hyper-responsiveness: provocation or peak expiratory flow variability? Br J Gen Pract 1997 Aug;47(421):487-92.

(26) Goldstein MF, Veza BA, Dunsky EH, Dvorin DJ, Belecanech GA, Haralabatos IC. Comparisons of peak diurnal expiratory flow variation, postbronchodilator FEV(1) responses, and methacholine inhalation challenges in the evaluation of suspected asthma. Chest 2001 Apr;119(4):1001-10.

(27) Parameswaran K, Belda J, Sears MR. Use of peak flow variability and methacholine responsiveness in predicting changes from pre-test diagnosis of asthma. Eur Respir J 1999 Dec;14(6):1358-62.

(28) Thiadens HA, de Bock GH, Dekker FW, Huysman JA, Van Houwelingen JC, Springer MP, et al. Identifying asthma and chronic obstructive pulmonary disease in patients with persistent cough presenting to general practitioners: descriptive study. BMJ 1998 Apr 25;316(7140):1286-90.

(29) Ulrik CS, Postma DS, Backer V. Recognition of asthma in adolescents and young adults: which objective measure is best? J Asthma 2005 Sep;42(7):549-54.

(30) Drake S, Wang R, Healy L, Roberts SA, Murray CS, Simpson A, et al. Diagnosing Asthma With and Without Aerosol-Generating Procedures. J Allergy Clin Immunol Pract 2021 Jul 21.

(31) Dean BW, Birnie EE, Whitmore GA, Vandemheen KL, Boulet LP, Fitzgerald JM, et al. Between-Visit Variability in FEV1 as a Diagnostic Test for Asthma in Adults. Ann Am Thorac Soc 2018 Sep;15(9):1039-46.

(32) ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med 2005 Apr 15;171(8):912-30.

(33) Spahn JD, Malka J, Szefler SJ. Current application of exhaled nitric oxide in clinical practice. J Allergy Clin Immunol 2016 Nov;138(5):1296-8.

(34) Haccuria A, Michils A, Michiels S, Van MA. Exhaled nitric oxide: a biomarker integrating both lung function and airway inflammation changes. J Allergy Clin Immunol 2014 Sep;134(3):554-9.

(35) Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011 Sep 1;184(5):602-15.

(36) Pavord ID, Siddiqui S, Papi A, Corren J, Sher LD, Bardin P, et al. Dupilumab Efficacy in Patients Stratified by Baseline Treatment Intensity and Lung Function. J Asthma Allergy 2020;13:701-11.

(37) Arora R, Thornblade CE, Dauby PA, Flanagan JW, Bush AC, Hagan LL. Exhaled nitric oxide levels in military recruits with new onset asthma. Allergy Asthma Proc 2006 Nov;27(6):493-8.

(38) Cirillo I, Ricciardolo FL, Medusei G, Signori A, Ciprandi G. Exhaled nitric oxide may predict bronchial hyperreactivity in patients with allergic rhinitis. Int Arch Allergy Immunol 2013;160(3):322-8.

(39) Cordeiro D, Rudolphus A, Snoey E, Braunstahl GJ. Utility of nitric oxide for the diagnosis of asthma in an allergy clinic population. Allergy Asthma Proc 2011 Mar;32(2):119-26.

(40) Fortuna AM, Feixas T, Gonzalez M, Casan P. Diagnostic utility of inflammatory biomarkers in asthma: exhaled nitric oxide and induced sputum eosinophil count. Respir Med 2007 Nov;101(11):2416-21.

(41) Fukuhara A, Saito J, Sato S, Sato Y, Nikaido T, Saito K, et al. Validation study of asthma screening criteria based on subjective symptoms and fractional exhaled nitric oxide. Ann Allergy Asthma Immunol 2011 Dec;107(6):480-6.

(42) He L, Wei M, Luo J, Du W, Zhang L, Zhang L, et al. Re-evaluation of the diagnostic value of fractional exhaled nitric oxide & its impact in patients with asthma. Indian J Med Res 2018 Oct;148(4):441-8.

(43) Heffler E, Guida G, Marsico P, Bergia R, Bommarito L, Ferrero N, et al. Exhaled nitric oxide as a diagnostic test for asthma in rhinitic patients with asthmatic symptoms. Respir Med 2006 Nov;100(11):1981-7.

(44) Kaplan AG. Chronic Cough in Adults: Make the Diagnosis and Make a Difference. Pulm Ther 2019 Jun;5(1):11-21.

(45) Karrasch S, Linde K, Rucker G, Sommer H, Karsch-Volk M, Kleijnen J, et al. Accuracy of FENO for diagnosing asthma: a systematic review. Thorax 2017 Feb;72(2):109-16.

(46) Katsoulis K, Ganavias L, Michailopoulos P, Bikas C, Dinapogias E, Kontakiotis T, et al. Exhaled nitric oxide as screening tool in subjects with suspected asthma without reversibility. Int Arch Allergy Immunol 2013;162(1):58-64.

(47) Korevaar DA, Westerhof GA, Wang J, Cohen JF, Spijker R, Sterk PJ, et al. Diagnostic accuracy of minimally invasive markers for detection of airway eosinophilia in asthma: a systematic review and meta-analysis. Lancet Respir Med 2015 Apr;3(4):290-300.

(48) Kostikas K, Papaioannou AI, Tanou K, Koutsokera A, Papala M, Gourgoulianis KI. Portable exhaled nitric oxide as a screening tool for asthma in young adults during pollen season. Chest 2008 Apr;133(4):906-13.

(49) Kowal K, Bodzenta-Lukaszyk A, Zukowski S. Exhaled nitric oxide in evaluation of young adults with chronic cough. J Asthma 2009 Sep;46(7):692-8.

(50) Malinovschi A, Backer V, Harving H, Porsbjerg C. The value of exhaled nitric oxide to identify asthma in smoking patients with asthma-like symptoms. Respir Med 2012 Jun;106(6):794-801.

(51) Martin MJ, Wilson E, Gerrard-Tarpey W, Meakin G, Hearson G, McKeever TM, et al. The utility of exhaled nitric oxide in patients with suspected asthma. Thorax 2016 Jun;71(6):562-4.

(52) Schleich FN, Asandei R, Manise M, Sele J, Seidel L, Louis R. Is FENO50 useful diagnostic tool in suspected asthma? Int J Clin Pract 2012 Feb;66(2):158-65.

(53) Schneider A, Schwarzbach J, Faderl B, Welker L, Karsch-Volk M, Jorres RA. FENO measurement and sputum analysis for diagnosing asthma in clinical practice. Respir Med 2013 Feb;107(2):209-16.

(54) Tilemann L, Gindner L, Meyer F, Szecsenyi J, Schneider A. Differences in local and systemic inflammatory markers in patients with obstructive airways disease. Prim Care Respir J 2011 Dec;20(4):407-14.

(55) Voutilainen M, Malmberg LP, Vasankari T, Haahtela T. Exhaled nitric oxide indicates poorly athlete's asthma. Clin Respir J 2013 Oct;7(4):347-53.

(56) Wang Y, Li L, Han R, Lei W, Li Z, Li K, et al. Diagnostic value and influencing factors of fractional exhaled nitric oxide in suspected asthma patients. Int J Clin Exp Pathol 2015;8(5):5570-6.

(57) Berkman N, Avital A, Breuer R, Bardach E, Springer C, Godfrey S. Exhaled nitric oxide in the diagnosis of asthma: comparison with bronchial provocation tests. Thorax 2005 May;60(5):383-8.

(58) Dupont LJ, Rochette F, Demedts MG, Verleden GM. Exhaled nitric oxide correlates with airway hyperresponsiveness in steroid-naive patients with mild asthma. Am J Respir Crit Care Med 1998 Mar;157(3 Pt 1):894-8.

(59) Ojanguren I, Plaza V. FeNO for Asthma Diagnosis in Adults: More Lights Than Shadows. Arch Bronconeumol 2021 Feb;57(2):85-6.

(60) Kaur R, Chupp G. Phenotypes and endotypes of adult asthma: Moving toward precision medicine. J Allergy Clin Immunol 2019 Jul;144(1):1-12.

(61) Nakagome K, Nagata M. Involvement and Possible Role of Eosinophils in Asthma Exacerbation. Front Immunol 2018;9:2220.

(62) Popovic-Grle S, Mehulic M, Pavicic F, Babic I, Beg-Zec Z. Clinical validation of bronchial hyperresponsiveness, allergy tests and lung function in the diagnosis of asthma in persons with dyspnea. Coll Antropol 2002 Dec;26 Suppl:119-27.

(63) Yurdakul AS, Dursun B, Canbakan S, Cakaloglu A, Capan N. The assessment of validity of different asthma diagnostic tools in adults. J Asthma 2005 Dec;42(10):843-6.

(64) Howarth PH. The airway inflammatory response in allergic asthma and its relationship to clinical disease. Allergy 1995;50(22 Suppl):13-21.

(65) Humbert M, Grant JA, Taborda-Barata L, Durham SR, Pfister R, Menz G, et al. High-affinity IgE receptor (FcepsilonRI)-bearing cells in bronchial biopsies from atopic and nonatopic asthma. Am J Respir Crit Care Med 1996 Jun;153(6 Pt 1):1931-7.

(66) Barnes PJ. Intrinsic asthma: not so different from allergic asthma but driven by superantigens? Clin Exp Allergy 2009 Aug;39(8):1145-51.

(67) Sunyer J, Anto JM, Castellsague J, Soriano JB, Roca J. Total serum IgE is associated with asthma independently of specific IgE levels. The Spanish Group of the European Study of Asthma. Eur Respir J 1996 Sep;9(9):1880-4.

(68) Jarvis D, Luczynska C, Chinn S, Potts J, Sunyer J, Janson C, et al. Change in prevalence of IgE sensitization and mean total IgE with age and cohort. J Allergy Clin Immunol 2005 Sep;116(3):675-82.

(69) Kerkhof M, Droste JH, de Monchy JG, Schouten JP, Rijcken B. Distribution of total serum IgE and specific IgE to common aeroallergens by sex and age, and their relationship to each other in a random sample of the Dutch general population aged 20-70 years. Dutch ECRHS Group, European Community Respiratory Health Study. Allergy 1996 Nov;51(11):770-6.

(70) Manise M, Bakayoko B, Schleich F, Corhay JL, Louis R. IgE mediated sensitisation to aeroallergens in an asthmatic cohort: relationship with inflammatory phenotypes and disease severity. Int J Clin Pract 2016 Jul;70(7):596-605.

(71) Haughney J, Morice A, Blyth KG, Lee AJ, Coutts A, McKnight E, et al. A retrospective cohort study in severe asthma describing commonly measured biomarkers: Eosinophil count and IgE levels. Respir Med 2018 Jan;134:117-23.

(72) Gerday S, Schleich F, Henket M, Guissard F, Paulus V, Louis R. Asthmatics with concordant eosinophilic disease classified according to their serum IgE status. Respir Med Res 2020 Nov 30;79:100797.

(73) Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med 2000 Jan;161(1):309-29.

(74) Joos GF, O'Connor B, Anderson SD, Chung F, Cockcroft DW, Dahlen B, et al. Indirect airway challenges. Eur Respir J 2003 Jun;21(6):1050-68.

(75) Coates AL, Wanger J, Cockcroft DW, Culver BH, Diamant Z, Gauvreau G, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017 May;49(5).

(76) Hallstrand TS, Leuppi JD, Joos G, Hall GL, Carlsen KH, Kaminsky DA, et al. ERS technical standard on bronchial challenge testing: pathophysiology and methodology of indirect airway challenge testing. Eur Respir J 2018 Nov;52(5).

(77) Porpodis K, Domvri K, Kontakiotis T, Fouka E, Kontakioti E, Zarogoulidis K, et al. Comparison of diagnostic validity of mannitol and methacholine challenges and relationship to clinical status and airway inflammation in steroid-naive asthmatic patients. J Asthma 2017 Jun;54(5):520-9.

(78) Louis R, Bougard N, Guissard F, Paulus V, Henket M, Schleich F. Bronchodilation Test with Inhaled Salbutamol Versus Bronchial Methacholine Challenge to Make an Asthma Diagnosis: Do They Provide the Same Information? J Allergy Clin Immunol Pract 2020 Feb;8(2):618-25.

(79) Topalovic M, Derom E, Osadnik CR, Troosters T, Decramer M, Janssens W. Airways resistance and specific conductance for the diagnosis of obstructive airways diseases. Respir Res 2015 Jul 22;16:88.

(80) Perez T, Chanez P, Dusser D, Devillier P. Small airway impairment in moderate to severe asthmatics without significant proximal airway obstruction. Respir Med 2013 Nov;107(11):1667-74.

(81) Postma DS, Brightling C, Baldi S, Van den Berge M, Fabbri LM, Gagnatelli A, et al. Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study. Lancet Respir Med 2019 May;7(5):402-16.

(82) Boulet LP, Turcotte H, Prince P, Lemiere C, Olivenstein R, Laprise C, et al. Benefits of low-dose inhaled fluticasone on airway response and inflammation in mild asthma. Respir Med 2009 Oct;103(10):1554-63.

(83) Juniper EF, Kline PA, Vanzieleghem MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. Am Rev Respir Dis 1990 Oct;142(4):832-6.

(84) Aaron SD, Vandemheen KL, Fitzgerald JM, Ainslie M, Gupta S, Lemiere C, et al. Reevaluation of Diagnosis in Adults With Physician-Diagnosed Asthma. JAMA 2017 Jan 17;317(3):269-79.

(85) Ledford DK, Lockey RF. Asthma and comorbidities. Curr Opin Allergy Clin Immunol 2013 Feb;13(1):78-86.

(86) Shaaban R, Zureik M, Soussan D, Neukirch C, Heinrich J, Sunyer J, et al. Rhinitis and onset of asthma: a longitudinal population-based study. Lancet 2008 Sep 20;372(9643):1049-57.

(87) Kocks JWH, Andringa HJH, van HE, Louis R, Ojanguren A, I, Riemersma RA, et al. Aeroallergen sensitization for detecting asthma in primary care: A diagnostic test accuracy study. Clin Exp Allergy 2021 Apr 29.

(88) Amelink M, de Nijs SB, Berger M, Weersink EJ, Ten BA, Sterk PJ, et al. Non-atopic males with adult onset asthma are at risk of persistent airflow limitation. Clin Exp Allergy 2012 May;42(5):769-74.

(89) de Groot JC, Storm H, Amelink M, de Nijs SB, Eichhorn E, Reitsma BH, et al. Clinical profile of patients with adult-onset eosinophilic asthma. ERJ Open Res 2016 Apr;2(2).

(90) Thomson NC, Chaudhuri R, Livingston E. Asthma and cigarette smoking. Eur Respir J 2004 Nov;24(5):822-33.

(91) Graff S, Bricmont N, Moermans C, Henket M, Paulus V, Guissard F, et al. Clinical and biological factors associated with irreversible airway obstruction in adult asthma. Respir Med 2020 Dec;175:106202.

(92) van HA, Castro CM, van de Geijn GJ, Mannaerts GH, Njo TL, Taube C, et al. Underdiagnosis and overdiagnosis of asthma in the morbidly obese. Respir Med 2013 Sep;107(9):1356-64.

(93) Halvorsen T, Walsted ES, Bucca C, Bush A, Cantarella G, Friedrich G, et al. Inducible laryngeal obstruction: an official joint European Respiratory Society and European Laryngological Society statement. Eur Respir J 2017 Sep;50(3).

(94) Balkissoon R, Kenn K. Asthma: vocal cord dysfunction (VCD) and other dysfunctional breathing disorders. Semin Respir Crit Care Med 2012 Dec;33(6):595-605.

(95) Walsted ES, Famokunwa B, Andersen L, Rubak SL, Buchvald F, Pedersen L, et al. Characteristics and impact of exercise-induced laryngeal obstruction: an international perspective. ERJ Open Res 2021 Apr;7(2).

(96) Gupta S, Hartley R, Khan UT, Singapuri A, Hargadon B, Monteiro W, et al. Quantitative computed tomography-derived clusters: redefining airway remodeling in asthmatic patients. J Allergy Clin Immunol 2014 Mar;133(3):729-38.

(97) Bommart S, Marin G, Molinari N, Knabe L, Petit A, Chanez P, et al. Club cell secretory protein serum concentration is a surrogate marker of small-airway involvement in asthmatic patients. J Allergy Clin Immunol 2017 Aug;140(2):581-4.

(98) Hoshino M, Ohtawa J. Effects of adding omalizumab, an anti-immunoglobulin E antibody, on airway wall thickening in asthma. Respiration 2012;83(6):520-8.

(99) Tunon-de-Lara JM, Laurent F, Giraud V, Perez T, Aguilaniu B, Meziane H, et al. Air trapping in mild and moderate asthma: effect of inhaled corticosteroids. J Allergy Clin Immunol 2007 Mar;119(3):583-90.

(100) Venegas JG, Winkler T, Musch G, Vidal Melo MF, Layfield D, Tgavalekos N, et al. Self-organized patchiness in asthma as a prelude to catastrophic shifts. Nature 2005 Apr 7;434(7034):777-82.

(101) Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nat Med 2012 May 4;18(5):716-25.

(102) Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. Lancet 2008 Sep 20;372(9643):1107-19.

(103) Bakakos P, Schleich F, Alchanatis M, Louis R. Induced sputum in asthma: from bench to bedside. Curr Med Chem 2011;18(10):1415-22.

(104) Hargreave FE. The investigation of airway inflammation in asthma: sputum examination. Clin Exp Allergy 1997 May;27 Suppl 1:36-40.

(105) Brightling CE. Clinical applications of induced sputum. Chest 2006 May;129(5):1344-8.

(106) Hastie AT, Moore WC, Meyers DA, Vestal PL, Li H, Peters SP, et al. Analyses of asthma severity phenotypes and inflammatory proteins in subjects stratified by sputum granulocytes. J Allergy Clin Immunol 2010 May;125(5):1028-36.

(107) Schleich FN, Manise M, Sele J, Henket M, Seidel L, Louis R. Distribution of sputum cellular phenotype in a large asthma cohort: predicting factors for eosinophilic vs neutrophilic inflammation. BMC Pulm Med 2013 Feb 26;13:11.

(108) Simpson JL, Scott R, Boyle MJ, Gibson PG. Inflammatory subtypes in asthma: assessment and identification using induced sputum. Respirology 2006 Jan;11(1):54-61.

(109) Schleich F, Brusselle G, Louis R, Vandenplas O, Michils A, Pilette C, et al. Heterogeneity of phenotypes in severe asthmatics. The Belgian Severe Asthma Registry (BSAR). Respir Med 2014 Dec;108(12):1723-32.

(110) Ntontsi P, Loukides S, Bakakos P, Kostikas K, Papatheodorou G, Papathanassiou E, et al. Clinical, functional and inflammatory characteristics in patients with paucigranulocytic stable asthma: Comparison with different sputum phenotypes. Allergy 2017 Nov;72(11):1761-7.

(111) Demarche S, Schleich F, Henket M, Paulus V, Van HT, Louis R. Detailed analysis of sputum and systemic inflammation in asthma phenotypes: are paucigranulocytic asthmatics really non-inflammatory? BMC Pulm Med 2016 Apr 5;16:46.

(112) Louis RE, Schleich FN. Granulocytic Airway Inflammation and Clinical Asthma Outcomes. Am J Respir Crit Care Med 2021 Apr 1;203(7):797-9.

(113) Hastie AT, Mauger DT, Denlinger LC, Coverstone A, Castro M, Erzurum S, et al. Mixed Sputum Granulocyte Longitudinal Impact on Lung Function in the Severe Asthma Research Program. Am J Respir Crit Care Med 2021 Apr 1;203(7):882-92.

(114) Pavord ID, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, et al. Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: a prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial. Lancet Respir Med 2020 Jul;8(7):671-80.

(115) Price DB, Buhl R, Chan A, Freeman D, Gardener E, Godley C, et al. Fractional exhaled nitric oxide as a predictor of response to inhaled corticosteroids in patients with non-specific respiratory symptoms and insignificant bronchodilator reversibility: a randomised controlled trial. Lancet Respir Med 2018 Jan;6(1):29-39.

(116) Smith AD, Cowan JO, Brassett KP, Filsell S, McLachlan C, Monti-Sheehan G, et al. Exhaled nitric oxide: a predictor of steroid response. Am J Respir Crit Care Med 2005 Aug 15;172(4):453-9.

(117) da SJ, Hilzendeger C, Moermans C, Schleich F, Henket M, Kebadze T, et al. Raised interferon-beta, type 3 interferon and interferon-stimulated genes - evidence of innate immune activation in neutrophilic asthma. Clin Exp Allergy 2017 Mar;47(3):313-23.

(118) Simpson JL, Grissell TV, Douwes J, Scott RJ, Boyle MJ, Gibson PG. Innate immune activation in neutrophilic asthma and bronchiectasis. Thorax 2007 Mar;62(3):211-8.

(119) Abdel-Aziz MI, Brinkman P, Vijverberg SJH, Neerincx AH, Riley JH, Bates S, et al. Sputum microbiome profiles identify severe asthma phenotypes of relative stability at 12 to 18 months. J Allergy Clin Immunol 2021 Jan;147(1):123-34.

(120) Azim A, Green B, Lau L, Rupani H, Jayasekera N, Bruce K, et al. Peripheral airways type 2 inflammation, neutrophilia and microbial dysbiosis in severe asthma. Allergy 2021 Jul;76(7):2070-8.

(121) Green RH, Brightling CE, Woltmann G, Parker D, Wardlaw AJ, Pavord ID. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. Thorax 2002 Oct;57(10):875-9.

(122) Schleich FN, Zanella D, Stefanuto PH, Bessonov K, Smolinska A, Dallinga JW, et al. Exhaled Volatile Organic Compounds Are Able to Discriminate between Neutrophilic and Eosinophilic Asthma. Am J Respir Crit Care Med 2019 Aug 15;200(4):444-53.

(123) Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, et al. After asthma: redefining airways diseases. Lancet 2018 Jan 27;391(10118):350-400.

(124) Louis R, Roche N. Personalised medicine: are we ready? Eur Respir Rev 2017 Sep 30;26(145).

(125) Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, et al. Treatable traits: toward precision medicine of chronic airway diseases. Eur Respir J 2016 Feb;47(2):410-9.

(126) McDonald VM, Clark VL, Cordova-Rivera L, Wark PAB, Baines KJ, Gibson PG. Targeting treatable traits in severe asthma: a randomised controlled trial. Eur Respir J 2020 Mar;55(3).

(127) Agusti A, Bafadhel M, Beasley R, Bel EH, Faner R, Gibson PG, et al. Precision medicine in airway diseases: moving to clinical practice. Eur Respir J 2017 Oct;50(4).

(128) Hannane A, Misane L, Devouassoux G, Colin C, Letrilliart L. Asthma patients' perception on their care pathway: a qualitative study. NPJ Prim Care Respir Med 2019 Apr 2;29(1):9.

(129) Gater A, Nelsen L, Fleming S, Lundy JJ, Bonner N, Hall R, et al. Assessing Asthma Symptoms in Adolescents and Adults: Qualitative Research Supporting Development of the Asthma Daily Symptom Diary. Value Health 2016 Jun;19(4):440-50.

(130) Duong M, Islam S, Rangarajan S, Teo K, O'Byrne PM, Schunemann HJ, et al. Global differences in lung function by region (PURE): an international, community-based prospective study. Lancet Respir Med 2013 Oct;1(8):599-609.

(131) Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med 2017 Sep;5(9):691-706.

(132) Gross NJ. What is this thing called love? --or, defining asthma. Am Rev Respir Dis 1980 Feb;121(2):203-4.

TABLES

Table 1: Operating Asthma definition

Typical symptoms including breathlessness, wheezing, cough, chest tightness and objective demonstration of excessive airway calibre fluctuation with at least one of the following define asthma both in primary and secondary care:

1. Peak flow variability ≥20% or spontaneous variation in FEV_1 ≥12% and 200 ml
2. Reversibility after bronchodilator inhalation with improvement in FEV_1 of ≥12% and 200 ml
3. Airway hyperresponsiveness: PC20-M (or H) <8 mg/ml (or 16 mg/ml in ICS treated patients), PD mannitol < 625 mg or FEV_1 fall ≥10% after exercise
4. Improvement in FEV_1 ≥12% and 200 ml after a two-week course of OCS or a 4-6 week course of ICS

FEV_1 = forced expiratory volume in one second; ICS = Inhaled corticosteroid; OCS = Oral corticosteroid; PC20-H = Provocation concentration causing 20% fall in FEV_1 with histamine; PC20-M = Provocation concentration causing 20% fall in FEV_1 with methacholine; PD = Provocation dose

Table 2: PICO questions

PICO 1 **Can airway obstruction measured by spirometry help diagnose asthma in adults with episodic/chronic suggestive symptoms?**

In patients with episodic/chronic symptoms suggestive of asthma

Index test: FEV_1/FVC ratio

Gold standard: Excessive airway calibre fluctuation (see definition, Table 1)

Outcomes: Diagnostic accuracy (sensitivity, specificity)

Time: Depending from the gold standard chosen: 2 weeks for PEF recording, 6 months follow up with repeated spirometry tests for reversibility test, one day for bronchial challenge

PICO 2: **Can PEF variability testing help diagnose asthma in adults with episodic/chronic suggestive symptoms?**

In patients with episodic/chronic symptoms suggestive of asthma

Index test: Peak flow variability (Minimal 2 weeks for Peak Flow recording as an index test)

Gold standard: Excessive airway calibre fluctuation (see definition, Table 1)

Outcomes: Diagnostic accuracy (sensitivity, specificity)

Time: Depending from the gold standard chosen: 2 weeks for PEF recording, 6 months follow up with repeated spirometry tests for reversibility test, one day for bronchial challenge

PICO 3: **Can measuring fractional exhaled nitric oxide (FeNO) help diagnose asthma in adults with episodic/chronic suggestive symptoms?**

In patients with episodic/chronic symptoms suggestive of asthma

Index test: FeNO

Gold standard: Excessive airway calibre fluctuation (see definition, Table1)

Outcomes: Diagnostic accuracy (sensitivity, specificity)

Time: Depending from the gold standard chosen: 2 weeks for PEF recording, 6 months follow up with repeated spirometry tests for reversibility test, one day for bronchial challenge

PICO 4: **Can measuring blood eosinophil count help diagnose asthma in adults with episodic/chronic suggestive symptoms?**

In patients with episodic/chronic symptoms suggestive of asthma

Index test: Blood eosinophil count

Gold standard: Excessive airway calibre fluctuation (see definition, Table1)

Outcomes: Diagnostic accuracy (sensitivity, specificity)

Time: Depending from the gold standard chosen: 2 weeks for PEF recording, 6 months follow up with repeated spirometry tests for reversibility test, one day for bronchial challenge

PICO 5: **Can measuring total serum IgE help diagnose asthma in adults with episodic/chronic suggestive symptoms?**

In patients with episodic/chronic symptoms suggestive of asthma

Index test: Total or specific IgE (RAST) to common aeroallergens

Gold standard: Excessive airway calibre fluctuation (see definition, Table1)

Outcomes: Diagnostic accuracy (sensitivity, specificity)

Time: Depending from the gold standard chosen: 2 weeks for PEF recording, 6 months follow up with repeated tests for reversibility test, one day for bronchial challenge

PICO 6: **Can combining FeNO, blood eosinophils and IgE help diagnose asthma in adults with episodic/chronic suggestive symptoms?**

In patients with episodic/chronic symptoms suggestive of asthma

Index test: Combination of tests (Blood eosinophils + FeNO + IgE)

Gold standard: Excessive airway calibre fluctuation (see definition, Table 1)

Outcomes: Diagnostic accuracy (sensitivity, specificity)

Time: Depending from the gold standard chosen: 2 weeks for PEF recording, 6 months follow up with repeated tests for reversibility test, one day for bronchial challenge

PICO 7: **Can bronchial challenge testing help diagnose asthma in adults with episodic/chronic suggestive symptoms?**

In patients with episodic/chronic symptoms suggestive of asthma

Index test: Bronchial challenge tests (Methacholine, Histamine, Mannitol, Exercise)

Gold standard: Reversibility (see definition, Table1)

Outcomes: Diagnostic accuracy (sensitivity, specificity)

Time: Demonstration of reversibility before or during at least 6 months of follow-up

PICO 8: **Can measuring of sGaw and RV/TLC help in the diagnosis of asthma with episodic/chronic suggestive symptoms?**

In patients with episodic/chronic symptoms suggestive of asthma

Index test: sGaw and RV/TLC ratio (Whole body plethysmography)

Gold standard: Positive Bronchial challenge (see definition, Table 1)

Outcomes: Diagnostic accuracy (sensitivity, specificity)

Time: One day

Table 3: Understanding the strength of the recommendation

Target group	Strong recommendations*	Conditional (weak) recommendations
Patients	Most people in your situation would want the recommended course of action and only a small proportion would not	The majority of people in your situation would want the recommended course of action but many would not
Clinicians	Most patients should receive the recommended course of action	Recognize that different choices will be appropriate for different patients and that you must make greater effort to help each patient to arrive at a management decision consistent with his or her value values and preferences; decision aids and shared decision are particularly useful
Policy markers	The recommendation can be adopted as a policy in most situations	Policy making will require substantial debate and involvement of many stakeholders
* : strong recommendations based on high quality evidence will apply to most patients for whom these recommendations are made, but they may not apply to all patients in all conditions ; no recommendation can take into account all of the unique features of individual patients and clinical circumstances.		

Table 4: Recommendations on PICO questions

PICO 1 **Can airway obstruction measured by spirometry help diagnose asthma in adults with episodic/chronic suggestive symptoms?**

Recommendation

- The TF recommends to perform spirometry as part of the diagnostic work-up of adults aged 18 years with suspected asthma (strong recommendation for the test, low quality of evidence)

Remarks

- An FEV_1/FVC < LLN or 75% should be considered supportive of an asthma diagnosis and should prompt a reversibility test
- A normal spirometry does not exclude asthma

PICO 2 **Can PEF variability testing help diagnose asthma in adults with episodic/chronic suggestive symptoms?**

Recommendation

- The TF suggests not recording PEF variability as the primary test to make a diagnosis of asthma (conditional recommendation against the test, low quality of evidence)

Remarks

- Serial PEF may be considered if if spirometry is normal and no other lung function test available including spirometry and bronchial challenge

- PEF should be monitored over a two-week period and a variation of 20% considered as supportive of asthma diagnosis
- PEF variability < 20% does not rule out asthma
- PEF may be especially useful in case of suspicion of occupational asthma

PICO 3 **Can measuring fractional exhaled nitric oxide (FeNO) help diagnose asthma in adults with episodic/chronic suggestive symptoms?**

Recommendation

- The TF suggests to measure fraction exhaled nitric oxide (FeNO) as part of the diagnostic work-up of adults aged 18 years with suspected asthma (conditional recommendation for the test, moderate quality of evidence)

Remarks

- A cut-off of 40 ppb offers the best compromise between sensitivity and specificity while a cut-off of 50 ppb has a high specificity > 90% and is therefore supportive of asthma diagnosis
- A FeNO value less than 40 ppb does not rule out asthma
- FeNO values are markedly reduced by smoking and treatment with ICS and dupilumab

PICO 4 **Can measuring blood eosinophil count help diagnose asthma in adults with episodic/chronic suggestive symptoms?**

Recommendation

- The TF suggests not measuring blood eosinophil count to make a diagnosis of asthma (conditional recommendation against the test, low quality of evidence)

Remarks

- Blood eosinophil count does not define asthma but rather contributes to phenotyping

PICO 5 Can measuring total serum IgE help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Recommendation

- The TF suggests not measuring total serum IgE to make a diagnosis of asthma (conditional recommendation against the test, low quality of evidence)

Remarks

- Total serum IgE does not define asthma but rather contributes to phenotyping

PICO 6 Can combining FeNO, blood eosinophils and IgE help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Recommendation

- The TF suggests not combining FeNO, blood eosinophils and serum IgE to make a diagnosis of asthma (conditional recommendation against the test, moderate quality of evidence)

PICO 7 Can bronchial challenge testing help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Recommendation

- The TF suggests bronchial challenge testing should be performed in secondary care to confirm a diagnosis of asthma in adults when the diagnosis was not

previously established in primary care (conditional recommendation for the test, low quality of evidence)

Remarks

- A provocative concentration of methacholine (PC20 M) or histamine (PC20H) < 8 in steroid naïve patients and < 16 mg/ml in patient receiving regular inhaled corticoids supports a diagnosis of asthma
- Indirect challenges such as mannitol or exercise may be considered in patients who remain negative with direct constricting agents

PICO 8 Can measuring of sGaw and RV/TLC help in the diagnosis of asthma with episodic/chronic suggestive symptoms?

Recommendation

The TF suggests not measuring sGaw and RV/TLC by whole body plethysmography to make a diagnosis of asthma (conditional recommendation against the tests, low quality of evidence)

Remarks

- sGaw does not perform better than FEV1/FVC ratio to predict positive methacholine challenge in patients with normal baseline FEV1
- RV/TLC > 130% predicted has a high specificity (> 90%) but poor sensitivity (25%) to predict a positive methacholine challenge in patient with normal FEV1/FVC

Table 5: Patient perspectives of asthma diagnosis: Patient advice to health professionals and illustrative quotes

Patient advice to health professionals • Communicate clearly with patients that there is no single test to diagnose asthma and that several steps may be needed • Be responsive to the patient's needs and preferences on how many tests to complete within a single visit • Consider rest periods between tests to improve the patient experience • Consider seasonal and work-related variation in asthma if test results do not appear to match the patient's experience of their symptoms • Explain the risks of stopping medication and the procedures in place if the patient experiences increased symptoms	
Getting a diagnosis	"My experience has been that there is a great deal of guesswork involved and I'm sure most people would just walk away with whatever diagnosis they are offered, no matter how little it resembles their experience. You just have to keep being a thorn in the side of your doctor get to the bottom of it. It's a hassle for both you and your doctor but getting your condition under control is well worth it." [HealthUnlocked, 2020].
Phasing of tests	"Well, yes, in my case it is necessary [to test] because the complaints come back every summer, every spring. So most probably there is something more behind it." [HealthUnlocked, 2020]
Stopping medications	"Had my first ever [lung] function test done this evening. FeNo was fine at 13. Kind of frustrating as I was told to continue using my inhalers when I checked yet turns out I should have stopped them […] As I had taken my inhalers this morning she wasn't going to do reversibility and then decided why not yet reversibility was only 13.5% […] now left really confused and annoyed I was told to continue meds when I was meant to stop them." [HealthUnlocked, 2020] "I have done one histamine (negative, due to stupid instructions on stopping medications), one mannitol (positive, I checked the medications instructions myself) […] my input would just be to triple-check you're stopping all the meds at the right time as I find it's complex with different types at different times before, and they don't always give helpful instructions." [HealthUnlocked, 2020]
Understanding their results	"I always have to ask for my [spirometry] results and … feel like I'm being a nuisance asking for them. I have no

	understanding of the context of my results i.e. how I compare to others of my age with my condition? Are my results viewed as good or bad?" [Johnson, *ERJ Open Res*, 2020, in press] "Saw nurse this morning who told me she doesn't think I have asthma because although the preventer inhaler I was given has made my peak flows go up, I get symptoms when my peak flow is above the average for my age height weight etc (450) and I don't feel I'm my normal self until I'm like 470-500. See specialist in Feb. More confused than ever". [HealthUnlocked, 2020]
Trial of treatment	"I had to ask, I had to go back several times with my condition deteriorating […] But one day I was in such, I had such a lot of chest pain and I just couldn't breathe that I just made myself an emergency appointment and said to her, "Look I think it's asthma, I've got this family history, of very severe asthma in several family members I'm in such pain, would you not think it appropriate to try and prescribe me some asthma medication and let's just see if that improves my condition." So in a sense I diagnosed myself, but [the doctor] did agree to that and that's when I started on some fairly low doses of Ventolin plus a Beclazone inhaler and that did help me." [Healthtalk.org, Being diagnosed with asthma, 2017] "The doctor had given me a blue inhaler, but kind of hadn't shown me how to use it." [Healthtalk.org, Being diagnosed with asthma, 2017]

Experiences of being diagnosed later in life	"I just assumed people got it as young children and kept it or got rid of it, 'cause I know children now can reduce or get rid of their symptoms, but I hadn't realised that you could be diagnosed as an adult with it." [Healthtalk.org, Adult onset of asthma, 2017]. "I was actually diagnosed with asthma round about my 47th birthday […] Probably looking back I didn't actually manage things terribly well, because there is, when you first are diagnosed, especially the sort of age that I was diagnosed at, there was just that feeling of, well, just why me?" [Healthtalk.org, Being diagnosed with asthma, 2017]
Psycho-social impact of diagnosis	"I would say that it's really important to listen to your patients. Because they are the experts in how they're feeling. And to see asthma as more than something that affects our airways. It actually affects us as, as people, it affects our lives. There's a huge adjustment that you have to make when you're first diagnosed. I went from seeing myself as a healthy person with no, no health worries and problems at all to somebody who might have an asthma attack tomorrow that they don't survive. Or even this afternoon. And that's a huge adjustment that you have to make. […] I would ask health professionals to talk to us about how it's affecting us in the round not just how it's affecting our breathing. [Healthtalk.org, Dealing with health professionals, 2017] "There was a say five minutes after I'd actually left the GP, after the chat with the doctor, there was five minutes before I went and collected my prescription where I was kind of depressed. You know, there was a […] slump but then I decided, you know, "This isn't going to be a big thing and I'm going to get out. I'm going to train harder. It's not going to affect my lifestyle." [Healthtalk.org, Being diagnosed with asthma, 2017] "Just been diagnosed with asthma by the nurse after 3 months of issues […] New to this to be honest and I'm

finding it quite a challenge to adapt to. I'm 38. It seems pretty bleak outlook [to be honest] constantly battling to breathe easy." [HealthUnlocked, 2020]

"I don't want to be different and I don't want my health to deteriorate but going in there with that attitude isn't going to get me anywhere. And I think for those people who are newly diagnosed that is almost impossible, to go in there and be calm and clear-headed about it. You can't in the beginning, especially before diagnosis, because you haven't, you might have no idea why you're ill. Why you feel like you have no energy, why you can't do certain things, why you can't do certain jobs. Your career can be affected by it. Your home life is affected by it. Your social life is affected by it. And I think people who are newly diagnosed have got to give themselves time to come to terms with it. And that doesn't necessarily mean accepting it. For some people accepting you're ill will never happen. But it doesn't mean that you can't get your head round it and deal with it. [Healthtalk.org, Emotions and coping with asthma, 2017]

Table 6: GRADE table: Can airway obstruction measured by spirometry (FEV_1/FVC ratio) help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Sensitivity	0.51 to 0.69
Specificity	0.28 to 0.76

Baseline Prevalence	20% Typically seen in primary care	50% Typically seen in specialist care

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	4 studies [1,2,3,4] 1451 patients	diagnostic accuracy study	serious [a]	not serious	serious [b]	not serious [c]	none	102 to 138	255 to 345	⊕⊕◯◯ LOW
False negatives								62 to 98	155 to 245	
True negatives	4 studies [1,2,3,4] 1451 patients	diagnostic accuracy study	serious [a]	not serious	serious [b]	not serious [c]	none	224 to 608	140 to 380	⊕⊕◯◯ LOW
False positives								192 to 576	120 to 360	

Explanations

a. Limitations in the selection of patients with suspected disease. Spectrum bias potentially leads to inflated estimation of the diagnostic performance.
b. Pooled data could not be obtained and is represented as a range. Probably due to a threshold effect – accuracy values represent best balance between sensitivity and specificity at a cut-off around FEV1/FVC ratio of 77%. Specificity and absolute TN and FP effects per 1000 patients tested are highly variable.
c. Imprecision of data is mainly due to heterogeneity of data and representation of ranges instead of pooled data.
Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded

References

1. Nekoee H., Graulich E., Schleich F., Guissard F., Paulus V., Henket M., et al. (2020) Are type-2 biomarkers of any help in asthma diagnosis? ERJ Open Res 6:(2):00169–02020
2. Hunter CJ., Brightling CE., Woltmann G., Wardlaw AJ., Pavord ID. (2002) A Comparison of the Validity of Different Diagnostic Tests in Adults With Asthma. Chest 121:(4):1051–1057
3. Bougard N, Nekoee H, Schleich F, Guissard F, Paulus V, Donneau AF, Louis R. Assessment of diagnostic accuracy of lung function indices and FeNO for a positive methacholine challenge. Biochem Pharmacol. 2020 Sep;179:113981.
4. Stanbrook MB, Chapman KR, Kesten S. Gas trapping as a predictor of positive methacholine challenge in patients with normal spirometry results. Chest. 1995 Apr;107(4):992-5.

Table 7: GRADE table: Can Peak Expiratory Flow Variability testing help diagnose asthma in patients with episodic/chronic suggestive symptoms ?

Sensitivity	0.05 to 0.93
Specificity	0.75 to 1.00

Baseline Prevalence	20% Typically seen in primary care	50% Typically seen in specialist care

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	6 studies[1,2,3,4,5,6] 1372 patients	diagnostic accuracy study	serious [a]	not serious [b,c]	serious [d]	not serious [e]	none	10 to 186	25 to 465	⨁⨁◯◯ **LOW**
False negatives								14 to 190	35 to 475	
True negatives	6 studies[1,2,3,4,5,6] 1372 patients	diagnostic accuracy study	serious [a]	not serious [b,c]	serious [d]	not serious [e]	none	600 to 800	375 to 500	⨁⨁◯◯ **LOW**
False positives								0 to 200	0 to 125	

Explanations

a. Limitations in the selection of patients with suspected disease. Spectrum bias potentially leads to inflated estimation of the diagnostic performance.
b. Confidence not limited due to indirectness although1 study included patients aged >7, 1 study included patients aged 13-23
c. Confidence not limited due to indirectness although 1 study selected patients with symptoms of cough only and 1 study 46% of patients on ICS whilst being tested
d. Pooled data could not be obtained and is represented as a range. Sensitivity, specificity and absolute effects per 1000 patients tested are highly variable.
e. Imprecision of data is mainly due to heterogeneity of data and representation of ranges instead of pooled data.
Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded

References

1. Goldstein, . Comparisons of Peak Diurnal Expiratory Flow Variation, Postbronchodilator FEV1 Responses, and Methacholine Inhalation Challenges in the Evaluation of Suspected Asthma. Chest ; 2001.
2. Ulrik, . Recognition of Asthma in Adolescents and Young Adults: Which Objective Measure is Best?. Journal of Asthma; 2005.
3. Thiadens, . Value of measuring diurnal peak flow variability in the recognition of asthma: a study in general practice. ERJ; 1998.
4. Nair, . Use of peak flow variability and methacholine responsiveness in predicting changes from pre-test diagnosis of asthma. ERJ; 1999.
5. Otter, . Testing bronchial hyper-responsiveness: provocation or peak expiratory flow variability?. British Journal of General Practice,; 1997.
6. Hunter CJ, Brightling CE,Woltmann G,Wardlaw AJ,Pavord ID.. A comparison of the validity of different diagnostic tests in adults with asthma. Chest; 2002.

Table 8a: GRADE table: Can FeNO (25 ppb) help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Sensitivity	0.53 (95% CI: 0.33 to 0.72)
Specificity	0.72 (95% CI: 0.61 to 0.81)

Baseline Prevalence	20% Typically seen in primary care	50% Typically seen in specialist care

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	6 studies[1,2,3,4,5,6] 1535 patients	diagnostic accuracy study	not serious [a]	not serious	serious [b]	not serious [c]	none	106 (66 to 144)	265 (165 to 360)	⊕⊕⊕◯ MODERATE
False negatives								94 (56 to 134)	235 (140 to 335)	
True negatives	6 studies[1,2,3,4,5,6] 1535 patients	diagnostic accuracy study	not serious [a]	not serious	serious [b]	not serious [c]	none	576 (488 to 648)	360 (305 to 405)	⊕⊕⊕◯ MODERATE
False positives								224 (152 to 312)	140 (95 to 195)	

Explanations

a. Following the Quadas2 assessment of risk of bias, despite patient selection was not totally homogenous in the included studies, the study design, index test, reference standard and flow and timing were similar in all the included studies.

b. Sensitivity, specificity and absolute effects per 1000 patients tested are highly variable across different studies using same cut-off (25 ppb).
c. Imprecision of data is mainly due to heterogeneity
Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded

References

1. Arora R, Thornblade CE, Dauby PA, Flanagan JW, Bush AC, Hagan LL. Exhaled nitric oxide levels in military recruits with new onset asthma. Allergy Asthma Proc. 2006 Nov-Dec;27(6):493-8. doi: 10.2500/aap.2006.27.2904. PMID: 17176784.
2. Nekoee H, Graulich E, Schleich F, et al. Are type-2 biomarkers of any help in asthma diagnosis? ERJ Open Res 2020; 6: 00169-2020
3. Heffler E, Guida G, Marsico P, Bergia R, Bommarito L, Ferrero N, Nebiolo F, De Stefani A, Usai A, Bucca C, Rolla G. Exhaled nitric oxide as a diagnostic test for asthma in rhinitic patients with asthmatic symptoms. Respir Med. 2006 Nov;100(11):1981-7. doi: 10.1016/j.rmed.2006.02.019. Epub 2006 Apr 3. PMID: 16584881.
4. Katsoulis K, Ganavias L, Michailopoulos P, Bikas C, Dinapogias E, Kontakiotis T, Kostikas K, Loukides S. Exhaled nitric oxide as screening tool in subjects with suspected asthma without reversibility. Int Arch Allergy Immunol. 2013;162(1):58-64. doi: 10.1159/000350221. Epub 2013 Jun 26. PMID: 23816757.
5. Malinovschi A, Backer V, Harving H, Porsbjerg C. The value of exhaled nitric oxide to identify asthma in smoking patients with asthma-like symptoms. Respir Med. 2012 Jun;106(6):794-801. doi: 10.1016/j.rmed.2012.02.009. Epub 2012 Mar 8. PMID: 22405608.
6. Schneider A, Schwarzbach J, Faderl B, Welker L, Karsch-Völk M, Jörres RA. FENO measurement and sputum analysis for diagnosing asthma in clinical practice. Respir Med. 2013 Feb;107(2):209-16. doi: 10.1016/j.rmed.2012.10.003. Epub 2012 Oct 27. PMID: 23107283.

Table 8b: GRADE table: Can FeNO (40 ppb) help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Sensitivity	0.61 (95% CI: 0.37 to 0.81)
Specificity	0.82 (95% CI: 0.75 to 0.87)

Baseline Prevalence	20% Typically seen in primary care	50% Typically seen in specialist care

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	6 studies[1,2,3,4,5,6] 1638 patients	diagnostic accuracy study	not serious [a]	not serious	serious [b]	not serious [c]	none	122 (74 to 162)	305 (185 to 405)	⊕⊕⊕◯ MODERATE
False negatives								78 (38 to 126)	195 (95 to 315)	
True negatives	6 studies[1,2,3,4,5,6] 1638 patients	diagnostic accuracy study	not serious [a]	not serious	serious [b]	not serious [c]	none	656 (600 to 696)	410 (375 to 435)	⊕⊕⊕◯ MODERATE
False positives								144 (104 to 200)	90 (65 to 125)	

Explanations

a. Following the Quadas2 assessment of risk of bias, despite patient selection was not totally homogenous in the included studies, the study design, index test, reference standard and flow and timing were similar in all the included studies.
b. Sensitivity, specificity and absolute effects per 1000 patients tested are highly variable across different studies using same cut-off (25 ppb).
c. Imprecision of data is mainly due to heterogeneity
Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded

References

1. Arora R, Thornblade CE, Dauby PA, Flanagan JW, Bush AC, Hagan LL. Exhaled nitric oxide levels in military recruits with new onset asthma. Allergy Asthma Proc. 2006 Nov-Dec;27(6):493-8. doi: 10.2500/aap.2006.27.2904. PMID: 17176784.
2. Heffler E, Guida G, Marsico P, Bergia R, Bommarito L, Ferrero N, Nebiolo F, De Stefani A, Usai A, Bucca C, Rolla G. Exhaled nitric oxide as a diagnostic test for asthma in rhinitic patients with asthmatic symptoms. Respir Med. 2006 Nov;100(11):1981-7. doi: 10.1016/j.rmed.2006.02.019. Epub 2006 Apr 3. PMID: 16584881.

3. Fukuhara A, Saito J, Sato S, Sato Y, Nikaido T, Saito K, Fukuhara-Nakagawa N, Inokoshi Y, Ishii T, Tanino Y, Ishida T, Munakata M. Validation study of asthma screening criteria based on subjective symptoms and fractional exhaled nitric oxide. Ann Allergy Asthma Immunol. 2011 Dec;107(6):480-6. doi: 10.1016/j.anai.2011.09.002. Epub 2011 Oct 1. PMID: 22123376.
4. Kowal K, Bodzenta-Lukaszyk A, Zukowski S. Exhaled nitric oxide in evaluation of young adults with chronic cough. J Asthma. 2009 Sep;46(7):692-8. doi: 10.1080/02770900903056187. PMID: 19728207.
5. Pedrosa M, Cancelliere N, Barranco P, López-Carrasco V, Quirce S. Usefulness of exhaled nitric oxide for diagnosing asthma. J Asthma. 2010 Sep;47(7):817-21. doi: 10.3109/02770903.2010.491147. PMID: 20718633.
6. Nekoee H, Graulich E, Schleich F, et al. Are type-2 biomarkers of any help in asthma diagnosis? ERJ Open Res 2020; 6: 00169-2020

Table 8c: GRADE table: Can FeNO (50 ppb) help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Sensitivity	0.19 to 0.56
Specificity	0.77 to 0.95

Baseline Prevalence	20% Typically seen in primary care	50% Typically seen in specialist care

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	3 studies 858 patients	diagnostic accuracy study	not serious [a]	not serious	not serious [b]	serious [c]	none	38 to 112	95 to 278	⊕⊕⊕◯ MODERATE
False negatives								88 to 162	222 to 405	
True negatives	3 studies 858 patients	diagnostic accuracy study	not serious [a]	not serious	not serious [b]	serious [c]	none	616 to 760	384 to 475	⊕⊕⊕◯ MODERATE
False positives								40 to 184	25 to 116	

Explanations

a. Following the Quadas2 assessment of risk of bias, despite the interpretation of the index test could have introduced some bias in 2/3 studies, the study design, reference standard and flow and timing were similar in all the included studies.
b. Pooled data could not be obtained and is represented as a range. Sensitivity, specificity and absolute effects per 1000 patients tested are highly variable.
c. Imprecision of data is mainly due to heterogeneity of data and representation of ranges instead of pooled data.
Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded

References

1. Heffler E, Guida G, Marsico P, Bergia R, Bommarito L, Ferrero N, Nebiolo F, De Stefani A, Usai A, Bucca C, Rolla G. Exhaled nitric oxide as a diagnostic test for asthma in rhinitic patients with asthmatic symptoms. Respir Med. 2006 Nov;100(11):1981-7. doi: 10.1016/j.rmed.2006.02.019. Epub 2006 Apr 3. PMID: 16584881.
2. Malinovschi A, Backer V, Harving H, Porsbjerg C. The value of exhaled nitric oxide to identify asthma in smoking patients with asthma-like symptoms. Respir Med. 2012 Jun;106(6):794-801. doi: 10.1016/j.rmed.2012.02.009. Epub 2012 Mar 8. PMID: 22405608.
3. Nekoee H, Graulich E, Schleich F, et al. Are type-2 biomarkers of any help in asthma diagnosis? ERJ Open Res 2020; 6: 00169-2020

Table 9: GRADE table: Can measuring blood eosinophil count help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Sensitivity	0.15 to 0.59
Specificity	0.39 to 1.00

Baseline Prevalence	20% Typically seen in primary care	50% Typically seen in specialist care

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	5 studies [1,2,3,4,5] 1286 patients	diagnostic accuracy study	serious [a]	not serious	serious [b]	not serious [c]	none	30 to 118	75 to 295	⨁⨁◯◯ LOW
False negatives								82 to 170	205 to 425	
True negatives	5 studies [1,2,3,4,5] 1286 patients	diagnostic accuracy study	serious [a]	not serious	serious [b]	not serious [c]	none	312 to 800	195 to 500	⨁⨁◯◯ LOW
False positives								0 to 488	0 to 305	

Explanations

a. Limitations in the selection of patients with suspected disease. Spectrum bias potentially leads to inflated estimation of the diagnostic performance.
b. Pooled data could not be obtained and is represented as a range. Sensitivity, specificity and absolute effects per 1000 patients tested are highly variable. Probably due to a threshold effect – accuracy values represent best balance between sensitivity and specificity typically at a cut-off between 4 and 6%.
c. Imprecision of data is mainly due to heterogeneity of data and representation of ranges instead of pooled data.
Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded

References

1. Popović-Grle S., Mehulić M., Pavicić F., Babić I., Beg-Zec Z. (2002) Clinical validation of bronchial hyperresponsiveness, allergy tests and lung function in the diagnosis of asthma in persons with dyspnea. Coll Antropol 26 Suppl:119–27
2. Yurdakul AS., Dursun B., Canbakan S., Çakaloğlu A., Çapan N. (2005) The Assessment of Validity of Different Asthma Diagnostic Tools in Adults. J Asthma 42:(10):843–846
Hunter CJ., Brightling CE., Woltmann G., Wardlaw AJ., Pavord ID. (2002) A Comparison of the Validity of Different Diagnostic Tests in Adults With Asthma. Chest 121:(4):1051–1057

3. Tilemann L., Gindner L., Meyer F., Szecsenyi J., Schneider A. (2011) Differences in local and systemic inflammatory markers in patients with obstructive airways disease. Prim Care Respir J 20:(4):407–413
4. Nekoee H., Graulich E., Schleich F., Guissard F., Paulus V., Henket M., et al. (2020) Are type-2 biomarkers of any help in asthma diagnosis? ERJ Open Res 6:(2):00169–02020

Table 10: GRADE table: Can measuring total serum IgE be used to diagnose asthma in adults with episodic/chronic suggestive symptoms?

Sensitivity	0.33 to 0.51
Specificity	0.72 to 0.85

Baseline Prevalence	20% Typically seen in primary care	50% Typically seen in specialist care

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	4 studies [1,2,3,4] 1176 patients	diagnostic accuracy study	serious [a]	not serious	serious [b]	not serious [c]	none	66 to 102	164 to 255	⨁⨁◯◯ LOW
False negatives								98 to 134	245 to 336	
True negatives	4 studies [1,2,3,4] 1176 patients	diagnostic accuracy study	serious [a]	not serious	not serious	not serious [c]	none	576 to 680	360 to 425	⨁⨁⨁◯ MODERATE
False positives								120 to 224	75 to 140	

Explanations

a. Limitations in the selection of patients with suspected disease. Spectrum bias potentially leads to inflated estimation of the diagnostic performance.
b. Pooled data could not be obtained and is represented as a range. Sensitivity, specificity and absolute effects per 1000 patients tested are highly variable. Probably due to a threshold effect – accuracy values represent best balance between sensitivity and specificity typically at a cut-off between 90-132 U/mL
c. Imprecision of data is mainly due to heterogeneity of data and representation of ranges instead of pooled data.
Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded

References

1. Popović-Grle S., Mehulić M., Pavicić F., Babić I., Beg-Zec Z. (2002) Clinical validation of bronchial hyperresponsiveness, allergy tests and lung function in the diagnosis of asthma in persons with dyspnea. Coll Antropol 26 Suppl:119–27
2. Yurdakul AS., Dursun B., Canbakan S., Çakaloğlu A., Çapan N. (2005) The Assessment of Validity of Different Asthma Diagnostic Tools in Adults. J Asthma 42:(10):843–846

3. Tilemann L., Gindner L., Meyer F., Szecsenyi J., Schneider A. (2011) Differences in local and systemic inflammatory markers in patients with obstructive airways disease. Prim Care Respir J 20:(4):407–413
4. Nekoee H., Graulich E., Schleich F., Guissard F., Paulus V., Henket M., et al. (2020) Are type-2 biomarkers of any help in asthma diagnosis? ERJ Open Res 6:(2):00169–02020

Table 11: GRADE table: Can combining FeNO, blood eosinophils and IgE help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Sensitivity	0.46 (95% CI: 0.37 to 0.52)
Specificity	0.74 (95% CI: 0.64 to 0.69)

Baseline Prevalence	20% Typically seen in primary care	50% Typically seen in specialist care

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	1 studies[1] 702 patients	diagnostic accuracy study	serious [a]	not serious	not serious	not serious	none	92 (74 to 104)	230 (185 to 260)	⊕⊕⊕◯ MODERATE
False negatives								108 (96 to 126)	270 (240 to 315)	
True negatives	6 studies[1,2,3,4,5,6] 1638 patients	diagnostic accuracy study	serious [a]	not serious	not serious	not serious	none	592 (512 to 552)	370 (320 to 345)	⊕⊕⊕◯ MODERATE
False positives								208 (248 to 288)	130 (155 to 180)	

Explanations

a. Limitations in the selection of patients with suspected disease. Spectrum bias potentially leads to inflated estimation of the diagnostic performance.
Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded

References

1. Nekoee H., Graulich E., Schleich F., Guissard F., Paulus V., Henket M., et al. (2020) Are type-2 biomarkers of any help in asthma diagnosis? ERJ Open Res 6:(2):00169–02020

Table 12: GRADE table: Can Bronchial Challenge Testing help diagnose asthma in patients with episodic/chronic symptoms suggestive of asthma?

Sensitivity	0.63 to 0.97
Specificity	0.12 to 1.00

Baseline Prevalence	20% Typically seen in primary care	50% Typically seen in specialist care

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	6 studies [1,2,3,4,5,6] 1158 patients	diagnostic accuracy study	serious [a]	not serious [b,c,d]	not serious [e,f]	not serious [g]	none	126 to 194	315 to 485	⊕⊕⊕◯ **MODERATE**
False negatives								6 to 74	15 to 185	
True negatives	6 studies [1,2,3,4,5,6] 1158 patients	diagnostic accuracy study	serious [a]	not serious [b,c,d]	Serious [e,f]	not serious [g]	none	96 to 800	60 to 500	⊕⊕◯◯ **LOW**
False positives								0 to 704	0 to 440	

Explanations

a) Limitations in the selection of patients with suspected disease. Spectrum bias potentially leads to inflated estimation of the diagnostic performance.
b) Confidence not limited due to indirectness although Ulrik et al study conducted in general population and not secondary care
c) Confidence not limited due to indirectness although Hunter study - patients were on asthma treatment for a median duration of 2 years prior to investigations. 37 on SABA PRN, 32 on ICS and 3 on oral prednisolone.
d) Confidence not limited due to indirectness although Yurdakul - 12% smokers, 48% on ICS treatment prior to investigations.
e) Pooled data could not be obtained and is represented as a range. Sensitivity, specificity and absolute effects per 1000 patients tested are highly variable.
f) 3 studies used 8mg/ml methacholine cut-off, 3 studies used 16mg/ml cut-off for methacholine/histamine challenge
g) Imprecision of data is mainly due to heterogeneity of data and representation of ranges instead of pooled data.

Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded

References

1. Porpodis, . Comparison of diagnostic validity of mannitol and methacholine challenges and relationship to clinical status and airway inflammation in steroid naïve asthmatic patients. Journal of Asthma; 2017.
2. Louis, . Bronchodilation Test with Inhaled Salbutamol Versus Bronchial Methacholine Challenge to Make an Asthma Diagnosis: Do They Provide the Same Information?. JACI in Practice; 2019.
3. Yurdakul, . The Assessment of Validity of Different Asthma Diagnostic Tools in Adults. J of Asthma; 2005.
4. Ulrik, . Recognition of Asthma in Adolescents and Young Adults: Which Objective Measure is Best?. Journal of Asthma; 2005.
5. Hunter, . A Comparison of the Validity of Different Diagnostic Tests in Adults With Asthma*. Chest; 2002.
6. Goldstein, . Comparisons of Peak Diurnal Expiratory Flow Variation, Postbronchodilator FEV1 Responses, and Methacholine Inhalation Challenges in the Evaluation of Suspected Asthma*. Chest; 2001.

Table 13: GRADE table: Can sGAW measurement help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Sensitivity	0.50 to 0.51
Specificity	0.71 to 0.74

Baseline Prevalence	20% Typically seen in primary care	50% Typically seen in specialist care

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	2 studies [1,2] 921 patients	diagnostic accuracy study	serious [a]	serious [b]	not serious	not serious	none	100 to 102	250 to 255	⊕⊕◯◯ LOW
False negatives								98 to 100	245 to 250	
True negatives	2 studies [1,2] 921 patients	diagnostic accuracy study	serious [a]	serious [b]	not serious	not serious	none	568 to 592	355 to 370	⊕⊕◯◯ LOW
False positives								208 to 232	130 to 145	

Explanations

a. Limitations in the selection of patients with suspected disease. Spectrum bias potentially leads to inflated estimation of the diagnostic performance.
b.Topalovic 2015 included patients with obstructive disease including COPD and bronchiectasis. The diagnosis of asthma was unclear and the authors focused on non-obstructive asthma
Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded

References

1. Bougard N, Nekoee H, Schleich F, Guissard F, Paulus V, Donneau AF, Louis R. Assessment of diagnostic accuracy of lung functio n indices and FeNO for a positive methacholine challenge. Biochem Pharmacol. 2020 Sep;179:113981.

2. Topalovic M, Derom E, Osadnik CR, Troosters T, Decramer M, Janssens W; Belgian Pulmonary Function Study Investigators. Airways resistance and specific conductance for the diagnosis of obstructive airways diseases. Respir Res. 2015 Jul 22;16(1):88.

Table 14: GRADE table: Can RV/TLC measurement help diagnose asthma in adults with episodic/chronic suggestive symptoms ?

Sensitivity	0.28 to 0.71
Specificity	0.68 to 0.88

Baseline Prevalence	20% Typically seen in primary care	50% Typically seen in specialist care

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	2 studies [1,2] 770 patients	diagnostic accuracy study	serious [a]	not serious	serious [b]	not serious [c]	none	56 to 142	140 to 355	⊕⊕◯◯ LOW
False negatives								58 to 144	145 to 360	
True negatives	2 studies [1,2] 770 patients	diagnostic accuracy study	serious [a]	not serious	serious [b]	not serious [c]	none	544 to 704	340 to 440	⊕⊕◯◯ LOW
False positives								96 to 256	60 to 160	

Explanations

a. Limitations in the selection of patients with suspected disease. Spectrum bias potentially leads to inflated estimation of the diagnostic performance.
b. Pooled data could not be obtained and is represented as a range. Probably due to a threshold effect – accuracy values represent best balance between sensitivity and specificity at a cut-off around RV/TLC ratio of 102 to >125%. Absolute effects per 1000 patients tested are highly variable.
c. Imprecision of data is mainly due to heterogeneity of data and representation of ranges instead of pooled data.

Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded

References

1. Bougard N, Nekoee H, Schleich F, Guissard F, Paulus V, Donneau AF, Louis R. Assessment of diagnostic accuracy of lung function indices and FeNO for a positive methacholine challenge. Biochem Pharmacol. 2020 Sep;179:113981.

2. Stanbrook MB, Chapman KR, Kesten S. Gas trapping as a predictor of positive methacholine challenge in patients with normal spirometry results. Chest. 1995 Apr;107(4):992-5.

FIGURES

Figure Legend

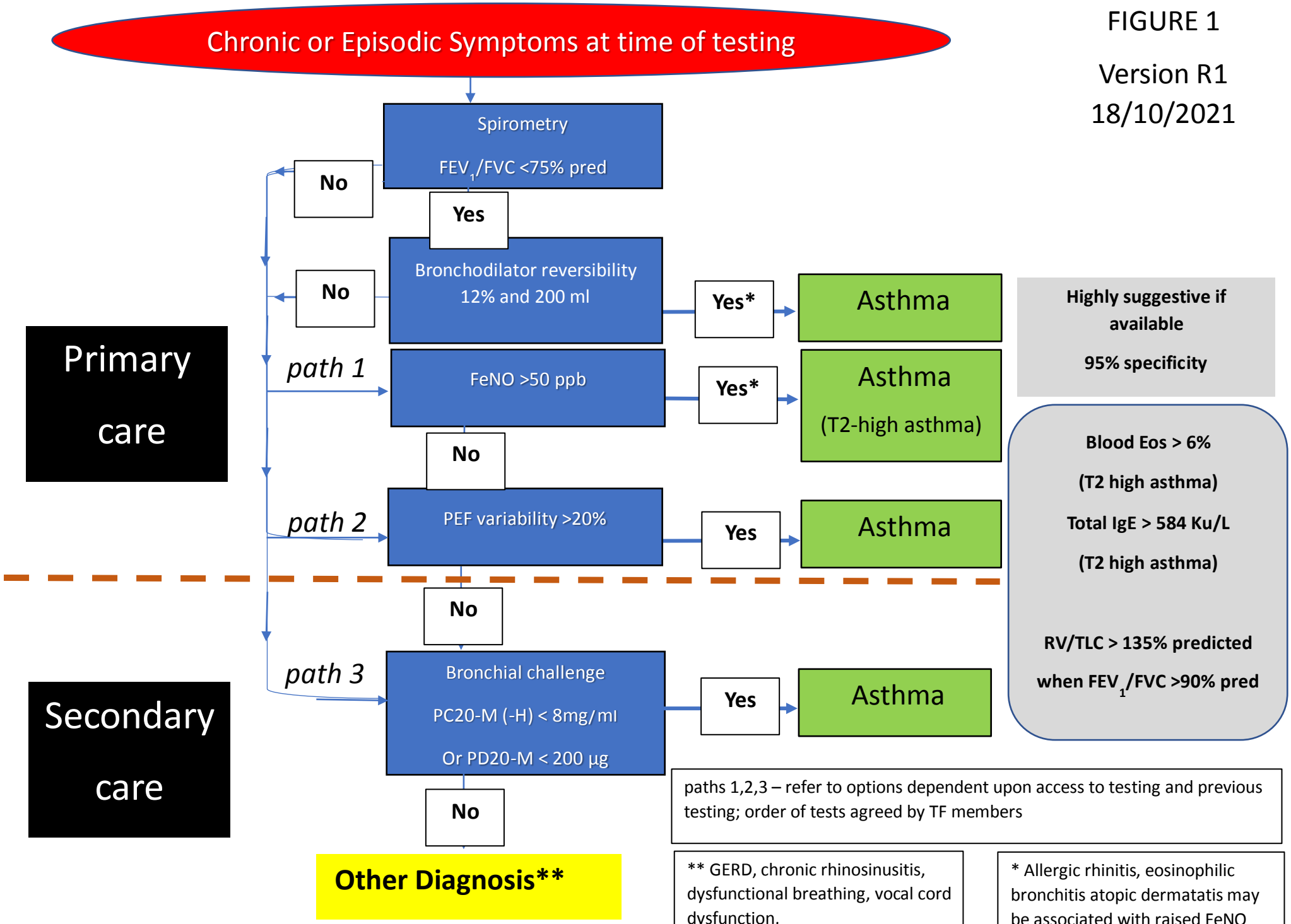
Algorithm for asthma diagnosis in adults with current symptoms. The algorithm was constructed by distinguishing primary from secondary care. It was constructed based on both the literature evidence and clinical experience of the task force members. Three paths to diagnosis were individualised. All the paths place spirometry as the key starting investigation, which was accepted by all TF members. If spirometry with reversibility to bronchodilators cannot confirm the diagnosis we propose three paths which are dependent on the local available resources and health care organisation.

A vote among the TF members (N=17) on the preferred path gave 9 votes for path 1 and 4 votes for both path 2 and path 3. While the majority of the TF members recognised the interest of using FeNO as a support to asthma diagnosis, the best threshold for FeNO was debated and subjected to a written vote after each member had received the GRADE tables. The threshold 50 ppb received 10 votes and the 40 ppb received 5 votes. Two TF members were not able to participate.

PEF variability is assessed over a two-week period.

FIGURE 1

Version R1
18/10/2021



Supplementary Table 1: **Task Force and PICO group composition**

Name	Email	Affiliation	Country	Expertise	Function
Renaud **Louis**	r.louis@uliege.be	CHU Liege, University of Liege	Belgium	Chest physician, Senior	Chair Coordination of meetings and drafting manuscript Supervision of PICO 5
Omar **Usmani**	o.usmani@imperial.ac.uk	Imperial College London	UK	Chest physician, Senior	Co-Chair Coordination of meetings and drafting manuscript
Matteo **Bonini**	matteobonini@tiscali.it	Sapienza University Rome	Italy	Chest physician, Junior	WG leader for PICO 4 and 5
Inigo **Ojanguren**	iojanguren@vhebron.net	Vall d'Hebron University Hospital Barcelona	Spain	Chest physician, Junior	WG leader for PICO 3 and 6 Narrative on phenotyping
Imran **Satia**	imransatia@gmail.com	McMaster University, Hamilton	Canada	Chest physician, Junior	WG leader for PICO 2 and 7
Florence **Schleich**	fschleich@chuliege.be	CHU Liege, University of Liege	Belgium	Chest physician, Junior	WG leader for PICO 1 and 8
Courtney **Coleman**	courtney.coleman@europeanlung.org	European Lung Foundation	UK	European Lung Foundation (ELF) representative	Coordination of lay members contributing to this task force
Arnaud **Bourdin**	arnaud01009157@gmail.com	University Montpelier	France	Chest physician, Senior	Supervision of PICO 8 Narrative on lung imaging
Louis-Philippe **Boulet**	lpboulet@med.ulaval.ca	University Laval Quebec	Canada	Chest physician, Senior	Narrative on patients already treated
Roland **Buhl**	Roland.Buhl@unimedizin-mainz.de	University Mainz	Germany	Chest physician, Senior	Supervision of PICO 2
Marco **Idzko**	marco.idzko@meduniwien.ac.at	University Vienna	Austria	Chest physician, Senior	Member

Janwillem **Kocks**	janwillem@gpri.nl	General Practitioners Research Institute	Netherlands	GP, Senior	Supervision of PICO 3 Narrative on phenotyping
Stelios **Loukides**	loukstel@med.uoa.gr	University of Athens	Greece	Chest physician, Senior	Narrative on phenotyping
Alberto **Papi**	ppa@unife.it	University Ferrara	Italy	Chest physician, Senior	Member
Celeste **Porsbjerg**	celeste.porsbjerg@regionh.dk	Bispepjerg Hospital	Denmark	Chest physician, Senior	Supervision of PICO 1
Joan **Soriano**	jbsoriano2@gmail.com	Hospital Universitario La Princesa Madrid	Spain	Chest physician, Senior	Supervision of PICO 4
Daniel **Schuermans**	Daniel.Schuermans@uzbrussel.be	UZ Brussel VUB	Belgium	Registered nurse, Senior	Member
Anneke **Ten brinke**	a.ten.brinke@znb.nl	Medical Center Leeuwarden	Netherlands	Chest physician, Senior	Supervision of PICO 7 Narrative on comorbidities
Mike **Thomas**	d.m.thomas@soton.ac.uk	University Southampton	UK	GP, Senior	Supervision of PICO 6 Narrative on phenotyping
Karen **Needham**	auntykaz23@icloud.com	Independent	UK	Patient	Testimony of patient experience
David **Rigau**	DRigau@santpau.cat	ERS	Spain	ERS methodologist	Overview of the all process in GRADeing and formulation of recommendations. Supervision of Junior's work. Assistance in drafting Until March 2020
Thomy **Tonia**	thomy.tonia@ersnet.org	ERS	Switzerland	ERS methodologist	Overview of the all process in GRADeing and formulation of recommendations. Supervision of Junior's work. Assistance in drafting From March 2020 until now

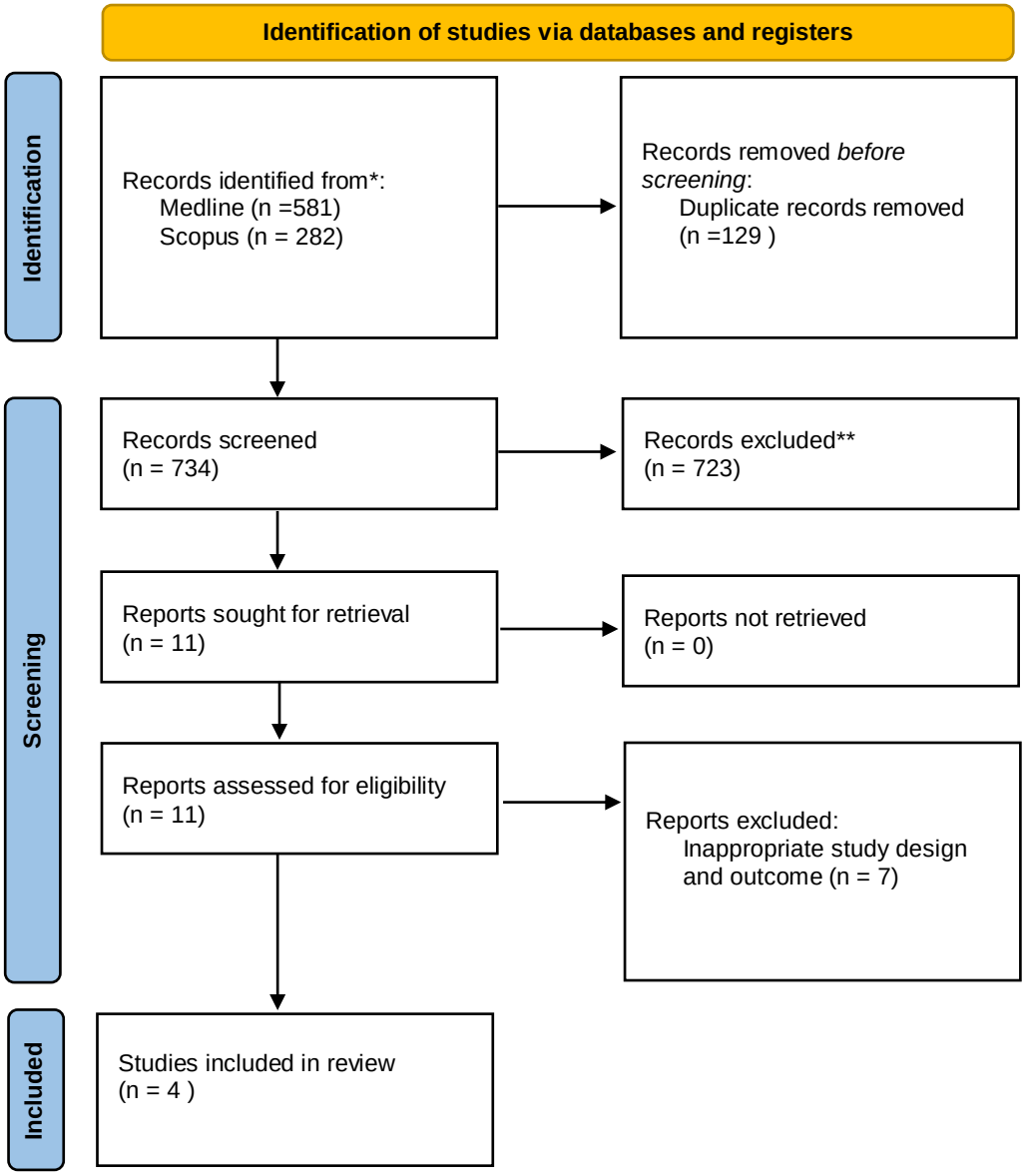
Online supplementary Table 2. Comparison with other asthma statements

	ERS	GINA	NICE	NHBLI- NAEPP
Care Setting	Primary and Secondary Care	Primary and Secondary Care	Primary and Secondary Care	Primary and Secondary Care
Patient or Public Partners	Yes	No	Yes	Yes. Specific Focus Groups and Interviews
Panel Composition	European Lung Foundation GPs Respiratory Physicians Respiratory Nurse	Specialists GP	Public Health Consultant GPs Asthma Nurse Paediatricians Pharmacist Physiologist Respiratory Physician	Paediatric and Adults Allergists/Pulmonologists Internal, Family and Emergency Medicine Health Policy Experts
Frequency	First publication	Twice-Yearly Reviews	As Needed	Not Applicable
Methodology	PICO Framework Systematic literature reviews Meta-analyses Risk of bias assessment with QUADAS Checklist GRADE approach for assessing the quality of the evidence Evidence to Decision Framework	Literature Search including previously conducted Systematic Reviews Individual and Committee Evaluation (Relevance, Quality, Reliability)	Systematic literature reviews Meta-analyses Risk of bias assessment with QUADAS Checklist GRADE approach for assessing the quality of the evidence Evidence to Decision Framework	Systematic literature reviews, Meta-analyses GRADE approach for assessing the quality of the evidence Evidence to Decision Framework
Patient Population	Adults (>16 years old) with suspected asthma	All ages with suspected asthma	All ages with suspected asthma	All ages with suspected asthma
Diagnostic Tests Evaluated or Included in Statement	●Spirometry (FEV1/FVC<LLN, 75%) ●Peak Flow Variability ●FeNO ●Bloods Eosinophils	●Symptoms FEV1/FVC<0.75 ●Bronchodilator Reversibility ●Peak Flow Variability	●Symptoms alone ●History of Atopy ●Exercise induced symptoms ●Effects of Drugs: beta-blockers, aspirin, NSAIDs	●FeNO

	●Total IgE ●Combination FeNO, Blood Eosinophils, IgE ●Bronchial Challenge ●Bronchodilator Reversibility ●Airway Resistance sGaw and RV/TLC	●FeNO ●Improvement in FEV1 after ICS (4-weeks) ●FEV1 variability between visits ●Blood Eosinophils for eligibility of biologic treatment	●Occupational Asthma ●Spirometry/flow volume ●Bronchodilator Reversibility ●Peak Flow Variability ●Skin Prick Testing ●Total and Specific IgE ●FeNO ●Blood Eosinophils ●Bronchial Challenges inc. Exercise Challenge	
Therapies Evaluated	No	Yes	Yes	Yes
Independent Peer Reviewed	Yes	Sent out for open consultation.	Sent out for open consultation.	Yes Sent out for open consultation as well. Reviewed by NIH and U.S. Department of Health and Human Services
Intended Applicability	Global	Global	National Health Service (NHS), UK	U.S.
Cost-Effectiveness Evaluated	No	No	Yes	No

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

Table 3a: Can airway obstruction measured by spirometry help diagnose asthma in adults with episodic/chronic suggestive symptoms?



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Online supplementary Table 3b

QUESTION

Can airway obstruction measured by spirometry help diagnose asthma in adults with episodic/chronic suggestive symptoms?	
POPULATION:	Population of adults (>18 yrs old) with diagnostic uncertainty of asthma
INDEX TEST:	FEV_1/FVC
GOLD STANDARD	1. Bronchodilation > 12% AND > 200 ml 2. Airway hyperresponsiveness: PC20 < 16 mg/ml (or 8 mg/ml) of Methacholine (or Histamine) or PD mannitol < 625 mg or fall in FEV1 > 10% after exercise

ASSESSMENT

Test accuracy

How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate X Varies ○ Don't know	Low sensitivity ranging from 52.6% (Stanbrook et al) to 82% (Bougard et al) to 61% (49.5-72.5) (Hunter et al) Highly variable specificity ranging from 27.9% (Stanbrook et al) to 67% for Bougard et al (with 60% (38.5-81.5) for Hunter et al). Accuracy of 61% in Hunter's paper. In Nekoee's paper a threshold of 76% was found to provide the best compromise between sensitivity (51%) and specificity (76%). The AUC was 0,67	Almost half of the patients already receiving maintenance ICS in Hunter and Bougard papers. The threshold used by Stanbrook was FEV_1/FVC <90% predicted FEV1/FVC Threshold for Hunter: 76.6% Paper of Bougard et al: AUC 0.63. threshold 77% in the derivation cohort and AUC of 0,68 with a threshold at 79% in the validation cohort. Paper of Nekoee et al: AUC 0,67. Threshold 76% The study of Hunter et al. seems unclear in regards of the methods of inclusion (and treatment issues) of the population. We assessed inconsistency as a narrative way and we were able to report **inconsistency** in regards of specificity values with 60% (range 38.5 – 81.5) for

		FEV1/FVC >76.6% and 27.9% for FEV_1/FVC <90% predicted. A better consistency is observed for sensitivity 61% (range 49.5 – 72.5) for FEV_1/FVC >76.6% and 52.6% for FEV_1/FVC <90% predicted. We did not have access to confidence interval of the study of Stanbrook et al but it is likely that there are minimal or no overlap for specificity's confidence interval. Higher specificity in the paper of Bougard but FEV1/FVC was not an independent predictor in the multivariate analysis in that study.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small X Moderate ○ Large ○ Varies ○ Don't know	Lack of accuracy but first step in the diagnostic path Variable PPV, low NPV.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small X Trivial ○ Varies ○ Don't know	None	

Certainty of the evidence of test accuracy

What is the overall certainty of the evidence of test accuracy?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low **X** Low ○ Moderate ○ High ○ No included studies	Low Quality of Evidence	

Certainty of the evidence of management's effects

What is the overall certainty of the evidence of effects of the management that is guided by the test results?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low X Low ○ Moderate ○ High ○ No included studies	First step in the diagnostic path Low quality of evidence – few data in the literature – poor accuracy.	

Certainty of the evidence of test result/management

How certain is the link between test results and management decisions?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low X Low	In case of obstruction and significant reversibility, the diagnosis can be established and treatment can be started	The TF panel made a judgement of low certainty about the likelihood that the appropriate asthma

○ Moderate ○ High ○ No included studies	Low quality of evidence	management will follow on from test results.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention **X** Favors the intervention ○ Varies ○ Don't know	FEV_1/FVC is an index measured by spirometry, a necessary step in the path towards asthma diagnosis, in patients with symptoms suggestive of asthma but should not be used alone to make asthma diagnosis.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs X Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	FEV_1/FVC measurement by spirometry is feasible in primary care but requires a nurse to perform the spirometry.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced		

○ Probably reduced ○ Probably no impact X Probably increased ○ Increased ○ Varies ○ Don't know	None Identified	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know	FEV1/FVC measurement is easy and quick to perform. Not accessible at home. Completion at GP office or at the clinic.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes **X** Yes ○ Varies ○ Don't know	FEV1/FVC requires a spirometer, feasible in primary care, quick. More feasible than Bronchial Challenge in primary care.	

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the	Conditional recommendation for the intervention	**Strong recommendation for the intervention**

○	○	comparison ○	○	●

CONCLUSIONS

Recommendation

The TF recommends performing spirometry as part of the diagnostic work-up of adults aged 18 years with suspected asthma (strong recommendation for the intervention, low quality of evidence). An FEV_1/FVC <LLN or <75%, higher than the commonly utilized 70% threshold, should be considered supportive of an asthma diagnosis and should prompt further testing (see Algorithm)

A normal spirometry does not exclude asthma

Justification

Physiological airflow obstruction and fluctuation of airway caliber, that is usually reversible are recognized as hallmarks of asthma. Though the quality of evidence was low the TF recommends spirometry as the first test to be conducted in the diagnostic work-up. Over-diagnosis, which occurs in approximately 30% of patients with asthma diagnosed in primary care, occurs in part because spirometry in not performed andhas a substantial risk of harm due to inappropriate treatment side-effects, costs, and lack of proper diagnosis[4]. Therefore, a strong recommendation can be made despite low quality of evidence. Spirometry is readily available both in

primary and secondary care, even though it might not be used sufficiently in primary care. Our research found the FEV_1/FVC cut-off providing the best combination of sensitivity and specificity is close to 75%, a threshold well above the 70% threshold generally recognized as a marker of airway obstruction. However, sensitivity at a cut-off of 75% is close to 50% and much too low to rule out asthma. Likewise, at this cut-off, specificity remains below 80% making spirometry alone insufficient to rule in asthma with confidence.

Online supplementary Table 4: Lung function indices performance to make a diagnosis of asthma

Index test	N	Setting	Population	ICS treated	Reference	Asthma diagnosis N (%)	AUC	Cut-off	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	95% specificity
FEV1/FVC													
Stanbrook Chest 1995	500	Secondary care	Referred to a laboratory function	NA	PC20 M < 8mg/ml			90% predicted	53	28	24	57	NA
Hunter Chest 2002	89	Secondary care	Asthma symptoms	46%	PC20M < 8 mg/ml or BdR 15% or ΔPEF20%	69 (77%)	NA	77%	61 (49-72)	60 (38-81)	31	84	NA
Bougard Bioch Pharmacol 2020	129 training cohort	Secondary care	Referred to an asthma clinic	44%	PC20M< 16 mg/ml	85(66%)	0,63	77%	82	46	44	83	NA
	141 validation cohort	Secondary care	Referred to an asthma clinic	47%	PC20M< 16 mg/ml	96 (68%)	0,68	79%	69	67	49	82	NA
Nekoee ERJ open 2020	702	Secondary care	Asthma symptoms	0%	PC20M< 8mg/ml or BdR 12% and 200 ml	349 (50%)	0,67 (0,63-0,71)	76%	51(42-57)	76 (68-81)	61	68	68%
PEFR													
Den Otter Brit J Gen Pract1997	318	Primary care	Asthma symptoms	0%	Bd 9% predicted or PC20H < 8mg/ml	146 (46%)	NA	Variation ≥15%	5	97	60	60	NA
								Variation ≥10%	14	96	62	69	NA
								Variation ≥5%	56	69	66	56	
Thiadens ERJ 1998	170	Primary care	Persistent cough for at least 2 weeks	0%	PD20M < 15,6 µmol	43 (25%)	NA	Variation ≥20%	36	82	65	58	NA
								Variation ≥15%	56	73	70	58	NA
Parameswaran ERJ 1999	132	Secondary care	Asthma symptoms	NA	Chest physician judgment	56 (42%)	NA	Variation ≥20%	77	74	79	72	NA
Goldstein Chest 2000	57	Secondary care	Asthma symptoms	0%	PC20M, BdR, ICS response or fluctuation on several spirometry findings	41(72%)	NA	Variation ≥20%	54	75	39	85	NA
Hunter Chest 2002	89	Secondary care	Asthma symptoms	46%	PC20M < 8 mg/ml or BdR 15% or ΔPEF20%	69 (77%)	NA	Variation ≥22%	43 (31-55)	75 (56-94)	28	86	NA
Ulrik J Asthma 2005	609	Population survey	NA	NA	Self reported asthma	74 (12%)	NA	Variation ≥20%	47	90	92	41	NA

Index test	N	Setting	Population	ICS treated	Reference	Asthma diagnosis N (%)	AUC	Cut-off	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	95% specificity
SGaw													
Topalovic Respir Research 2016	349	Secondary care FEV1/FVC > LLN	Asthma symptoms Vs Healthy Subjects*	NA	Chest physician diagnosis (BC or BdR)	213 (61%)	NA	0,98 1/Kpas.sec	50	64	NA	75	NA
Bougard Bioch Pharmacol 2020	121 training cohort	Secondary care	Referred to an asthma clinic	45%	PC20M< 16 mg/ml	85(66%)	0,69	0,73 1/Kpas.sec	86	49	47	87	NA
Bougard Bioch Pharmacol 2020	149 validation cohort	Secondary care	Referred to an asthma clinic	47%	PC20M< 16 mg/ml	96 (68%)	0,62	0,87 1/Kpas.sec	51	71	45	76	NA
RV/TLC													
Stanbrook Chest 1995	169	Secondary care	Referred to a laboratory function FEV1/FVC > 90% predicted	NA	PC20M< 8mg/ml	72 (43%)	NA	120% predicted	29	81	54	61	NA
							NA	125% predicted	28	88	62	62	NA
							NA	130% predicted	24	91	65	61	NA
							NA	135% predicted	17	96	75	61	NA
							NA	140% predicted	10	97	70	59	NA
Bougard Bioch Pharmacol 2020	121 training cohort	Secondary care	Asthma symptoms	44%	PC20M < 16 mg/ml	85(66%)	0,74	99 % predicted	54	87	69	79	NA
	149 validation cohort	Secondary care	Asthma symptoms	47%	PC20M < 16 mg/ml	96 (68%)	0,75	102 % predicted	71	68	51	83	NA

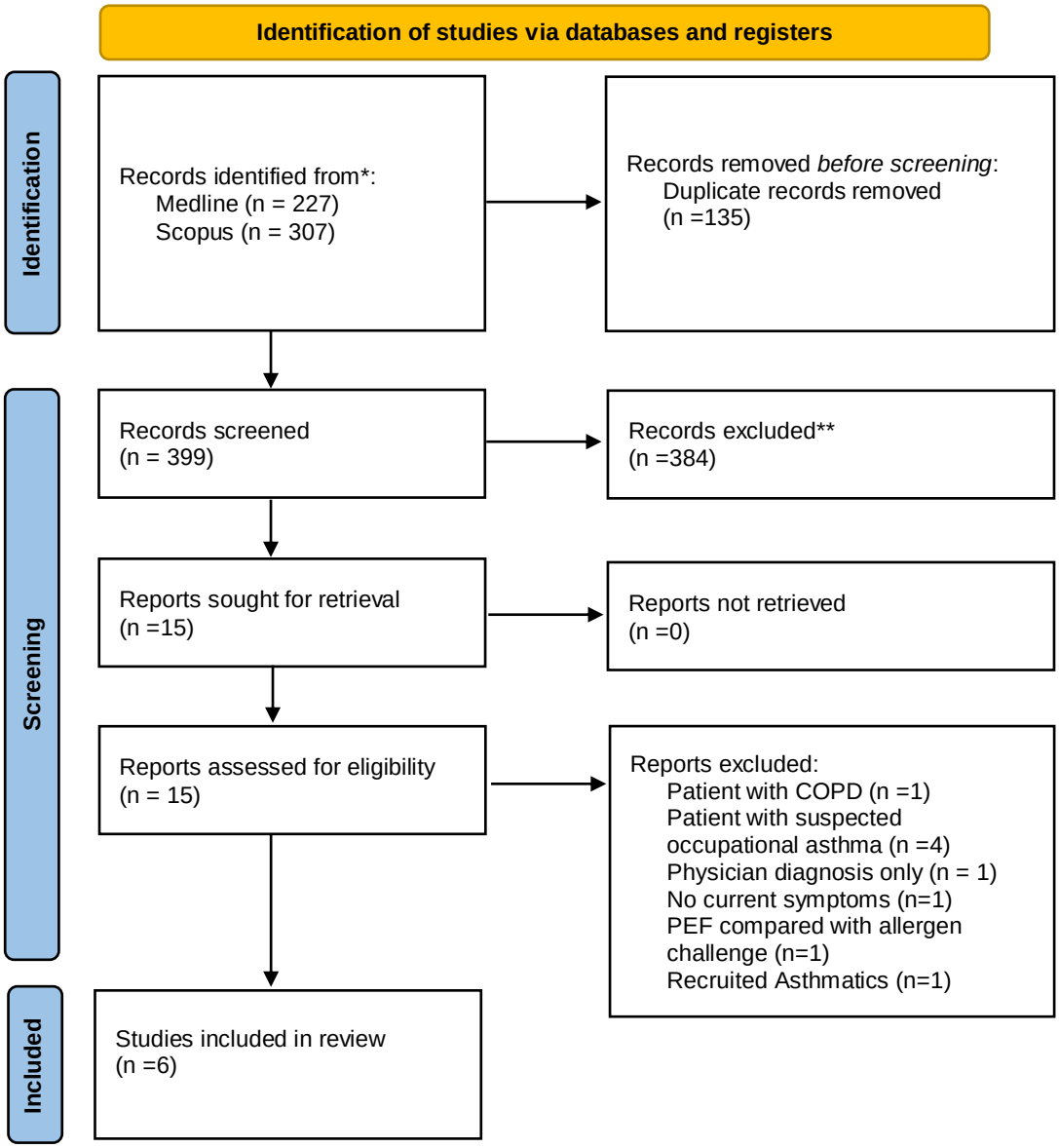
PC20M: provocative concentration of methacholine causing a fall in FEV1 of 20%

BdR: Bronchodilator reversibility

ΔPEF 20%: peak expiratory flow variability of at least 20%

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

Table 5a: Can PEF variability testing help diagnose asthma in adults with episodic/chronic suggestive symptoms?



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Online supplementary Table 5b

QUESTION

Can PEF variability testing help diagnose asthma in adults with episodic/chronic suggestive symptoms?	
POPULATION:	Population of adults (>18 yrs old) with diagnostic uncertainty of asthma
INDEX TEST:	PEFR
GOLD STANDARD	1.Bronchodilation > 12% AND > 200 ml 2. Airway hyperresponsiveness: PC20 < 16 mg/ml (or 8 mg/ml) of Methacholine (or Histamine) or PD mannitol < 625 mg or Fall in FEV1 > 10% after exercise

ASSESSMENT

Test accuracy

How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate **X** Varies ○ Don't know	Low sensitivity ranging from 0.05, 0.1, 0.12, 0.45, 0.93 (in retrospective secondary care) High specificity: 0.93-1.00 Accuracy and reliability of home recording unclear.	Completion rates around 50% in Goldstein study

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate **X** Large	High PPV, but low NPV. So if positive as a first test, then highly desirable	

○ Varies ○ Don't know		

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small **X** Trivial ○ Varies ○ Don't know	No direct undesirable effects. Discuss a bit about the impact of FALSE NEGATIVES (perhaps not very relevance if PEFR is part of a diagnostic algorithm and interpreted together with other tests with better sensitivity) Discuss a bit about the impact of FALSE POSITIVES (may lead to over-treatment)	

Certainty of the evidence of test accuracy

What is the overall certainty of the evidence of test accuracy?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low **X** Low ○ Moderate ○ High ○ No included studies	Low Quality of Evidence	

Certainty of the evidence of management's effects

What is the overall certainty of the evidence of effects of the management that is guided by the test results?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low		

○ Moderate **X** High ○ No included studies	If positive – higher certainty of asthma If negative – does not rule out asthma This question is related to the certainty about asthma treatment (i.e which is the overall certainty of asthma treatments?)	

Certainty of the evidence of test result/management

How certain is the link between test results and management decisions?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate **X** High ○ No included studies	If positive – then management of asthma can be started in primary care. No further testing required.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison **X** Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	There no harms of PEFR, so if PEFR is performed and the test is positive, then this is highly desirable. Is not consistent with the draft recommendation AGAINST the intervention. If the overall balance favors the intervention, some of the following criteria should go really against the intervention	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ○ Moderate costs ○ Negligible costs and savings X Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence identified. Some considerations here are related to feasibility these care additional considerations. PEFR are cheap, can be performed in all resource setting, whereas BDR/Bronchial Challenge is not easily universally available, and is more costly to perform. BDR alone feasible in primary care – quicker diagnosis, but requires spirometry, salbutamol, nurse to perform, interpretation training. Bronchial challenge not feasible in primary care.	In those with airflow obstruction or reduction in FEV1 – likelihood of diagnosing reversibility is greater.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies X Don't know	None Identified	PEFR requires self-monitoring / recording at home, compared to other tests it may generate inequities in low literacy population. However, there are other available tests not requiring self-monitoring / recording at home so there is probably no final impact if recommended

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no X Probably yes ○ Yes ○ Varies ○ Don't know	PEFR may become unrewarding, time consuming or anxiety provoking? some patients may prefer to undergo BDR over 15 mins than to do PEFR at home for 2 weeks and then come back for re-assessment. Risk of not performing correctly or not completing.	Clinicians and people involved in decision-making are also key stakeholders that may have something to say with regards to acceptability

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know	More feasible than Bronchial Challenge in primary care. No difference to BDR.	

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

The TF suggests not recording PEF variability as the primary test to make an asthma diagnosis (conditional recommendation against, low quality of evidence)

PEF may be considered if no other lung function test is available including spirometry and bronchial challenge

PEF should be monitored over a two--week period and a variation of >20% considered as supportive of asthma diagnosis

PEF variability <20% does not rule out asthma

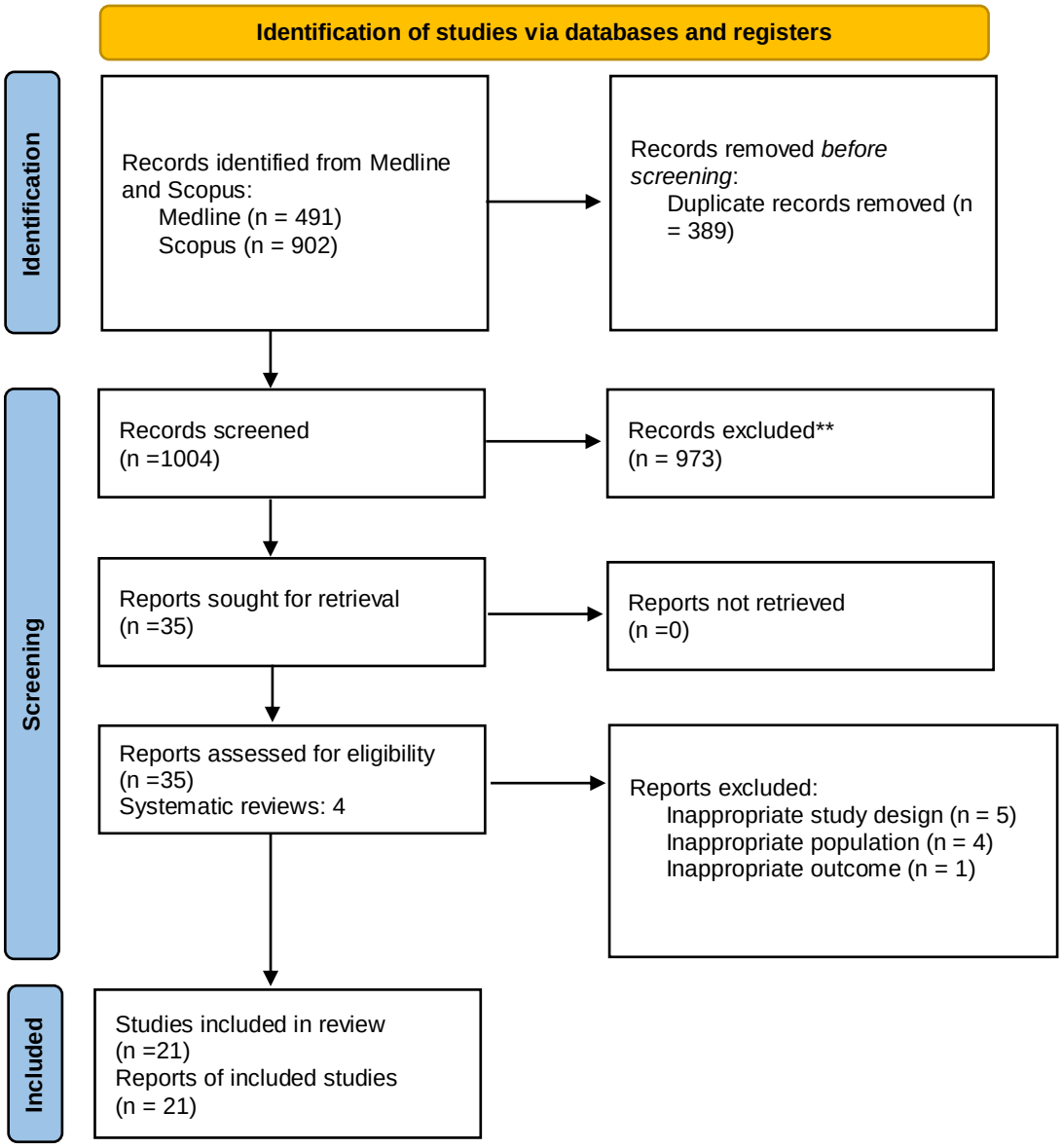
PEF may be especially useful to support a diagnosis of occupational asthma

Justification

Results from studies on PEF variability demonstrate a highly variable sensitivity, with lower sensitivities in studies where the prevalence of asthma was low. Completion of accurate peak flow diaries was poor, with results as low as 50% in one study[26], challenging the reliability, accuracy and feasibility of home PEF recording.In the absence of spirometry defined obstruction and significant BdR, PEF can be monitored over a two-week period particularly if access to bronchial challenge is limited. In the context of a patient with symptoms suggestive of asthma, a positive PEF variability of >20%, that is reliably performed, has a high positive predictive value. Thus, PEF monitoring may be of higher value to diagnose asthma in patients with highly variable day-to-day symptoms, where variable airflow obstruction might be easily detected, or in patients with suspected occupational asthma. We caution that lack of PEF variability does not rule out asthma and further objective testing should be performed.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

Table 6a: Can measuring fractional exhaled nitric oxide (FeNO) help diagnose asthma in adults with episodic/chronic suggestive symptoms?



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Online supplementary Table 6b

QUESTION

Can measuring fractional exhaled nitric oxide (FeNO) help diagnose asthma in adults with episodic/chronic suggestive symptoms?	
POPULATION:	Population of adults (>18 yrs old) with diagnostic uncertainty of asthma
INDEX TEST:	FENO
GOLD STANDARD :	1. Peak flow variability > 20% or spontaneous variation in FEV1 > 12% and 200 ml between several clinic visits 2. Bronchodilation > 12% AND > 200 ml 3. Airway hyperresponsiveness: PC20 < 16 mg/ml (or 8 mg/ml) of Methacholine (or Histamine) or PD mannitol < 625 mg or Fall in FEV1 > 10% after exercise 4. Improvement in FEV1 > 12% and 200 ml after a 2week course of OCS or a 4-week course of ICS

ASSESSMENT

Test accuracy How accurate is the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate X **Varies** ○ Don't know	Based on Youden Index, recommended cut-off values for asthma diagnosis was ranging from 15 ppb to 46 ppb. For the cut-off value of 25 ppb (6 studies) the overall sensitivity value was 0.53 (95% CI: 0.33 to 0.72) and the overall specificity was 0.72 (95% CI:0.61 to 0.81 For the cut-off value of 40 ppb (6 studies) overall sensitivity values was 0.61 (95% CI: 0.37 to 0.81) and the overall specificity value was 0.82 (95% CI: 0.75 to 0.87). For the cut off value of 50 ppb (3 studies) overall sensitivity was ranging from 0.19 to 0.56 and overall specificity was ranging from 0.77 to 0.95.	Given the wide range of recommended FeNO cut-off values for asthma diagnosis the panel decided to provide the overall sensitivity and specificity values for potentially the most useful cut-off values in clinical practice (25ppb, 40ppb and 50 ppb respectively). FeNO higher than 50 ppb is likely to indicate significant airway eosinophilia. It is also likely to indicate that a symptomatic patient has steroid-responsive airway inflammation. In this context, anti-asthmatic treatment could be started.

		In a symptomatic adult patient with a FeNO of less than 25 ppb eosinophilic airway inflammation is unlikely. However, it does not discard asthma diagnosis.
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate X **Large** ○ Varies ○ Don't know	-For the cut off value of 25 ppb, in the clinical context of primary care (pre-test probability 30%), out of 1000 patients tested, 159 correspond to true positives and 504 correspond to true negatives. In secondary care (pre-test probability 50%), out of 1000 patients tested, 265 correspond to true positives and 360 correspond to true negatives. -For the cut off value of 40 ppb, in the clinical context of primary care (pre-test probability 30%), out of 1000 patients tested, 183 correspond to true positives and 574 correspond to true negatives. In secondary care (pre-test probability 50%), out of 1000 patients tested, 305 correspond to true positives and 410 correspond to true negatives. -For the cut off value of 50 ppb, in the clinical context of primary care (pre-test probability 30%), out of 1000 patients tested, true positives range from 57 to 167 and true negatives range from 537 to 665. In secondary care (pre-test probability 50%), out of 1000 patients tested, true positive range from 95 to 278 and true negatives range from 537 to 665.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large ○ Moderate ○ Small x **Trivial** ○ Varies ○ Don't know	-For the cut off value of 25 ppb, in the clinical context of primary care (pre-test probability 30%), out of 1000 patients tested, 141 correspond to false negatives and 196 correspond to false positives. In secondary care (pre-test probability 50%), out of 1000 patients tested, 235 correspond to false negatives and 140 correspond to false positives. -For the cut off value of 40 ppb, in the clinical context of primary care (pre-test probability 30%), out of 1000 patients tested, 117 correspond to false negatives and 126 correspond to false positives. In secondary care (pre-test probability 50%), out of 1000 patients tested, 195 correspond to false negatives and 90 correspond to false positives. -For the cut off value of 50 ppb, in the clinical context of primary care (pre-test probability 30%), out of 1000 patients tested, false negatives range from 133 to 247 and false positives range from 35 to 163. In secondary care (pre-test probability 50%), out of 1000 patients tested, false negatives range from 222 to 405 and false positives range from 25 to 116..	Since asthmatic patients with no T2 airway inflammation do not present FeNO increase, it does not seem reasonable to use this tool to rule out asthma.

Certainty of the evidence of test accuracy What is the overall certainty of the evidence of test accuracy?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low x **Moderate** ○ High ○ No included studies	-Sensitivity of the cut-off value of 25 ppb for the diagnosis of asthma was 0.53 (95% CI: 0.33 to 0.72) (Test accuracy (Grade): ⊕⊕⊕◯ MODERATE). Specificity of the cut-off value of 25 ppb for the diagnosis of asthma was 0.72 (95% CI: 0.61 to 0.81); (Test accuracy (Grade) ⊕⊕⊕◯ MODERATE). -Sensitivity of the cut-off value of 40 ppb for the diagnosis of asthma was 0.61 (95% CI: 0.37 to 0.81) (Test accuracy (Grade): ⊕⊕⊕◯ MODERATE). Specificity of the cut-off value of 40 ppb for the diagnosis of asthma was 0.82 (95% CI: 0.65 to 0.87); (Test accuracy (Grade) ⊕⊕⊕◯ MODERATE). -Sensitivity of the cut-off value of 50 ppb for the diagnosis of asthma	The systematic review revealed a best cut-off value (based on the Youden index) ranging from 15 to 46 ppb, presenting a wide range of sensibility and specificity values, showing a high variability between the results of the included studies. The heterogenicity of the presented results reflect a relevant limitation.

	was ranging from 0.19 to 0.56; (Test accuracy (Grade): ⊕⊕⊕◯ MODERATE)). Specificity of the cut-off value of 50 ppb for the diagnosis of asthma was ranging from 0.77 to 0.95; Test accuracy (Grade): ⊕⊕⊕◯ MODERATE). Not direct undesirable effects.	
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low X **Moderate** ○ High ○ No included studies	The included studies were retrospective cross-sectional and prospective cross-sectional studies.	If the result is positive, higher than 50 ppb, the probability of presenting asthma is higher.
Certainty of the evidence of test result/management How certain is the link between test results and management decisions?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate X **High** ○ No included studies	If positive (above 50 ppb)- the management of asthma can be started and response to ICS can be expected to be good. If negative (below 25 ppb) patients could still benefit from asthma treatment (no T2 asthma) so it would not be wise to discard asthma or asthma treatment.	The positivity of the test has been shown to be highly variable although above this limit (50 ppb) patients clearly benefit from starting asthma treatment.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention X **Favors the intervention** ○ Varies ○ Don't know	If FeNO is performed and the test is positive, anti-asthma treatment can be started. There are not direct or indirect harms related to the test, so performing the test is clearly beneficial.	

Resources required
How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings X **Moderate savings** ○ Large savings ○ Varies ○ Don't know	We did not look for evidence on costs.	Comparing to the rest of the tests used for asthma diagnosis, costs of performing FeNO do not exceed those required for the bronchodilator test or the bronchial provocation with methacholine.

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced X **Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know	We did not look for evidence on equity.	There not seem to be equity issues related to this test.

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes X **Yes** ○ Varies ○ Don't know	We did not look for evidence on acceptability.	No limitations identified related to acceptability, since it is an easy to perform, not time consuming, cheap and non-invasive technique. In this context the panel considers that the text is highly acceptable for patients, clinicians and policy makers.
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes X **Yes** ○ Varies ○ Don't know	We did not look for evidence on feasibility.	The panel considers that given the availability and the acceptable cost of performing FeNO, there are not limitations identified related to feasibility.

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The TF suggests measuring the fraction of exhaled nitric oxide (FeNO) as part of the diagnostic work-up of adults aged >18 years with suspected asthma (conditional recommendation for the intervention, moderate quality of evidence)

A cut-off value of 40 ppb offers the best compromise between sensitivity and specificity while a cut-off of 50 ppb has a high specificity >90% and is supportive of a diagnosis of asthma

A FeNO value <40 ppb does not rule out asthma and similarly high FeNO level do not define asthma

FeNO values are markedly reduced by smoking,treatment with ICS or anti-IL4/IL13-alpha antibody

Justification

Measuring FeNO is a point-of-care method that may be particularly useful in both primary and secondary care,[56]lthough it is not yet considered for reimbursement in most of European countries. A cut-off value above 40-50 ppb yields a high specificity (between 0.75 to 0.95), to rule in a diagnosis of asthma with confidence. However, the poor sensitivity (between 0.19 to 0.81) does not allow asthma to be ruled out, for values below 40 ppb. Although the TF recommends using FeNO to help in the diagnosis of asthma, we make it clear that high FeNO levels do not define asthma. High FeNO levels may be observed in patients with eosinophilic chronic bronchitis, allergic rhinitis or eczema who may deny any asthma symptoms and do not show bronchial hyperresponsiveness.

Subgroup considerations

FeNO is highly valuable in asthmatics with T2 inflammation although it is not useful for patients presenting no T2 inflammation. Its diagnostic accuracy is better for identifying eosinophilic asthma

Implementation considerations

The non invasive, not expensive and not invasive nature of the technique make the implementation easy to perform in most clinical scnearios.

~~Monitoring and evaluation~~

Research priorities

Further studies analyzing the utility of FeNO in combination with other T2 biomarkers for asthma diagnosis.

Online supplementary Table 7: FeNO indices performance to make a diagnosis of asthma

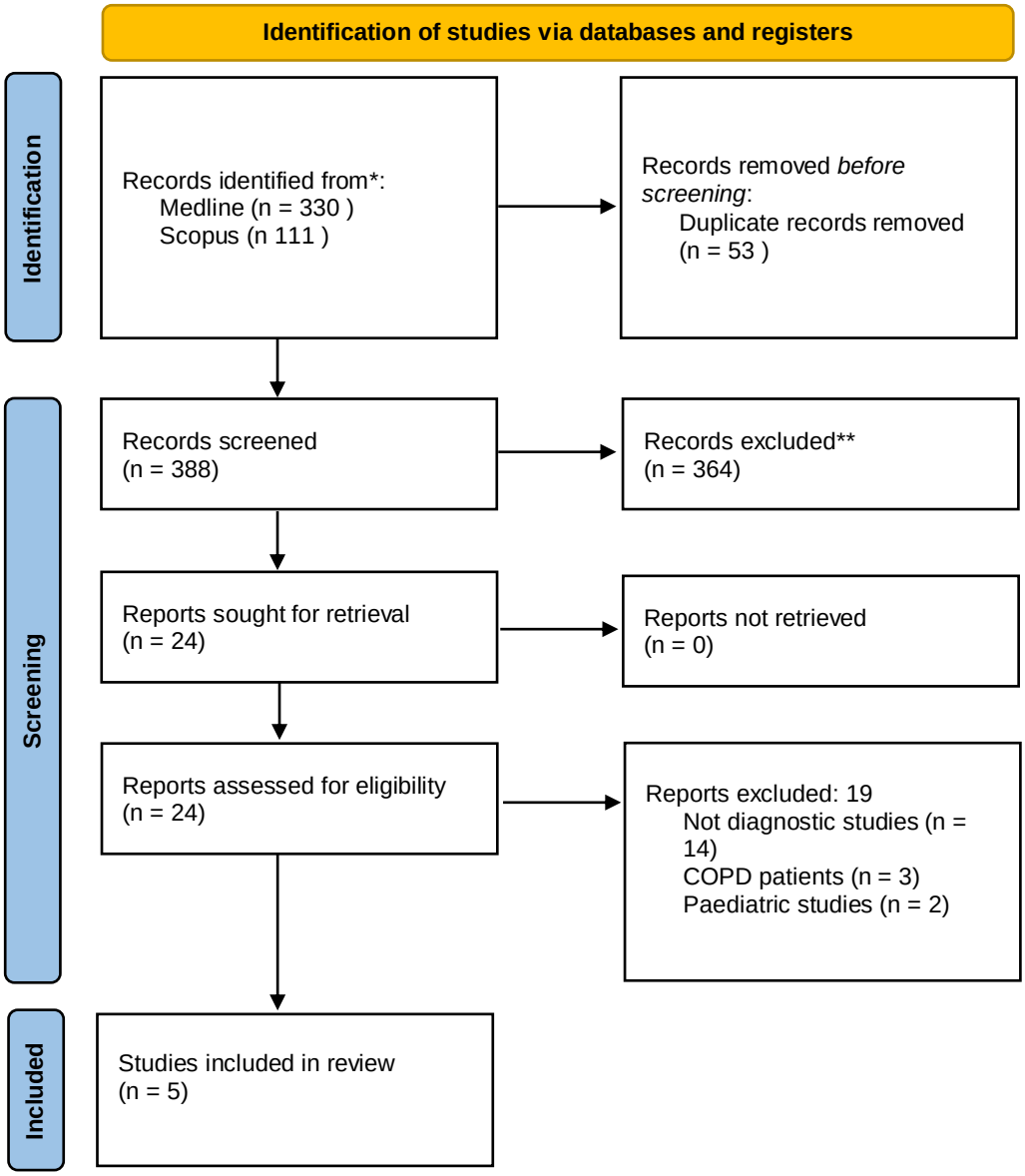
Index test	N	Setting	Population	ICS treated	Reference	Asthma diagnosis N (%)	AUC	Cut-off	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	95% specificity
FeNO													
Arora Allergy and Asthma Proceedings 2006	172	Secondary care	Asthma symptoms	0	BC	138 (80%)	0.628	17	63	58.8	86.1	28.2	NA
Cirillo Int Arch All Immunol 2017	211	Secondary care	Patients with persistent allergic rhinitis	0	BC	43 (20%)	0.9 (0.85-0.96)	37	79.1	90.55	NA	NA	NA
Cordeiro Allergy and Asthma Proceedings 2011	114	Secondary care	Adults submitted to an allergy clinic	0	BC	42 (37%)	0.86	27	78	92	86%	87%	NA
Fortuna Respir Med 2007	50	Secondary care	Asthma symptoms	0	BC	22 (44%)	0.8	20	77	64	62	78	NA
Fukuhara Annals of allergy, asthma and immunology 2011	61	Secondary care	Asthma symptoms	0	BdR	42 (69%)	NA	17	78.6	89.5	NA	NA	NA
He Indian J Med Res 2018	400	Secondary care	Asthma symptoms	NA	BC or BdR	265 (66%)	0.728	23.5	79.9	54.7	77.9	58.1	NA
Heffler Respir Med 2006	48	Secondary care	Asthma symptoms	0	BC	18 (37.5%)	0.78	36	78	60	53.84	81.81	NA
Katsoulis Int Arch All Immunol 2013	112	Secondary care	Asthma symptoms	0	BC	NA	0.691	32	47	85	NA	NA	NA
Kostikas Chest 2008	149	Secondary care	Asthma symptoms	0	BC or BdR or Improvement in FEV1 > 12% and 200 ml after a 2-week course of OCS or a 4 week course of ICS	63 (42%)	0.723	19	52.4	85.2	NA	NA	NA
Kowal J Asthma 2009	540	Secondary care	Adults with chronic cough	0	BC or BdR or Improvement in FEV1 > 12% and 200 ml after a 2-week course of OCS or a 4 week course of ICS	166 (30%)	0.924 (0.897-0.946)	40	88.3	82.6	72.6	92.1	NA
Malinovshi Resp Med 2012	282	Secondary care	Asthma symptoms	0	BC or BdR	96 (34%)	0.72	15	77.8	63.5	60	80	NA

Martin Thorax 2016	74	Primary care	Asthma symptoms	3 (0.8%)	BC	154 (39.2%)	0.62	NA	NA	NA	NA	NA	NA
Nekoee ERJ Open 2020	702	Secondary care	Asthma symptoms	0	BC	349 (49.7%)	0.6 (0.56-0.64)	36	30	85	66	55	72
Pedrosa J Asthma 2010	114	Secondary care	Asthma symptoms	21 (60%)	BC	35 (30.7%)	0.762 (0.667-0.857)	40	74.3	72.5	542	86.6	NA
Sato Respir Med 2008	71	Secondary care	Asthma symptoms	0	BC or BdR	30 (42.3%)	NA	38	79.2	91.3	NA	NA	NA
Schleich Int J Clin Pract	174	Secondary care	Asthma symptoms	0	BC	82 (47%)	0.62	34	35.4	95.4	88	62	NA
Schneider Respir Med 2013	393	Primary care	Suspicious of obstructive airway disease	3 (0.8%)	BC	154 (39.2%)	0.603 (0.528-0.677)	25	49	75	56	69	NA
Schneider Respir Res 2009	170	Primary care	Asthma symptoms	7 (4.4%)	BC	75 (46.9%)	0.645 (0.559-0.731)	46	32	93	80	61	NA
Tilemann Prim Care Respir J 2011	210	Primary care	Suspicious of obstructive airway disease	11 (5.2%)	BC or BdR	86 (41%)	0.618 (0.529-0.706)	46	29	92	71	65	NA
Voutilainen Clin Resp J 2013	174	Secondary care	Asthma symptoms	0	BC	54 (62%)	0.74 (0.63-0.85)	30	43	89	68	75	NA
Wang Int J Clin Exp Pathol 2014	923	Secondary care	Asthma symptoms	0	BC or BdR	125(30%)	0.758	64	52	94.35	61.75	82.83	NA

BC: bronchial challenge
BdR: bronchodilator reversibility
ICS: Inhaled corticosteroid
OCS: Oral corticosteroid

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

Table 8a: Can measuring blood eosinophil count help diagnose asthma in adults with episodic/chronic suggestive symptoms?



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Online supplementary Table 8b

QUESTION

Can measuring blood eosinophil count help diagnose asthma in adults with episodic/chronic suggestive symptoms?	
POPULATION:	Population of adults (>18 yrs old) with diagnostic uncertainty of asthma
INTERVENTION:	Blood eosinophil count
GOLD STANDARD:	1. Peak flow variability > 20% or spontaneous variation in FEV1 > 12% and 200 ml between several clinic visits 2. Bronchodilation > 12% AND > 200 ml 3. Airway hyperresponsiveness: PC20 < 16 mg/ml (or 8 mg/ml) of Methacholine (or Histamine) or PD mannitol < 625 mg or Fall in FEV1 > 10% after exercise 4. Improvement in FEV1 > 12% and 200 ml after a 2week course of OCS or a 4-week course of ICS

ASSESSMENT

Test accuracy
How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate X Inaccurate ○ Accurate ○ Very accurate ○ Varies ○ Don't know	Low test sensitivity (ranging from 0,15 to 0,59) High test specificity (ranging from 0,39 to 1) No data on blood eos expressed as absolute value. Studies have concentrated on blood eos expressed as % of leucocytes One study (Nekoee et al) provided the 95% specificity at 5,9%	Two large studies (one prospective from primary care and one retrospective from secondary care) providing similar AUC. AUC around 0,6. Thresholds ranging between 4-6%

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small X Moderate ○ Large ○ Varies ○ Don't know	BEC might be useful to endotype asthma and establish eligibility to biological treatment (particularly anti-IL-5) in severe forms of the disease. Recent evidence suggest also that it might be a marker for the necessity to use ICS. Blood eosinophils is better to phenotype than diagnose asthma	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small X Trivial ○ Varies ○ Don't know	No major undesirable effects. Pain and concerns related to venipuncture	

Certainty of the evidence of test accuracy

What is the overall certainty of the evidence of test accuracy?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low X Low ○ Moderate ○ High ○ No included studies		

Certainty of the evidence of management's effects

What is the overall certainty of the evidence of effects of the management that is guided by the test results?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low X Low ○ Moderate ○ High ○ No included studies	Recent data (included in the narrative section) suggest that blood eos > 150µl in newly diagnosed mild asthma makes ICS treatment necessary to prevent asthma exacerbation (Pavord I, Lancet Respir Med 2020)	

Certainty of the evidence of test result/management

How certain is the link between test results and management decisions?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low X Low ○ Moderate ○ High ○ No included studies		

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Results of the test not known immediately, as opposed to FeNO Statistical performance not better than FeNO Bronchial challenge tests show better PPV and NPV	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs X Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Non-expensive and easy to perform test	

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced X Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no X Probably yes ○ Yes ○ Varies ○ Don't know	Some patient may experience adverse event during the venipuncture.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know	Non-expensive and easy to perform test	

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

The TF suggests not measuring blood eosinophil count for asthma diagnosis (conditional recommendation, low quality of evidence)

Blood eosinophil count does not define asthma but rather contributes to phenotyping

Justification

BEC lacks sensitivity to diagnose asthma, with sensitivities ranging between 21% to 59% in the reported studies. A BEC does not provide immediate results at the time of the consultation in order to directly help the clinician, although as blood leukocyte differential is a test frequently performed for several indications in routine practice, it may be that a previous test is available at the time of the consultation. BEC cut-offs above 4% and 6% have a specificity greater than 80% and 95% respectively and may help the clinician to be confident in their diagnosis in patients with suggestive symptoms.

Online supplementary Table 9: Blood eosinophils and total serum IgE performance to make a diagnosis of asthma

	N		Population	ICS treated	Reference	AUC	Cut-off	Sensitivity	Specificity	NPV	PPV	95% specificity
Blood Eosinophils												
Hunter Chest 2002	89	Secondary care	Asthma symptoms	46%	BC or BdR or ΔPEF	?	6,3%	21	100	0,27	100	?
Yurdakul J Asthma 2005	100	Secondary care	Asthma symptoms	48%	BC or BdR or ΔPEF	?	?	59	71	51	77	?
Popovic-Glre Coll Antropol 2002	195	Secondary care	Asthma symptoms	0% ?	BdR	?	?	15	39	74	64	?
Tilemann Prim Care Respir J 2011	210	Primary care	Asthma symptoms	5%	BC or BdR	0,60 (0,52-0,68)	4,2%	36	83	65	59	?
Nekoee ERJ open 2020	702	Secondary care	Asthma symptoms	0%	BC or BdR	0,58 (0,54-0,62)	4,4%	23	91	54	72	5,9%
Total serum IgE												
Yurdakul J Asthma 2005	100	Secondary care	Asthma symptoms	48%	BC or BdR or ΔPEF	?	?	33	85	46	76	?
Popovic-Grle Coll Antropol 2002	195	Secondary care	Asthma symptoms	0%?	BdR	?	?	51	72	59	72	?
Tilemann Prim Care Respir J 2011	210	Primary care	Asthma symptoms	5%	BC or BdR	0,58	90 Ku/L	47	73	66	54	?
Nekoee ERJ open 2020	702	Secondary care	Asthma symptoms	0%	BC or BdR	0,57	132 Ku/L	41	78	57	64	584 Ku/L

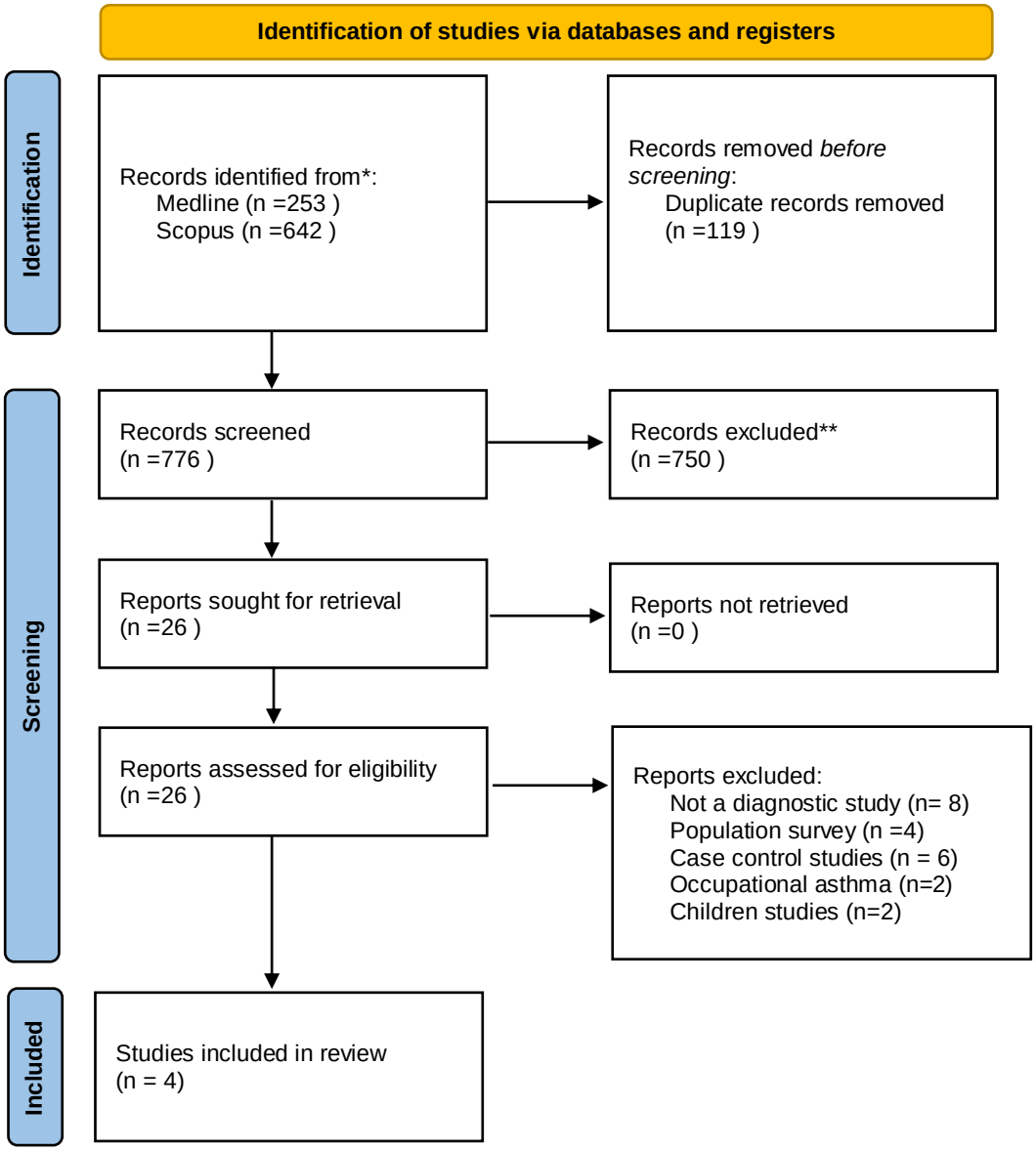
BC: bronchial challenge

BdR: bronchodilator reversibility test

ΔPEF: peak expiratory flow variability

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

Table 10a: Can measuring total serum IgE help diagnose asthma in adults with episodic/chronic suggestive symptoms?



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Online supplementary Table 10b

QUESTION

Can measuring total serum IgE help diagnose asthma in adults with episodic/chronic suggestive symptoms?	
POPULATION:	Population of adults (>18 yrs old) with diagnostic uncertainty of asthma
INTERVENTION:	Total serum IgE test
GOLD STANDARD :	1.Peak flow variability > 20% or spontaneous variation in FEV1 > 12% and 200 ml between several clinic visits 2. Bronchodilation > 12% AND > 200 ml 3. Airway hyperresponsiveness: PC20 < 16 mg/ml (or 8 mg/ml) of Methacholine (or Histamine) or PD mannitol < 625 mg or Fall in FEV1 > 10% after exercise 4. Improvement in FEV1 > 12% and 200 ml after a 2week course of OCS or a 4-week course of ICS

ASSESSMENT

Test accuracy
How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate X Inaccurate ○ Accurate ○ Very accurate ○ Varies ○ Don't know	Low test sensitivity (ranging from 0,33 to 0,51) Greater specificity (ranging from 0,72 to 0,85) One study (Nekoee et al) provided the 95% specificity at 584 Ku/L	Two large studies (one prospective from primary care and one retrospective from secondary care) providing similar AUC. AUC around 0,6. Thresholds ranging from 90 to 132 KU/L (Tilemann et al ; Nekoee et al)

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial	Total serum IgE might be useful to endotype asthma and establish eligibility to	

○ Small X Moderate ○ Large ○ Varies ○ Don't know	biological treatment in severe forms of the disease. An elevated level should prompt detailed investigation towards specific allergy	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small X Trivial ○ Varies ○ Don't know	No major undesirable effects. Pain and concerns related to venipuncture. Potential impact of other allergic comorbidities on test results.	

Certainty of the evidence of test accuracy

What is the overall certainty of the evidence of test accuracy?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low X Low ○ Moderate ○ High ○ No included studies	Few observational studies. No RCT	

Certainty of the evidence of management's effects

What is the overall certainty of the evidence of effects of the management that is guided by the test results?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low X Low ○ Moderate ○ High ○ No included studies	High total serum IgE suggests but not proves atopy, a condition often associated with asthma. The presence of atopy may drive some aspect of the treatment (allergen avoidance, immunotherapy, anti-IgE)	

Certainty of the evidence of test result/management

How certain is the link between test results and management decisions?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low X Low ○ Moderate ○ High ○ No included studies		

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Serum IgE has an insufficient sensitivity to diagnose asthma As a marker of airway inflammation FeNO offers a better alternative allowing for immediate results and, overall, slightly greater statistical performance Bronchial challenge tests show better PPV and NPV	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ○ Moderate costs X Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Non-expensive and easy to perform and to read test	

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced X Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no X Probably yes ○ Yes ○ Varies ○ Don't know		

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know	Non-expensive and easy to perform and to read test	

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

The TF suggests not measuring total serum IgE for asthma diagnosis (Conditional recommendation, low quality of evidence)

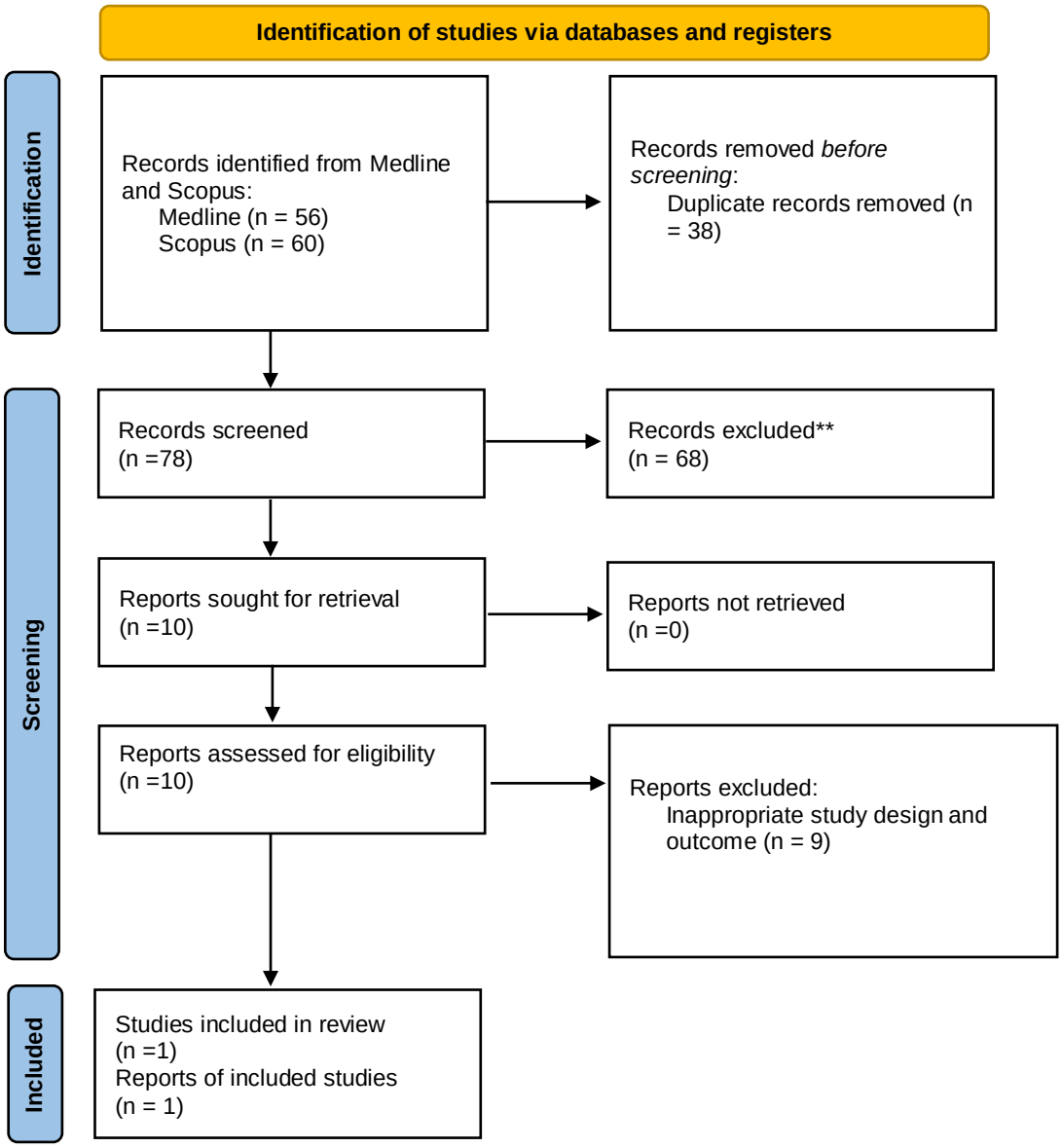
Total serum IgE does not define asthma but rather contributes to phenotyping

Justification

Total serum IgE should not be used for the diagnosis of asthma because of consistently poor sensitivities across the studies, reaching at best 51%. This is in line with the existence of a significant proportion of non IgE-mediated asthma, also called “intrinsic” asthma. Measuring total serum IgE does not provide immediate results at the time of the consultation. If specificity is better than sensitivity it remains limited at the cut-offs provided by the ROC curves, ranging from 39% to 85%. The value of measuring IgE may vary according to the population of patients investigated, the seasonal manifestations of the symptoms, the coexistence of allergic rhinitis and is likely to be more valid in young patients as IgE levels decline with age.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

Table 11a: Can combining FeNO, blood eosinophils and IgE help diagnose asthma in adults with episodic/chronic suggestive symptoms?



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Online supplementary Table 11b

QUESTION

Can combining FeNO, blood eosinophils and IgE help diagnose asthma in adults with episodic/chronic suggestive symptoms?	
POPULATION:	Population of adults (>18 yrs old) with diagnostic uncertainty of asthma
INDEX TEST:	Combination of total IgE, FeNO and blood eosinophilia
GOLD STANDARD:	1. Peak flow variability > 20% or spontaneous variation in FEV1 > 12% and 200 ml between several clinic visits 2. Bronchodilation > 12% AND > 200 ml 3. Airway hyperresponsiveness: PC20 < 16 mg/ml (or 8 mg/ml) of Methacholine (or Histamine) or PD mannitol < 625 mg or Fall in FEV1 > 10% after exercise 4. Improvement in FEV1 > 12% and 200 ml after a 2week course of OCS or a 4-week course of ICS

ASSESSMENT

Test accuracy How accurate is the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very inaccurate X **Inaccurate** ○ Accurate ○ Very accurate ○ Varies ○ Don't know	Only one study assessing this question. The unique study assessing this question reported a sensitivity of 0.46 (95% CI: 0.37 to 0.52) and a specificity of 0.74 (95% CI:0.64 to 0.69) for asthma diagnosis. Combining the three biomarkers did not increase the performance of the tests since the AUC remained at 0.6 (95 CI 0.56-0.64). Relying on the combination of T2 biomarkers (IgE, FeNO and eosinophilia) to make an asthma diagnosis in patients with suggestive symptoms lacks accuracy.	This observation also supports the concept that asthma may also be a non-T2 disease. The combination of these tests would not be helpful for non- T2 asthma, so it would not help ruling out asthma. Besides, the combination of the 3 biomarkers does not improve the diagnostic yield of each biomarker alone.

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
x **Trivial** ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	The study by Nekoee et al. reported that in the clinical context of primary care (pre-test probability 30%), out of 1000 patients tested, 138 correspond to true positives and 518 correspond to true negatives. In secondary care (pre-test probability 50%), out of 1000 patients tested, 230 correspond to true positives and 370 correspond to true negatives.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ○ Small x **Trivial** ○ Varies ○ Don't know	The study by Nekoee et al. reported that in the clinical context of primary care (pre-test probability 30%), out of 1000 patients tested, 162 correspond to false negatives and 182 correspond to false positives. In secondary care (pre-test probability 50%), out of 1000 patients tested, 270 correspond to false negatives and 130 correspond to false positives.	
Certainty of the evidence of test accuracy What is the overall certainty of the evidence of test accuracy?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
x **Very low** ○ Low ○ Moderate ○ High ○ No included studies	Results limited to a one single retrospective cross-sectional study: The combination of IgE, blood eosinophilia and FeNO for asthma diagnosis showed a sensitivity of 0.46 (95% CI: 0.37 to 0.52) and a specificity of 0.74 (95% CI:0.64 to 0.69) for asthma diagnosis (GRADE: ⊕⊕⊕◯ moderate quality of evidence) Combining the three biomarkers did not increase the performance of the tests since the AUC remained at 0.6 (95 CI 0.56-0.64)	
Certainty of the evidence of management's effects		

What is the overall certainty of the evidence of effects of the management that is guided by the test results?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low X **Moderate** ○ High ○ No included studies	Results limited to a single one retrospective cross-sectional study with moderate quality of evidence.	The combination of the different T2 biomarkers (IgE, FeNO and blood eosinophilia) does not seem to increase the diagnostic like hood of each test alone.
Certainty of the evidence of test result/management How certain is the link between test results and management decisions?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate X **High** ○ No included studies	Results limited to a single one retrospective cross-sectional study with low quality of evidence. If positive- the management of asthma can be started, although not addional benefit of combining these 3 tests was observed in the study by Nekoee e tal. Comparing to each test alone.	Useful when they are positive (high specificity) but not useful if they are negative; not useful to rule out asthma
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention X **Favors the intervention** ○ Varies ○ Don't know	Based on the only study available, combining these tests do not provide additional benefits comparing to each test alone, however no undesirable effects were observed related to performing the tests.	There no harms related to these tests so, if they are performed and the tests are positive, then this is highly desirable. If negative, asthma should not be ruled out.
Resources required		

How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings X **Moderate savings** ○ Large savings ○ Varies ○ Don't know	We did not look for this evidence.	Comparing to the rest of the tests used for asthma diagnosis, costs of performing FeNO, IgE and blood eosinophilia do not exceed those required for the bronchodilator test or the bronchial provocation with methacholine.
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced X **Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know	We did not look for evidence on equity.	There not seem to be equity issues related to this test.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes X **Yes** ○ Varies ○ Don't know	We did not look for evidence on acceptability.	No limitations identified related to acceptability, since they are easy to perform, not time consuming, cheap and non-invasive biomarkers. In this context the panel considers that the tests are highly acceptable for patients, clinicians and policy makers.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes X **Yes** ○ Varies ○ Don't know	We did not look for evidence on feasibility.	The panel considers that given the availability and the acceptable cost of performing IgE, blood eosinophilia and FeNO, there are not limitations identified related to feasibility.

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

We suggest not using the combination of IgE, blood eosinophilia and FeNO for the diagnosis of asthma in adults (conditional recommendation, low quality of evidence).

Justification

Subgroup considerations

The utility of the combination of the test would be limited to T2 asthma (eosinophilic asthma).

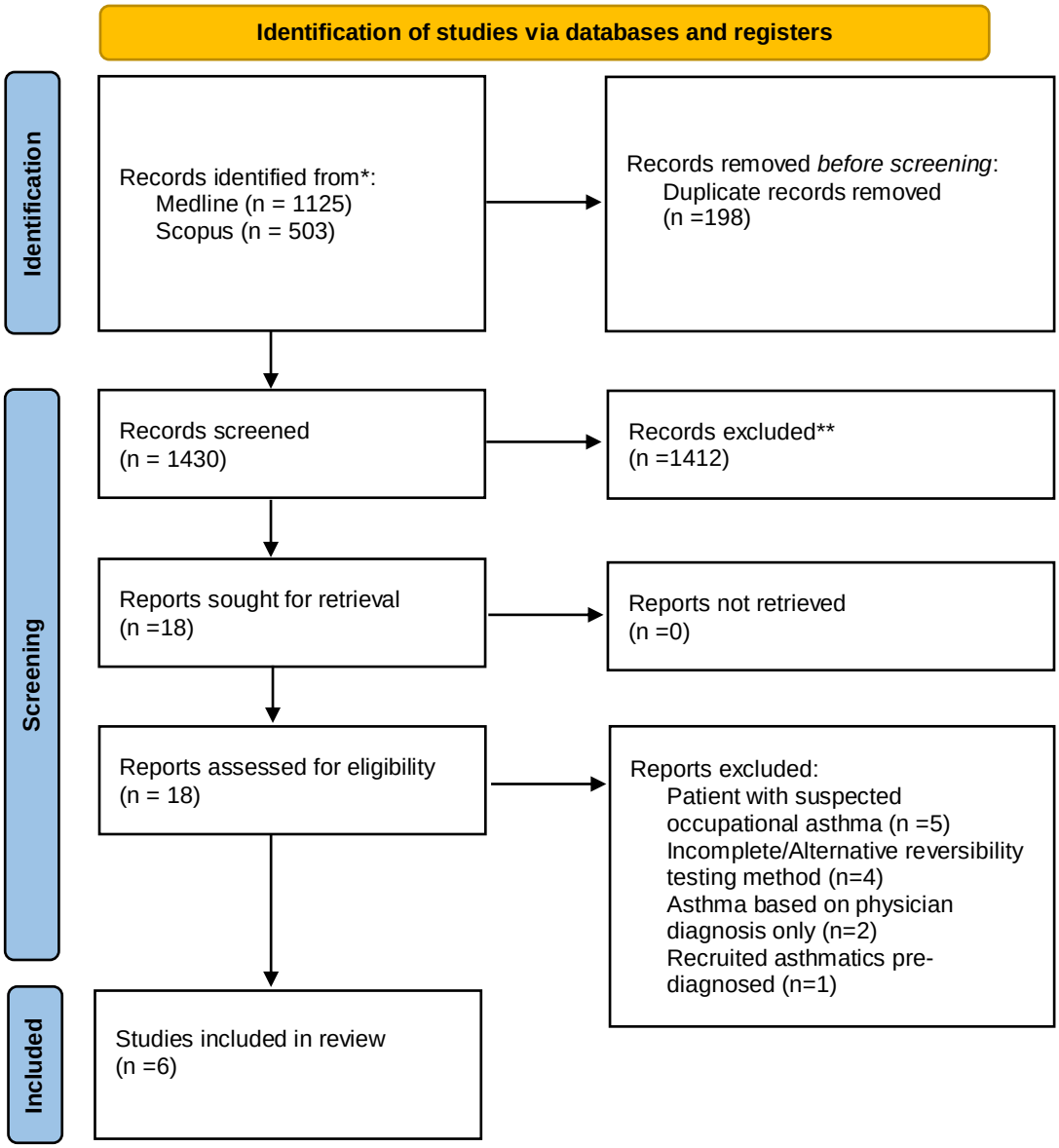
Although a large study, the only study that met the criteria was a single-centre secondary care assessment. Combining blood eosinophils, total serum IgE and FeNO does not seem to improve diagnostic accuracy as compared to performing one single test. Further studies are needed, particularly those in primary care.

Research priorities

Further good quality studies should be performed to assess the utility of the combination of blood eosinophils, IgE and FeNO for asthma diagnosis.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

Table 12a: Can bronchial challenge testing help diagnose asthma in adults with episodic/chronic suggestive symptoms?



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Online supplementary Table 12b

QUESTION

Can bronchial challenge testing help diagnose asthma in adults with episodic/chronic suggestive symptoms?	
POPULATION:	Population of adults (>18 yrs old) with diagnostic uncertainty of asthma
INDEX TEST:	Bronchial Challenge (Methacholine, Histamine, Mannitol)
GOLD STANDARD :	BDR Reversibility (>12% and 200 ml)

ASSESSMENT

Test accuracy

How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very inaccurate o Inaccurate X **Accurate** o Very accurate o Varies o Don't know	Bronchial challenge seems more accurate than BDR in diagnosing asthma Bronchial challenge testing has greater sensitivity between 0.63 (Porpodis study) to 0.96 (Yurdakul Study). BDR >12% varies from 0.1 (Ulrik study) to 0.61 (Goldstein)	BDR more likely to be positive in lower FEV1 (<90%) Sensitivity/Specificity much greater if high pre-test probability.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small o Moderate X **Large** o Varies	Making a correct diagnosis with a more sensitive and specific test is highly desirable.	

○ Don't know		

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small X **Trivial** ○ Varies ○ Don't know	No major undesirable effects of bronchial challenge testing. Mannitol is known to cause cough. Histamine can cause flushing, rashes. These are short lasting and reversible.	

Certainty of the evidence of test accuracy

What is the overall certainty of the evidence of test accuracy?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low X **Low** X **Moderate** ○ High ○ No included studies	For diagnosing asthma – moderate certainty For excluding asthma – low certainty, specificity is highly variable from 0.12-1	

Certainty of the evidence of management's effects

What is the overall certainty of the evidence of effects of the management that is guided by the test results?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate X **High** ○ No included studies	In the presence of a current symptoms, a positive bronchial challenge test will give a high confidence of initiating asthma management.	

Certainty of the evidence of test result/management

How certain is the link between test results and management decisions?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate X **High** ○ No included studies		

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison X **Probably favors the comparison** ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	No major undesirable effects of bronchial challenge testing. Mannitol is known to cause cough. Histamine can cause flushing, rashes.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs X **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Bronchial challenge testing requires more resources (staff, equipment, training, time) and cost of methacholine, histamine is greater. Mannitol kits are easier as they require no air source so can be performed in a low resource setting with a spirometry. Cost need to be balanced against the cost of a delayed or missed diagnosis, and inappropriate use of inhalers.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased X **Don't know**	None Identified	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no X **Probably yes** ○ Yes ○ Varies ○ Don't know	The tests are acceptable and safe. Patient's more likely to get a better indication whether or not they have asthma. Many patients taking long term ICS/LABA are often reluctant to withdraw from ICS/LABA – fearful of bronchoconstriction and cough (mannitol).	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no X **Probably yes** ○ Yes ○ Varies ○ Don't know	Hospitals: Increased cost for consumables, staff, training, time in physiology lab, space for equipment Patients: Need to ensure withdrawn off medication. Potentially takes longer time than BDR. Physiologist: Increased workload	

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The TF suggests bronchial challenge testing should be performed in secondary care to confirm asthma diagnosis in adults (Conditional recommendation for the intervention, low quality of evidence)

A provocative concentration of methacholine (PC20-M) or histamine (PC20-H) <8 mg/ml in steroid-naïve patients and <16 mg/ml in patient receiving regular inhaled corticosteroids supports a diagnosis of asthma

Indirect challenges such as mannitol or exercise may be considered in patients who remain negative with direct constricting agents

Justification

In making a conditional recommendation the TF balanced the desirable effects of making a diagnosis, against any undesirable effects, risks to patients and the resources required to implement and make bronchial challenge testing a feasible test. Although methacholine, histamine and mannitol are very safe, these tests require additional equipment, reagents, time in the laboratory, air

source, and trained staff, with access to resuscitation facilities and medical personnel in rare cases of severe bronchoconstriction. This will undoubtedly increase the costs in comparison to BdR testing. Mannitol challenge appeared slightly more specific than methacholine challenge, albeit one study.

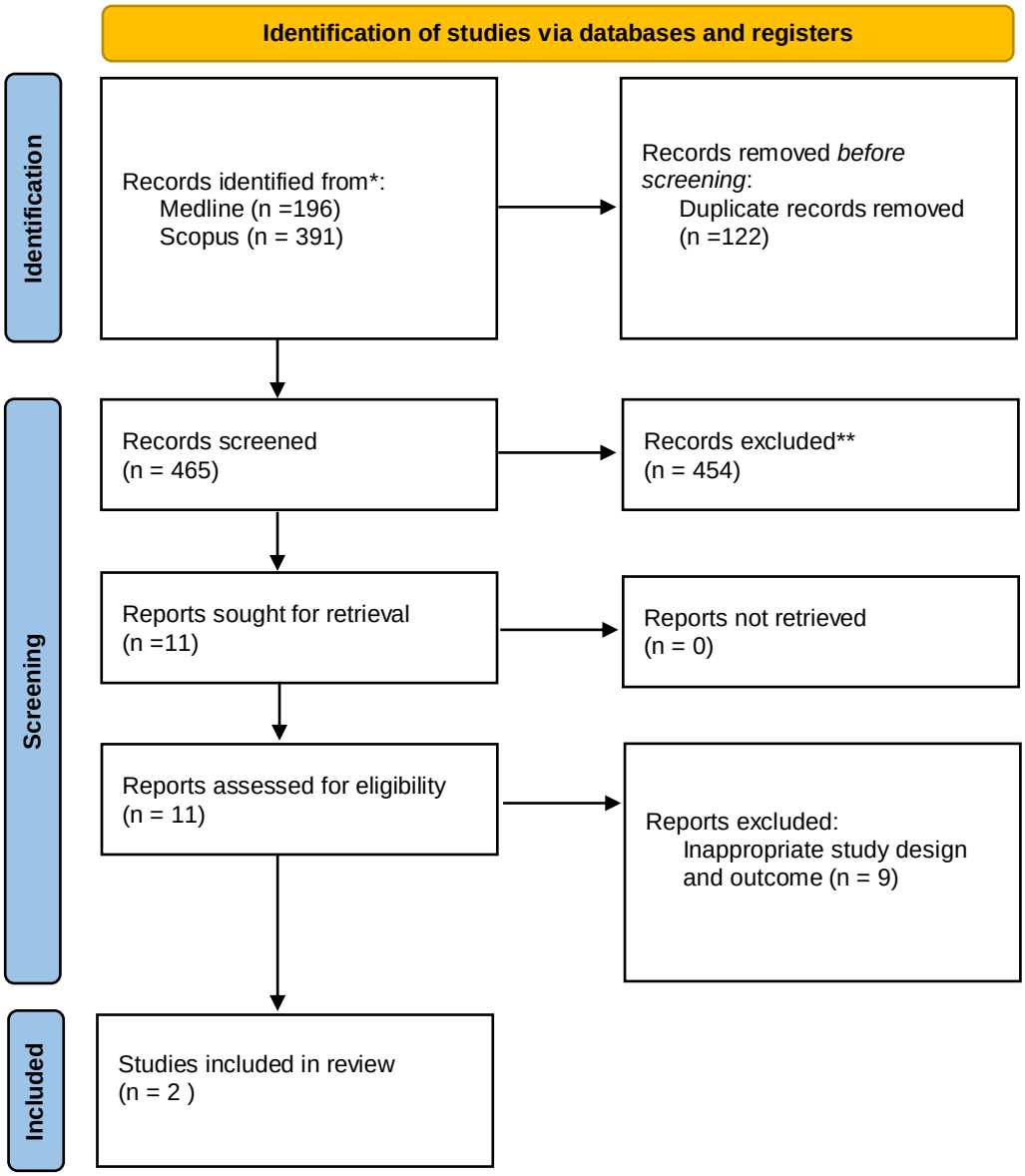
Table 13: Diagnostic performance of bronchodilator reversibility testing versus bronchial challenge to make a diagnosis of asthma

	N		Population	ICS treated	Asthma Diagnosis (%)	Cut-off	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Bronchodilator reversibility testing										
Goldstein Chest 2000	57	Referral from primary care to secondary care	Asthma symptoms	0%	48 (84%)	12% and 200 ml	6	100	16	100
Hunter Chest 2002	89	Secondary care	Asthma symptoms	46%	69 (77%)	2,9%	41	70	29	85
Yurdakul J Asthma 2005	100	Secondary care	Asthma symptoms	48%		15%	32	71	48	90
Ulrik J Asthma 2005	609	Population survey	Self reported asthma	?	74 (12%)	10%	9	93	88	16
Popordis J Asthma 2016	88	Secondary care	Asthma symptoms	0%	70 (79%)	12% and 200 ml	100	100	100	100
Louis JACI pract 2020	194	Secondary care	Asthma symptoms	0%	148 (76%)	12% and 200 ml	26	100	30%	100
Bronchial challenge										
Goldstein Chest 2000	57	Referral from primary care to secondary care	Asthma symptoms	0%	48 (84%)	PC20M < 8mg/ml	86	100	56	100
Hunter Chest 2002	89		Asthma symptoms	46%	69 (77%)	PC20M < 8 mg/ml	91	90	75	97
Yurdakul J Asthma 2005	100	Secondary care	Asthma symptoms	48%		PC20M < 8 mg/ml	97	78	93	87
Ulrik J Asthma 2005	609	Population survey	Self reported asthma	?	74 (12%)	PC20H < 16 mg/ml	93	94	99	69
Popordis J Asthma 2016	88	Secondary care	Asthma symptoms	0%	67 (76%)	PC20M < 16 mg/ml	63	86	36	94
	88	Secondary care	Asthma symptoms	0%	67 (76%)	PD15 Mannitol <635mg	64	95	45	98
Louis JACI pract 2020	194	Secondary care	Asthma symptoms	0%	148 (76%)	PC20 M < 8mg/ml	95	100	87	100

In two studies (Goldstein, Louis) asthma was diagnosed either by a significant bronchodilation or by positive bronchial challenge so that specificity was 100% for both tests. In Popordis study, asthma was diagnosed by symptoms + significant reversibility (12% and 200 ml) so that reversibility has 100% sensitivity and specificity

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

Table 14a: Can measuring of sGaw and RV/TLC help in the diagnosis of asthma with episodic/chronic suggestive symptoms?



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Online supplementary Table 14b

QUESTION

Can measuring of sGaw and RV/TLC help in the diagnosis of asthma with episodic/chronic suggestive symptoms?	
POPULATION:	Population of adults (>18 yrs old) with diagnostic uncertainty of asthma
INDEX TEST:	RV/TLC, sGaw
GOLD STANDARD :	1. Bronchodilation > 12% AND > 200 ml 2. Airway hyperresponsiveness: PC20 < 16 mg/ml (or 8 mg/ml) of Methacholine (or Histamine) or PD mannitol < 625 mg or Fall in FEV1 > 10% after exercis

ASSESSMENT

Test accuracy

How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate X Varies ○ Don't know	**RV/TLC** - Poor sensitivity ranging from 16.7% (Stanbrook et a, cut-offs 125%, 130% and 135%) to 54.5% in the paper of Bougard et al. - Good specificity ranging from 87% for Bougard et al (Threshold 99%) to 95.9% for Stanbrook et al. - Paper of Bougard et al: prediction of positive PC20: AUC: 0.74, p<0.0001) – the logistic regression analysis found that RV/TLC was significantly associated with positive PC20. **sGaw:** - Comparison with BD tests: Good specificity ranging from 74% (Topalovic et al, cut-off < 0.98) - Poor sensitivity: 50% (Topalovic et al) - Comparison with PC20M: highly variable sensitivity 86.4% - specificity 49.4% - Threshold <0.73 - Comparison with PC20M : Paper of Bougard: sGaw had intermediate AUC of 0.69 (p<0.0001) - prediction of positive PC20: AUC:0.69, p<0.0001.sGaw was not associated with PC20 In the logistic regression analysis.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small X Moderate o Large o Varies o Don't know	For RV/TLC: very good specificity but poor sensitivity. For sGaw: - good specificity for BD but poor specifitity for PC20 - poor sensitivity for BD, good sensitivity for PC20	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large o Moderate o Small X**Trivial** o Varies o Don't know	None	

Certainty of the evidence of test accuracy

What is the overall certainty of the evidence of test accuracy?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low **X** Low o Moderate o High o No included studies	Low quality of evidence for RV/TLC: few data in the literature. good specificity in the two studies detected in the literature. Low quality of evidence for sGaw– few data in the literature – poor accuracy.	

Certainty of the evidence of management's effects

What is the overall certainty of the evidence of effects of the management that is guided by the test results?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o High X No included studies		

Certainty of the evidence of test result/management

How certain is the link between test results and management decisions?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low X Low o Moderate o High o No included studies	Moderate quality of evidence for RV/TLC Low quality of evidence for sGaw	The TF panel made a judgement of low certainty about the likelihood that the appropriate asthma management will follow on from sGaw test results.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison X Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know	sGaw and RV/TLC are a test currently performed in patients with symptoms suggestive of asthma and **RV/TLC** can be used to approach asthma diagnosis (Bougard et al). When combined with FeNO, the prediction is even better to predict a positive PC20 according to Bougard et al. sGaw is not a good test for asthma diagnosis: poor specificity for PC20 and poor sensitivity for bronchodilation test.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs X Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	RV/TLC and sGaw measurement are feasible in secondary care (not available in primary care), requires lung function testing and a nurse to perform the test.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact X Probably increased ○ Increased ○ Varies ○ Don't know	None Identified	

Acceptability

Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know	RV/TLC and sGaw measurements are easy to perform. Requires measurment of lung volumes. Not accessible at home. Completion at the clinic.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes **X** Yes ○ Varies ○ Don't know	RV/TLC and sGaw requires a lung function cabin, not feasible in primary care. More comfortable to the patient than Bronchial Challenge.	

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

The TF suggests not measuring sGaw and RV/TLC by whole body plethysmography to help in the diagnosis of asthma (conditional recommendation against the intervention, low quality of evidence)

sGaw does not perform better than FEV_1/FVC ratio to predict positive methacholine challenge in patients with normal baseline FEV_1

RV/TLC >130% predicted has a high specificity (>90%) but poor sensitivity (25%) to predict a positive methacholine challenge in patient with normal FEV_1/FVC

Justification

The current evidence with RV/TLC is too limited to recommend using it to ascertain a diagnosis of asthma. The two studies suggest a high RV/TLC might be a useful physiological index to consider asthma diagnosis. Whole body plethysmography can provide sophisticated lung function measurements including the early physiological sign of hyperdistention as a consequence of small airway obstruction, not revealed by spirometry. Where RV/TLC may hold some promise, measuring sGaw does not bring additional value to the measurement FEV_1/FVC ratio by spirometry. Whole body plethysmography, however, requires technical expertise from laboratory personnel and the cost and relatively limited access even in specialist secondary care may preclude use of this test on a large scale.