



# European Respiratory Society clinical practice guidelines for the diagnosis of asthma in children aged 5–16 years

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**International ERS clinical practice guidelines recommend a combination of objective tests including spirometry, bronchodilator reversibility, fraction of exhaled nitric oxide and bronchial challenge testing to diagnose asthma in children aged 5–16 years** <https://bit.ly/32cRj5y>

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## Abstract

**Background** Diagnosing asthma in children represents an important clinical challenge. There is no single gold-standard test to confirm the diagnosis. Consequently, over- and under-diagnosis of asthma is frequent in children.

**Methods** A task force supported by the European Respiratory Society has developed these evidence-based clinical practice guidelines for the diagnosis of asthma in children aged 5–16 years using nine Population, Intervention, Comparator and Outcome (PICO) questions. The task force conducted systematic literature searches for all PICO questions and screened the outputs from these, including relevant full-text articles. All task force members approved the final decision for inclusion of research papers. The task force assessed the quality of the evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

**Results** The task force then developed a diagnostic algorithm based on the critical appraisal of the PICO questions, preferences expressed by lay members and test availability. Proposed cut-offs were determined based on the best available evidence. The task force formulated recommendations using the GRADE Evidence to Decision framework.

**Conclusion** Based on the critical appraisal of the evidence and the Evidence to Decision framework, the task force recommends spirometry, bronchodilator reversibility testing and exhaled nitric oxide fraction as first-line diagnostic tests in children under investigation for asthma. The task force recommends against

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diagnosing asthma in children based on clinical history alone or following a single abnormal objective test. Finally, this guideline also proposes a set of research priorities to improve asthma diagnosis in children in the future.

### Introduction

Asthma is the commonest chronic respiratory condition affecting ~5.5 million children in the European Union [1]. In many European healthcare settings, the diagnosis is based on clinical history and examination without further tests.

Several recent reports from Europe and North America have highlighted a high rate of asthma misdiagnosis, including over- and under-diagnosis [2–10].

Misdiagnosis in children often arises because respiratory symptoms are common in this age group. These are frequently nonspecific [11] and often represent episodes of viral respiratory tract infections [12, 13]. Some of these can be prolonged with clinical symptoms similar to asthma. Getting the correct diagnosis in children matters because over-diagnosis frequently results in over-treatment with corticosteroids [6, 14] with implications for healthcare costs [15], the risk of unnecessary side-effects and, in some cases, delay in establishing an important alternative diagnosis. Under-diagnosis with under-treatment of asthma results in unnecessary morbidity, poor quality of life and increased mortality in low-resource settings [16, 17].

Many asthma guidelines [18–20] recommend the use of objective tests to confirm the diagnosis in symptomatic patients. Spirometry, bronchodilator reversibility (BDR) testing and measurements of peak flow variability are recommended in some form by all the guidelines. UK National Institute for Health and Care Excellence (NICE) asthma guidelines also recommend the use of exhaled nitric oxide fraction ( $F_{ENO}$ ) [20]. Recommendations on the hierarchy and timing of objective tests varies considerably between guidelines. This has resulted in variation of diagnostic tests used across Europe and across different healthcare settings within individual countries.

Importantly, to date there are no child-focused evidence-based asthma diagnostic guidelines. The usual approach is to produce joint adult and paediatric asthma guidelines, and this often results in extrapolation from adult data where there is a lack of evidence in children. However, tests employed in adults under investigation for asthma may not be appropriate in children and the best cut-offs for many of the tests may not be the same in children and adults. This makes child-focused guidelines for the diagnosis of asthma essential.

The aim of this task force was to systematically review the evidence that supports the use of tests commonly used across Europe to diagnose asthma in children and to propose evidence-based clinical practice recommendations for the diagnosis of asthma in children aged 5–16 years.

### Methods

The methods are described in detail in the supplementary material.

#### *Task force composition*

The panel consisted of a multidisciplinary group including paediatricians, primary care physicians, researchers, patients and patient representatives. All members of the task force have either recognised clinical experience in the diagnosis of asthma practicing in various regions of Europe or personal experience with asthma as patients or are caregivers of children with asthma. Junior members and trainees affiliated with European paediatric asthma centres were active members of the committee (supplementary table S1).

Methodologists from the European Respiratory Society (ERS) provided expertise in guideline development following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for diagnostic tests [21]. Panel members disclosed potential conflicts of interest according to ERS policies at the start of the task force and prior to publication of this article.

Patient and parent representatives recruited to the task force through the European Lung Foundation (ELF) were involved from the beginning. They commented on the selection and scope of the Population, Intervention, Comparator and Outcome (PICO) questions, attended meetings, commented on the hierarchy of tests, contributed to the discussions relating to the Evidence to Decision for each PICO question and approved the final diagnostic algorithm. All the recommended tests to support asthma diagnosis were acceptable to patients and carers.

The task force was organised into four core centres (Leicester, Zurich, Bern and Aberdeen), each with PICO leads and junior members. The core centres divided the PICO questions between themselves. The other members of the task force each aligned themselves to two or three PICO questions so that each PICO was supported by a task force subgroup consisting of a core centre and additional task force members. The numbers in each PICO task force subgroup were evenly distributed. Junior members performed the initial screening of the outputs from the systematic literature reviews, coordinated the final selection of research papers and performed the initial quality of evidence assessment for each selected research paper. The other PICO subgroup members supported the PICO groups and were involved in selecting and approving the included research papers and reviewing the quality of the evidence. The whole task force was involved in all the key decisions such as selection of PICO questions, agreed recommendations for each PICO question, and the drafting and agreement on the diagnostic algorithm.

#### Formulation of the review questions

Review questions were formulated using the PICO format. The chairs initially proposed eight PICO questions based on common clinical practice in Europe. Early on during the task force, members discussed each PICO question to evaluate whether it should be included. The PICO questions were discussed during several rounds of telephone conferences and email discussions. Nine PICO questions were finally agreed at the first face-to-face task force meeting in 2018 (table 1).

#### Systematic literature review

For each PICO question, a systematic literature review was carried out and eligible papers had to include the diagnostic test in question plus at least one other objective test. For each question, the outcomes were diagnostic accuracy, sensitivity and specificity.

Librarians experienced with systematic reviews based at University Hospitals Leicester (UK) performed the systematic literature searches for all PICO questions covering the period from 1 January 1980 to 31 August 2019. They searched the MEDLINE (via OVID), Cochrane and Embase databases. Supplementary searches were undertaken by checking the references of included papers and by asking task force members if they were aware of additional papers not identified by the searches. The full details of all the searches are provided in the supplementary material.

**TABLE 1** The Population, Intervention, Comparator and Outcome (PICO) questions that this task force sought to answer with their respective comparator or reference standard

	Comparator/reference standard
PICO 1. In children aged 5–16 years under investigation for asthma, should the presence of the symptoms wheeze, cough and breathing difficulty be used to diagnose asthma?	Doctor diagnosis of asthma and one of the following: obstructive spirometry, BDR, challenge testing, $F_{eNO}$ , 2-week PEFR variability
PICO 2. In children aged 5–16 years under investigation for asthma, should an improvement in symptoms following a trial of preventer medication be used to diagnose asthma?	Doctor diagnosis of asthma and one of the following: obstructive spirometry, BDR, challenge testing, $F_{eNO}$ , 2-week PEFR variability
PICO 3. In children aged 5–16 years under investigation for asthma, should spirometry testing be used to diagnose asthma?	Doctor diagnosis of asthma and one of the following: challenge testing, BDR, $F_{eNO}$ , 2-week PEFR variability
PICO 4. In children aged 5–16 years under investigation for asthma, should BDR testing be used to diagnose asthma?	Doctor diagnosis of asthma and one of the following: challenge testing, $F_{eNO}$ , 2-week PEFR variability
PICO 5. In children aged 5–16 years under investigation for asthma, should $F_{eNO}$ testing be used to diagnose asthma?	Doctor diagnosis of asthma and one of the following: obstructive spirometry, BDR, challenge testing, 2-week PEFR variability
PICO 6. In children aged 5–16 years under investigation for asthma, should PEFR variability be used to diagnose asthma?	Doctor diagnosis of asthma and one of the following: obstructive spirometry, BDR, challenge testing, $F_{eNO}$
PICO 7. In children aged 5–16 years under investigation for asthma, should allergy testing be used to diagnose asthma?#	Doctor diagnosis of asthma and one of the following: obstructive spirometry, BDR, challenge testing, $F_{eNO}$ , 2-week PEFR variability
PICO 8. In children aged 5–16 years under investigation for asthma, should direct bronchial challenge testing including methacholine and histamine be used to diagnose asthma?	Doctor diagnosis of asthma and one of the following: obstructive spirometry, BDR, $F_{eNO}$ , 2-week PEFR variability
PICO 9. In children aged 5–16 years under investigation for asthma, should indirect bronchial challenge testing including exercise and mannitol be used to diagnose asthma?	Doctor diagnosis of asthma and one of the following: obstructive spirometry, BDR, $F_{eNO}$ , 2-week PEFR variability

BDR: bronchodilator reversibility;  $F_{eNO}$ : exhaled nitric oxide fraction; PEFR: peak expiratory flow rate. #: food allergens were not included.

### **Screening of search results**

At least two task force members from each core group reviewed all the titles and abstracts identified by each of the literature searches. They agreed on the inclusion of full-text manuscripts. The screening results were shared with the task force PICO group for comments. The whole task force discussed and agreed the final selection of studies included for each PICO question during a face-to-face meeting. Research papers were only included if all the task force members agreed that they fulfilled the *a priori* inclusion criteria. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagrams showing the search process for each PICO question are available in supplementary figure S1. Tables listing all the full-text articles, which were screened, are shown in the supplementary material.

### **Study designs**

In clinical practice, caregivers bring children with respiratory symptoms to the doctor. These symptoms may be compatible with a diagnosis of asthma. Confirming or refuting the diagnosis represents a clinical challenge due to the absence of a gold-standard test. Therefore, we only included studies that replicated this clinical scenario and included studies that had followed consecutive patients with relevant respiratory symptoms referred for asthma diagnosis. The diagnosis was then either confirmed or excluded using objective tests. This approach also allowed us to calculate the sensitivity and specificity of the index test. We excluded case-control studies for this reason. We included cohort studies.

### **Reference standard**

In the absence of a universally accepted reference standard for the diagnosis of asthma, the task force agreed to accept a “doctor diagnosis of asthma” supported by at least one abnormal comparator test as the standard with which to compare the index test of interest for each PICO. This standard was chosen for the following reasons: a diagnosis made by a doctor following a careful medical history and clinical examination is an important criterion for a diagnosis of asthma. However, studies have shown that a diagnosis of asthma based on this approach results in considerable rates of misdiagnosis in children [3]. Therefore, a doctor diagnosis had to be supported by at least one abnormal objective test. The task force agreed on the following comparator tests: spirometry, BDR,  $F_{eNO}$ , 2-week peak expiratory flow rate (PEFR) variability test, direct and indirect bronchial challenge tests.

The task force agreed not to include “trial of treatment” and “allergy testing” as comparator tests, but to evaluate the usefulness of a trial of treatment and allergy testing to diagnose asthma in children as separate PICO questions instead.

We have addressed important aspects relating to asthma diagnosis, such as hierarchy and timing of objective tests, cut-off points of objective tests and confounders. Because we did not formally assess the evidence for these aspects, we present the results based on the Delphi process and discussions using the Evidence to Decision tables without making formal recommendations.

### **Quality of evidence and strength of recommendations**

We used the GRADE approach through the entire process, from grading the quality of the evidence, to determining the strength of the recommendations. GRADE represents a rigorous methodology to evaluate the quality of evidence and is considered the gold standard for grading the strength of evidence-based recommendations in healthcare due to its structured approach and transparency. In keeping with the GRADE approach, we formulated from the outset clear clinical PICO questions. Task force members assessed the quality of the evidence by evaluating risk of bias, indirectness, inconsistency, imprecision and other factors [22–26].

The task force based recommendations for the asthma diagnostic algorithm on the strength of the evidence, test availability and factors such as sensitivity and specificity of the index test. Using the Evidence to Decision framework [27], the task force considered additional factors such as test availability, feasibility and patient and caregiver acceptability and access to specialist tests. The GRADE and Evidence to Decision tables for all the PICO questions are shown in the supplementary material.

### **Patient- and caregiver-important perspectives**

The GRADE approach emphasises the importance of recommendations based on the impact on patient-important outcomes [25]. The patient representatives of the task force fully endorsed that an accurate diagnosis was an important outcome, because it leads to a better recognition of their child’s problems by physicians. Patient representatives stated that this would lead to treatment that is more effective, would reduce overtreatment in some children and generally improve health and quality of life. However, diagnostic accuracy studies do not provide direct evidence for the improvement of

patient-important outcomes; consequently, the confidence in results of test accuracy studies can be judged, at best, as moderate.

#### *Development of recommendations and the diagnostic algorithm*

The task force used the Evidence to Decision framework [27] as well as an informal consensus development method [28] to agree each recommendation and to build the diagnostic algorithm. This involved a face-to-face meeting where the whole task force discussed and agreed the recommendations and the tests recommended to support a diagnosis of asthma in children, based on the literature searches, the “GRADEing” of the evidence and the Evidence to Decision framework.

Once the provisional recommendations and the building blocks of the diagnostic algorithm were agreed, the task force used free discussion to reach consensus and agree a provisional hierarchy of tests and a prototype diagnostic algorithm.

In order to obtain the most reliable consensus of opinion of our expert group we employed a modified Delphi process using repeated iterative online voting [29]. All the recommendation statements and all the steps of the diagnostic algorithm that had been developed and discussed at the face-to-face meeting were listed in an online questionnaire and circulated to the whole task force. In each round, panel members were asked to mark “agree” or “disagree” beside each statement, and provide comments. Recommendation statements and the diagnostic algorithm were modified after each round. The whole task force finally approved the final version after three rounds of online voting. Responses were not anonymous and the task force defined consensus *a priori* as agreement by  $\geq 75\%$  of the participants.

### **Results**

#### *Results of literature reviews and task force recommendations*

Several definitions for asthma exist [18, 30, 31]. The task force agreed on the following definition of asthma. “Asthma is a disease that includes the symptoms of wheeze, cough and breathing difficulty together with reversible airways obstruction, airway inflammation and bronchial hyperresponsiveness. However, asthma is a heterogeneous and variable condition and frequently not all of the above are present in each individual patient at the same time.”

The task force emphasises that the words to describe asthma symptoms vary considerably depending on language, culture, education and age of the patient. In addition, young children may describe pain in the abdomen due to difficulty pinpointing the lungs. The results of the evidence assessment gave rise to the recommendations listed in table 2.

#### *Results of the literature reviews and task force recommendations for PICO 1–9*

*PICO 1. In children aged 5–16 years under investigation for asthma, should the presence of the symptoms wheeze, cough and breathing difficulty be used to diagnose asthma?*

##### **Recommendation**

- The task force recommends against diagnosing asthma based on symptoms alone (strong recommendation against the intervention, moderate quality of evidence).

##### **Remarks**

- Recurrent wheeze, cough and breathing difficulty are key symptoms of asthma. The task force considers a history of recurrent reported wheeze or wheeze on auscultation as the most important symptom of asthma.
- Children with chronic cough (*i.e.* cough for >4 weeks) as the only symptom are unlikely to have asthma and should be investigated according to the ERS guidelines for chronic cough in children [32], and a referral for further investigations to exclude differential diagnoses should be considered.

##### **Background**

Asthma symptoms vary over time and may respond to bronchodilator treatment. Wheeze is a key feature of asthma, but the term is poorly understood by clinicians and patients [33]. Wheeze is a soft polyphonic noise or whistling sound heard mainly during expiration and is caused by turbulent airflow occurring simultaneously in many airways of different calibre. Parents often describe stridor and rattles as wheeze. Moreover, the word wheeze does not have an equivalent in many languages [34]. Other symptoms that caregivers often report are cough and breathing difficulty with or without exercise. Most asthma definitions include the presence of respiratory symptoms such as wheeze, cough, breathing difficulty and others.

**TABLE 2** Evidence-based recommendations for the use of each of the tests considered for asthma diagnosis in children aged 5–16 years in primary, secondary or tertiary care

	Recommendation	Remarks
<b>PICO 1.</b> In children aged 5–16 years under investigation for asthma, should the presence of the symptoms wheeze, cough and breathing difficulty be used to diagnose asthma?	<ul style="list-style-type: none"> <li>The task force recommends against diagnosing asthma based on symptoms alone (strong recommendation against the intervention, moderate quality of evidence)</li> </ul>	<ul style="list-style-type: none"> <li>Recurrent wheeze, cough and breathing difficulty are key symptoms of asthma. The task force considers a history of recurrent reported wheeze or wheeze on auscultation as the most important symptom of asthma</li> <li>Children with chronic cough (<i>i.e.</i> cough for &gt;4 weeks) as the only symptom are unlikely to have asthma and should be investigated according to the ERS guidelines for chronic cough in children [32] and a referral for further investigations to exclude differential diagnoses should be considered</li> </ul>
<b>PICO 2.</b> In children aged 5–16 years under investigation for asthma, should an improvement in symptoms following a trial of preventer medication be used to diagnose asthma?	<ul style="list-style-type: none"> <li>The task force recommends against using an improvement in symptoms after a trial of preventer medication alone to diagnose asthma (conditional recommendation against the intervention, based on clinical experience)</li> </ul>	<ul style="list-style-type: none"> <li>The task force did not find any evidence for or against a trial of preventer medication to diagnose asthma in children aged 5–16 years</li> <li>Despite the lack of evidence, based on clinical experience, the task force members agreed that a trial of preventer medication can be considered; but only in symptomatic children with abnormal spirometry and negative bronchodilator response. In such cases, the objective tests spirometry and, if indicated, BDR should be repeated after 4–8 weeks</li> </ul>
<b>PICO 3.</b> In children aged 5–16 years under investigation for asthma, should spirometry testing be used to diagnose asthma?	<ul style="list-style-type: none"> <li>The task force recommends spirometry as part of the diagnostic work-up of children aged 5–16 years with suspected asthma (strong recommendation for the intervention, moderate quality of evidence)</li> </ul>	<ul style="list-style-type: none"> <li>An FEV<sub>1</sub>/FVC &lt;LLN or &lt;80%, or an FEV<sub>1</sub> &lt;LLN or &lt;80% pred should be considered supportive of an asthma diagnosis. It is important to be aware that not all children are able to perform a sufficient FVC manoeuvre, resulting in a false normal FEV<sub>1</sub>/FVC ratio</li> <li>A normal spirometry result does not exclude asthma</li> </ul>
<b>PICO 4.</b> In children aged 5–16 years under investigation for asthma, should BDR testing be used to diagnose asthma?	<ul style="list-style-type: none"> <li>The task force recommends BDR testing in all children with FEV<sub>1</sub> &lt;LLN or &lt;80% pred and/or FEV<sub>1</sub>/FVC &lt;LLN or &lt;80% (strong recommendation for the intervention, based on clinical experience)</li> </ul>	<ul style="list-style-type: none"> <li>Consider an increase in FEV<sub>1</sub> ≥12% and/or ≥200 mL following inhalation of 400 µg SABA as diagnostic of asthma</li> <li>BDR &lt;12% does not exclude asthma</li> <li>Most task force members consider BDR testing when baseline spirometry is normal if the clinical history is strongly suggestive of asthma</li> </ul>
<b>PICO 5.</b> In children aged 5–16 years under investigation for asthma, should F <sub>eNO</sub> testing be used to diagnose asthma?	<ul style="list-style-type: none"> <li>The task force recommends measurement of F<sub>eNO</sub> as part of the diagnostic work-up of children aged 5–16 years with suspected asthma (strong recommendation for the intervention, moderate quality of evidence)</li> </ul>	<ul style="list-style-type: none"> <li>A F<sub>eNO</sub> value ≥25 ppb in a child with asthma symptoms should be considered as supportive of a diagnosis of asthma</li> <li>A F<sub>eNO</sub> value &lt;25 ppb does not exclude asthma</li> </ul>
<b>PICO 6.</b> In children aged 5–16 years under investigation for asthma, should PEFr variability be used to diagnose asthma?	<ul style="list-style-type: none"> <li>The task force recommends against PEFr variability testing as the primary objective test on its own to diagnose asthma in children aged 5–16 years (conditional recommendation against the intervention, moderate quality of evidence)</li> </ul>	<ul style="list-style-type: none"> <li>Other objective tests are preferred, but a PEFr variability test can be considered in healthcare settings lacking other objective tests</li> <li>If a PEFr variability test is used the result should be based on 2 weeks of measurements, ideally using electronic peak flow meters</li> <li>A cut-off of ≥12% in PEFr variability should be considered a positive test</li> <li>A PEFr variability of &lt;12% does not exclude asthma</li> </ul>
<b>PICO 7.</b> In children aged 5–16 years under investigation for asthma, should allergy testing be used to diagnose asthma?	<ul style="list-style-type: none"> <li>The task force recommends against the use skin-prick tests to aeroallergens as diagnostic tests for asthma (strong recommendation against the intervention, moderate quality of evidence)</li> <li>The task force recommends against the use of serum total and specific IgE tests as diagnostic tests for asthma (strong recommendation against the intervention, moderate quality of evidence)</li> </ul>	

Continued

TABLE 2 Continued

	Recommendation	Remarks
<b>PICO 8. In children aged 5–16 years under investigation for asthma, should direct bronchial challenge testing including methacholine and histamine be used to diagnose asthma?</b>	<ul style="list-style-type: none"> <li>The task force recommends a direct bronchial challenge test using methacholine in children aged 5–16 years under investigation for asthma where asthma diagnosis could not be confirmed with first-line objective tests (conditional recommendation for the intervention, low quality of evidence)</li> </ul>	<ul style="list-style-type: none"> <li>A PC<sub>20</sub> value of <math>\leq 8</math> mg·mL<sup>-1</sup> should be considered as a positive test</li> <li>The task force found no evidence for or against performing histamine challenge tests in children under investigation for asthma</li> </ul>
<b>PICO 9. In children aged 5–16 years under investigation for asthma, should indirect bronchial challenge testing including exercise and mannitol be used to diagnose asthma?</b>	<ul style="list-style-type: none"> <li>The task force recommends an indirect bronchial challenge test using a treadmill or a bicycle in children aged 5–16 years under investigation for asthma with exercise related symptoms where asthma diagnosis could not be confirmed with first line objective tests (conditional recommendation for the intervention, moderate quality of evidence)</li> </ul>	<ul style="list-style-type: none"> <li>A fall in FEV<sub>1</sub> of &gt;10% from baseline should be taken as a positive test</li> <li>A mannitol challenge can be considered as an alternative to exercise challenge. However, due to its limited availability in most countries, and the fact that children often find the test unpleasant, mannitol challenge should be best avoided in favour of other challenge tests</li> </ul>

PICO: Population, Intervention, Comparator and Outcome; BDR: bronchodilator reversibility; F<sub>eNO</sub>: exhaled nitric oxide fraction; PEFr: peak expiratory flow rate; ERS: European Respiratory Society; FEV<sub>1</sub>: forced expiratory volume in 1 s; FVC: forced vital capacity; LLN: lower limit of normal; SABA: short-acting  $\beta_2$ -agonist; PC<sub>20</sub>: provocative concentration of methacholine that results in a 20% drop in FEV<sub>1</sub>.

#### Review of evidence directly addressing PICO 1

We included four observational published studies (from Switzerland, Inner Mongolia, the Netherlands and Brazil) that fulfilled the inclusion criteria (supplementary table S2). All four reported the relationship between reported wheeze and subsequent asthma diagnosis (table 3) [35–38]. Wheeze, cough and breathing difficulty was by parental/caregiver report in all four studies. Any prior inhaled corticosteroids (ICS) treatment was withheld for 3 days before lung function testing in one study [35],  $\geq 1$  month in a second study [36] and not mentioned in the remaining two. Overall, the sensitivity of wheeze to correctly identify a child with asthma ranged between 0.55 and 0.86 and the specificity between 0.64 and 0.90 (supplementary tables S3 and S5). Cough and breathing difficulty were much less specific for asthma, ranging from very low to low depending on the study. Results for breathing difficulty were variable and this symptom generally was very nonspecific.

#### Justification of the recommendation

Overall, the sensitivity of wheeze to correctly identify a child with asthma ranged between 0.55 and 0.86 and the specificity between 0.64 and 0.90. Using the presence of the symptoms wheeze, cough and breathing difficulty alone results in misdiagnosis in a considerable number of children. The task force agreed that sensitivity and specificity of wheeze was not strong enough to confirm a diagnosis of asthma on its own.

Cough and breathing difficulty are nonspecific symptoms and should not be used to diagnose asthma (supplementary tables S4 and S5).

#### Key unanswered questions and future research needs

Further studies are needed that combine symptoms with other predictors of asthma, such as the presence of other atopic features, family history, *etc.*, to test whether this increases the sensitivity and/or specificity of symptoms to diagnose asthma. In addition, further studies are needed investigating the diagnostic accuracy of wheeze heard by a medical doctor and video recordings of wheezing children made by parents or carers.

#### *PICO 2. In children aged 5–16 years under investigation for asthma, should an improvement in symptoms following a trial of preventer medication be used to diagnose asthma?*

##### Recommendation

- The task force recommends against using an improvement in symptoms after a trial of preventer medication alone to diagnose asthma (conditional recommendation against the intervention, based on clinical experience).

**TABLE 3** Summary of the key recommendations for the diagnosis of asthma in children from three frequently cited current asthma guidelines

Diagnostic recommendations for children	
GINA 2020 strategy document [18]	Recommends spirometry and BDR testing or 2 weeks of twice-daily PEFR variability measurements to investigate for asthma.
BTS/SIGN asthma guideline 2019 [19]	States that asthma is a clinical diagnosis. Lung function tests influence the probability of an asthma diagnosis, and BTS/SIGN recommend comparing the results of lung function tests undertaken while a patient is asymptomatic with those undertaken when the patient is symptomatic to detect variation over time to aid diagnosis.
UK NICE guideline 2017 [20]	The guideline stipulates that two positive objective tests are required in children aged 5–16 years to confirm the diagnosis of asthma. Spirometry (and BDR if spirometry is obstructed) and $F_{eNO}$ are recommended as first-line tests.

GINA: The Global Initiative for Asthma; BTS: British Thoracic Society; SIGN: Scottish Intercollegiate Guidelines Network; NICE: National Institute for Health and Care Excellence; BDR: bronchodilator reversibility; PEFR: peak expiratory flow rate;  $F_{eNO}$ : exhaled nitric oxide fraction.

#### Remarks

- The task force did not find any evidence for or against a trial of preventer medication to diagnose asthma in children aged 5–16 years.
- Despite the lack of evidence, based on clinical experience, the task force members agreed that a trial of preventer medication can be considered, but only in symptomatic children with abnormal spirometry and negative bronchodilator response. In such cases, the objective tests spirometry and, if indicated, BDR testing should be repeated after 4–8 weeks.

#### Background

A trial of preventer medication with ICS, either alone or in combination with a long-acting  $\beta_2$ -agonist (LABA), or leukotriene receptor antagonist (LTRA) is widely used by clinical practitioners to evaluate the response in children with suspected asthma. The treatment trial consists of starting ICS or LTRA treatment empirically in a child presenting with symptoms of asthma, without performing additional objective tests. The child is reviewed after a period of 4–8 weeks and the diagnosis of asthma is then often made based on symptom improvement alone at clinical review.

#### Review of evidence directly addressing PICO 2

We found no study where children with asthma symptoms but no confirmed diagnosis received a trial of treatment and investigation with at least one objective test. Most studies did not meet the inclusion criteria because they investigated the effectiveness of the trial medication in children already diagnosed with asthma.

#### Justification of the recommendation

Despite the lack of evidence to support a recommendation, the task force members are well aware that a trial of preventer medication is widely employed by clinicians to evaluate the response in children with symptoms of asthma. The main reason for this is remaining diagnostic uncertainty and because spirometry and  $F_{eNO}$  confirm asthma only in a minority of children seen during routine clinical reviews in children [39–41]. The task force discussed and agreed that a trial of treatment with ICS can be considered, but only in steroid-naïve or -nonadherent children with asthma symptoms in whom initial tests have not been able to confirm the diagnosis. Objective tests should be repeated after 4–8 weeks [18, 42–44].

The difference in our diagnostic approach is that the task force does not recommend diagnosis of asthma on the basis of improvements in reported symptoms alone following the treatment trial, but to base the diagnosis on a significant improvement in lung function and symptoms after completion of the trial of treatment. This recommendation is supported by the Global Initiative for Asthma (GINA) 2020 strategy document [18]. Additionally, GINA proposes a supervised stepping down of preventer medication in conjunction with lung function tests to confirm or refute the presence of (active) asthma (supplementary table S6).

#### Key unanswered questions and future research needs

There is a need for validation studies investigating the diagnostic accuracy and limitations of preventer medication treatment trials in preventer-naïve school-aged children. Studies need to assess the type, dosage



and the length of the treatment trial period, taking into account factors such as proper inhaler technique, adherence to medication and the season during which the trial is conducted.

*PICO 3. In children aged 5–16 years under investigation for asthma, should spirometry testing be used to diagnose asthma?*

#### Recommendation

- The task force recommends to perform spirometry as part of the diagnostic work-up of children aged 5–16 years with suspected asthma (strong recommendation for the intervention, moderate quality of evidence).

#### Remarks

- A forced expiratory volume in 1 s (FEV<sub>1</sub>)/forced vital capacity (FVC) below the lower limit of normal (LLN) or <80%, or an FEV<sub>1</sub> <LLN or <80% predicted should be considered supportive of an asthma diagnosis. It is important to be aware that not all children are able to perform a sufficient FVC manoeuvre, resulting in a false normal FEV<sub>1</sub>/FVC ratio.
- A normal spirometry result does not exclude asthma.

#### Background

Spirometry is a noninvasive physiological test, which measures the volume and flow rate of air during inhalation and exhalation. The most commonly reported parameters are FEV<sub>1</sub> and FVC and the ratio of FEV<sub>1</sub> to FVC. The FEV<sub>1</sub> represents the volume of air (L) expired in the first second and the FVC (L) is the total volume of air expired from the start of the manoeuvre to the end. A reduced FEV<sub>1</sub>/FVC ratio indicates airway obstruction.

A standardised procedure for performing spirometry has been published jointly by the ERS and the American Thoracic Society (ATS) [45].

The task force strongly recommends the use of LLN to define abnormal spirometry, but the panel agreed to accept a fixed cut-off for FEV<sub>1</sub>/FVC and FEV<sub>1</sub> <80% pred where LLN is not available, because this cut-off reasonably closely approximates LLN. In a large recent UK study using a fixed cut-off of 80% for FEV<sub>1</sub>/FVC and FEV<sub>1</sub> % pred, airflow obstruction was falsely identified in 6.4% of children aged 5–16 years [41] compared to using LLN.

#### Review of evidence directly addressing PICO 3

Our search strategy was designed to identify studies addressing the diagnostic accuracy of spirometry using the LLN or a fixed cut-off for FEV<sub>1</sub> and/or FEV<sub>1</sub>/FVC to diagnose asthma in children aged 5–16 years. Three studies fulfilled the inclusion criteria (supplementary table S7) [35, 46, 47]. All were observational, cross-sectional studies comparing the diagnostic accuracy of spirometry in school-aged children against a second objective test.

Studies using a fixed cut-off for FEV<sub>1</sub> of <80% pred or FEV<sub>1</sub>/FVC <80% to diagnose asthma in children showed low sensitivity (0.12–0.52) and moderate to high specificity (0.72–0.93) [35, 46, 47] (supplementary tables S8 and S9). Only one study utilised Global Lung Function Initiative (GLI) reference equations to determine predicted values [35]. This study reported the diagnostic accuracy of FEV<sub>1</sub> z-score ≤0.8 with a sensitivity of 0.44 and specificity of 0.77.

#### Justification of recommendation

Good-quality spirometry can detect airway obstruction, the hallmark of asthma. Obstructed spirometry with positive BDR confirms the diagnosis. Spirometry testing is fairly quick and noninvasive and an experienced operator can obtain good quality data from the majority of children aged ≥5 years [41, 48]. The equipment is portable and the test is widely available; however, availability in primary care is variable. It is important to emphasise that spirometry as a one-off measurement has a low sensitivity and is therefore poor at ruling out asthma. Because of the variable nature of the condition, when the asthma is controlled, spirometry is frequently normal [40, 41]. Serial measurements may be required to confirm the diagnosis [19]. Abnormal spirometry has good specificity for asthma (supplementary table S9).

#### Key unanswered questions and future research needs

There is an urgent need for studies in children assessing the ideal timing and the frequency of spirometry measurements to improve the sensitivity of the test.

*PICO 4. In children aged 5–16 years under investigation for asthma, should BDR testing be used to diagnose asthma?*

#### Recommendation

- The task force recommends BDR testing in all children with  $FEV_1 < LLN$  or  $< 80\%$  pred and/or  $FEV_1/FVC < LLN$  or  $< 80\%$  (strong recommendation for the intervention, based on clinical experience).

#### Remarks

- Consider an increase in  $FEV_1 \geq 12\%$  and/or  $\geq 200$  mL following inhalation of 400  $\mu$ g of a short-acting  $\beta_2$ -agonist as diagnostic of asthma.
- BDR  $< 12\%$  does not exclude asthma.
- Most task force members consider BDR testing when baseline spirometry is normal if the clinical history is strongly suggestive of asthma.

#### Background

The BDR test measures changes in lung function following inhalation of a short-acting bronchodilator. BDR is a test of bronchial lability, the hallmark of asthma. ERS/ATS test procedures and interpretation of results have been published [45, 49].

#### Review of evidence directly addressing PICO 4

We found no studies directly addressing the diagnostic accuracy of BDR testing in school-aged children using a second objective test, which were the inclusion criteria. However, variable airflow limitation is the hallmark of asthma and the presence of variable airflow limitation demonstrated by BDR testing is part of the definition of asthma stated in all major international asthma guidelines such as GINA and the British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) guidelines [18–20, 30, 31]. The literature searches revealed that most studies, including most of those included in these clinical practice guidelines, used the presence of BDR as evidence to confirm the diagnosis of asthma [35, 36, 46, 47, 50].

#### Additional evidence

The main uncertainty about BDR relates to its low sensitivity, and in children there is no direct evidence to support a robust cut-off for BDR. A change in  $FEV_1$  (L) of  $\geq 12\%$  and/or  $\geq 200$  mL is widely used in children to define the presence of BDR. However, this cut-off is derived from adult studies. Paediatric studies reported the mean change in  $FEV_1$  (L) post-bronchodilator to be 2.2–2.7% from baseline in healthy children [51, 52] compared with 8.6–10.7% in those with a history of asthma. The reported values for sensitivity and specificity using a 12% cut-off in children are 0.35–0.36 and 0.90–0.98, respectively [52, 53]. Despite providing important information, we excluded these studies from the evidence synthesis, because they did not fulfil the inclusion criteria, namely a second objective test within the reference standard.

#### Justification of recommendation

Even though we did not find any studies investigating the diagnostic accuracy of BDR testing, we recommend BDR testing in all children with abnormal spirometry. Variable airflow limitation is a defining feature of asthma, as stated in major international asthma guidelines such as GINA and BTS/SIGN, and a positive BDR in conjunction with obstructed spirometry has a high accuracy at confirming the diagnosis in children with relevant clinical signs and symptoms. Most studies included in these guidelines use a positive BDR test as the reference standard to support the diagnosis of asthma. In a child with relevant clinical symptoms, abnormal spirometry and positive BDR test, treatment can be started immediately. Importantly, a child with abnormal spirometry and no evidence of BDR could have a restrictive lung disease or fixed airways obstruction and referral should be considered to specialist care for further investigations. The task force agreed with the cut-off for BDR of 12% in children, in agreement with previous studies in children [52, 53] and existing international asthma guidance [18–20, 49]. The task force acknowledges that BDR testing has low sensitivity, especially at the 12% threshold, but good specificity for a diagnosis of asthma in children [52]. The task force acknowledges that there are resource implications, but based on the high specificity of the test, its noninvasive nature and its availability, the task force recommends BDR testing in children with obstructed spirometry and/or low  $FEV_1$  (supplementary table S10).

The task force considered that BDR testing is a noninvasive procedure and usable results are obtained in the majority of children. Spirometry and BDR can be performed in any healthcare setting and the results are immediately available. Equipment and consumables costs are moderate, but the test is time consuming and there are training requirements. Reversible airflow obstruction is the hallmark of asthma and it would make little sense to perform spirometry but not BDR in cases where spirometry is abnormal/obstructed.

### Key unanswered questions and future research needs

We need validation studies in children to investigate the diagnostic accuracy and limitations of BDR testing in asthma using different cut-offs, compared with an appropriate reference standard, which includes a second objective test. Different studies need to assess the type and dosage of short-acting bronchodilator used, and when to perform BDR testing (*i.e.* for all children, or only when FEV<sub>1</sub> or FEV<sub>1</sub>/FVC is <LLN).

### PICO 5. In children aged 5–16 years under investigation for asthma, should F<sub>eNO</sub> testing be used to diagnose asthma?

#### Recommendation

- The task force recommends the measurement of F<sub>eNO</sub> as part of the diagnostic work-up of children aged 5–16 years with suspected asthma (strong recommendation for the intervention, moderate quality of evidence).

#### Remarks

- A F<sub>eNO</sub> value ≥25 ppb in a child with asthma symptoms should be considered as supportive of a diagnosis of asthma.
- A F<sub>eNO</sub> value <25 ppb does not exclude asthma.

### Background

F<sub>eNO</sub> was first measured in exhaled air by GUSTAFSSON *et al.* [54] in 1991, and subsequently has been shown to be increased in asthma and regarded as an indirect marker of eosinophilic airway inflammation [55]. Measurement is noninvasive, can be obtained in most children aged ≥5 years and results are available in a few minutes using portable desktop equipment. Success in the routine clinical setting is variable in children aged 5–7 years [48].

International guidelines describe a standardised methodology and provide clinical interpretation of F<sub>eNO</sub> measurements [55]. F<sub>eNO</sub> has been recommended as a useful test to support a diagnosis of asthma in adults and children [20].

Multiple factors have been reported to influence measurement [55], including subject-related factors such as age, height and ethnicity; lifestyle factors such as smoking, diet and exercise; and environmental exposures such as pollen [55]. Atopy is associated with elevated F<sub>eNO</sub>, independent of asthma [55]. Asthma treatments including ICS [56] and LTRA reduce F<sub>eNO</sub> by between 25% and 50% [57].

### Review of evidence directly addressing the question

Four recent systematic reviews investigated the accuracy of F<sub>eNO</sub> in the diagnosis of asthma in children [58–61]. Four observational studies in children fulfilled the inclusion criteria [35, 46, 47, 50]. Unpublished data were provided by the authors of a fifth study [36]. A summary of this published evidence on F<sub>eNO</sub> is shown in supplementary table S11.

The overall diagnostic accuracy of the test is moderate, since conclusions are based on non-weighted average F<sub>eNO</sub> values without 95% confidence intervals. F<sub>eNO</sub> values of 19 ppb and 25 ppb showed the equal highest Youden's index (sensitivity + specificity – 100) shown in supplementary table S13.

The influence of ICS treatment on the results was considered; participants in the study reported by BROUWER *et al.* [36] had withheld any ICS for 4 weeks. In contrast, in the study reported by SIVAN *et al.* [46], one-third of cases finally categorised as asthma were using ICS at the time of testing. WOO *et al.* [50] included only steroid-naïve children, and finally, in the studies by GRZELEWSKI *et al.* [47] and DE JONG *et al.* [35], 11% and 19% of children, respectively, were on controller medication at the time of F<sub>eNO</sub> measurement.

The task force explored whether there might be subgroups of children in whom F<sub>eNO</sub> may be particularly suited to diagnosing/excluding asthma and one study showed that children with allergy show better accuracy for F<sub>eNO</sub> testing [50].

The five studies fulfilling the criteria for inclusion [35, 36, 46, 47, 50] reported sensitivity and specificity results for different cut-points for F<sub>eNO</sub>. These are shown in supplementary table S11.

### Justification of recommendation

Although the diagnostic accuracy of  $F_{eNO}$  is moderate, the results of our review show that evidence exists to support  $F_{eNO}$  as a useful test to diagnose asthma in children (supplementary table S14).  $F_{eNO}$  testing is a relatively simple, noninvasive test that is highly acceptable to children and their caregivers. There are equipment and consumables costs to be considered. The task force panel agreed that a single recommended cut-off value was essential. The panel agreed that 25 ppb was the best cut-off value based on the mean sensitivity (0.57) and specificity (0.81) values (supplementary tables S12 and S13) at this cut-point. To reach this decision the panel considered the harm from over-treatment arising from false positive results and the remit of the task force, which was to provide recommendations on diagnosing asthma and not on excluding asthma. The task force acknowledges that any cut-off relating to continuous variables such as  $F_{eNO}$  are to some extent arbitrary and confidence into the result increases with greater distance from the cut-off value. Furthermore, the task force emphasises the importance of interpreting  $F_{eNO}$  as part of a wider clinical assessment.

### Key unanswered questions and future research needs

We need studies investigating the sensitivity and specificity of  $F_{eNO}$  in ICS-naïve child populations presenting with symptoms of asthma and studies that further explore the role of  $F_{eNO}$  in nonatopic children with asthma symptoms. Studies are required to establish the “washout” time after cessation of ICS or LTRA before  $F_{eNO}$  can be used for diagnostic testing. In addition, we need better technology to routinely test  $F_{eNO}$  in children aged  $\leq 5$  years.

### PICO 6. In children aged 5–16 years under investigation for asthma, should PEFr variability be used to diagnose asthma?

#### Recommendation

- The task force recommends against PEFr variability testing as the primary objective test on its own to diagnose asthma in children aged 5–16 years (conditional recommendation against the intervention, moderate quality of evidence).

#### Remarks

- Other objective tests are preferred, but a PEFr variability test can be considered in healthcare settings lacking other objective tests.
- If a PEFr variability test is used the result should be based on 2 weeks of measurements, ideally using electronic peak flow meters.
- A cut-off of  $\geq 12\%$  in PEFr variability should be considered a positive test.
- A PEFr variability of  $<12\%$  does not exclude asthma.

### Background

PEFR is a physiological measurement of the largest flow of exhalation that can be achieved from maximal inspiration, expressed in  $L \cdot \text{min}^{-1}$ . Peak expiratory flow should be recorded as the best of three forced expiratory blows immediately after a full inspiration with the patient either standing or sitting. The PEFr variability is calculated as the difference between the highest and lowest PEFr expressed as a percentage of the average PEFr. PEFr variability as a diagnostic test is supported by the BTS/SIGN and the UK NICE guidelines and the GINA 2020 asthma strategy document [18–20].

### Review of evidence directly addressing PICO 6

One study met our inclusion criteria (supplementary table S15). BROUWER *et al.* [36] studied the usefulness of home spirometry and PEFr variability in diagnosing asthma in children consecutively referred to secondary care with nonspecific respiratory symptoms. Children performed home spirometry and peak flow measurements using an electronic device, twice daily for 2 weeks. Using a pre-defined cut-off of 12.3% (based on above 95% confidence interval of normal values in children) the sensitivity and specificity of PEFr variability were 0.5 and 0.72, respectively (supplementary tables S16 and S17).

### Justification of recommendation

PEFR variability has been included as an optional test in the diagnostic algorithm; however, spirometry (with BDR where appropriate) and  $F_{eNO}$  are preferred first-line diagnostic tests. There is limited evidence to support PEFr variability as an asthma-diagnostic tool (supplementary table S17). The only evidence to support its use is as a PEFr diary with twice-daily measurements for  $\geq 2$  weeks. More frequent testing may have greater sensitivity [62], but is offset by decreasing adherence to the test by children and their families [63]. The use of electronic meters and diaries may help to overcome some of the adherence issues [64].

### Key unanswered questions and future research needs

We need more studies to assess the diagnostic use and accuracy of PEFV variability in children. Future research should involve larger numbers of treatment-naïve children referred with asthma symptoms who are investigated by means of PEFV variability and other objective tests.

### *PICO 7. In children aged 5–16 years under investigation for asthma, should allergy testing be used to diagnose asthma?*

#### Recommendations

- The task force recommends against the use of skin-prick tests to aeroallergens as diagnostic tests for asthma (strong recommendation against the intervention, moderate quality of evidence).
- The task force recommends against the use of serum total and specific IgE tests as diagnostic tests for asthma (strong recommendation against the intervention, moderate quality of evidence).

### Background

Allergic sensitisation to aeroallergens is common among all children and even more common among children with asthma. Aeroallergens are common triggers of asthma symptoms. Common aeroallergens are house dust mites, animal dander, pollens and moulds. Allergic sensitisation to aeroallergens can be measured in several ways, but the most commonly used are skin-prick test or specific IgE measurement.

### Skin-prick tests

Skin-prick tests use the presence and degree of cutaneous reactivity as a marker for allergic sensitisation. A wheal size of  $\geq 3$  mm compared to negative control is considered a positive test [65]. Skin-prick testing is not practical in patients who have extensive eczema, dermatographism, urticaria or who are taking antihistamines or other medications, which interfere with the proper interpretation of the test results [65, 66].

### Allergen-specific IgE tests

The allergen-specific IgE can be detected by a radioallergosorbent test or by ELISA [67]. Different systems can measure allergen-specific IgE. The cut-off for a positive test to diagnose allergic sensitisation in children is commonly defined as  $<0.35$  kU·L<sup>-1</sup>.

### Review of evidence directly addressing PICO 7

Four observational studies met our inclusion criteria (supplementary table S18) [35, 36, 47, 50]. However, only one study directly assessed allergy tests as an index test [35], even though it was possible to calculate the diagnostic accuracy of allergy tests from the other three studies as well. Most studies were excluded because they assessed prevalence and patterns of allergic sensitisation in children with a prior asthma diagnosis or in healthy populations. Skin-prick testing had a sensitivity of 0.77–0.90 and specificity of 0.23–0.40 for one positive test, and sensitivity of 0.79 and specificity of 0.53 for two positive tests (supplementary tables S19 and S21). Specific IgE measurements had a sensitivity of 0.58–0.90 and a low specificity of 0.56–0.65 (supplementary tables S20 and S21).

### Justification of recommendation

Evidence from the available studies suggests that skin-prick tests and specific IgE measurements have a limited value to diagnose asthma. The low specificity is likely to lead to an over-diagnosis of asthma, particularly in children with other atopic diseases. Nonallergic asthma, in contrast, will be under-diagnosed if physicians rely on allergy tests for asthma diagnosis.

However, after diagnosis, allergy tests can be useful for asthma management, in particular to describe the phenotype and to plan individualised prevention measures.

Considering the low specificity, the task force recommends against allergy testing as a diagnostic test for asthma in children (supplementary table S21).

### Key unanswered questions and future research needs

Allergy tests are useful in patients already diagnosed with asthma, to determine measures of tertiary prevention, *i.e.* avoidance of clinically relevant allergens that trigger asthma attacks or maintain chronic symptoms. Carefully designed clinical studies in children with suspected asthma are essential to provide more evidence on their role in diagnosing asthma.

*PICO 8. In children aged 5–16 years under investigation for asthma, should direct bronchial challenge testing including methacholine and histamine be used to diagnose asthma?*

#### Recommendation

- The task force recommends a direct bronchial challenge test using methacholine in children aged 5–16 years under investigation for asthma where asthma diagnosis could not be confirmed with first-line objective tests (conditional recommendation for the intervention, low quality of evidence).

#### Remarks

- A provocative concentration of methacholine that results in a 20% drop in FEV<sub>1</sub> (PC<sub>20</sub>) value of  $\leq 8 \text{ mg} \cdot \text{mL}^{-1}$  should be considered as a positive test.
- The task force found no evidence for or against performing histamine challenge tests in children under investigation for asthma.

#### Background

One of the hallmarks of asthma is airway hyperresponsiveness (AHR), which is characterised by an increased sensitivity and exaggerated response to stimuli resulting in airway obstruction [68]. Direct bronchial challenge testing is performed with different chemical substances to test nonspecific bronchial responsiveness to a variety of stimuli such as methacholine (a neurotransmitter substance) or histamine (a mediator substance) directly interacting with receptors on airway smooth muscle. In individuals with asthma, the response occurs at a lower dose and to a greater degree compared to children without AHR. An ERS task force has revised the recommendations for methacholine bronchial challenge tests [69]. The results are based on the PC<sub>20</sub> or the delivered dose of methacholine resulting in a 20% fall in FEV<sub>1</sub> (provocative dose (PD<sub>20</sub>)). As results are comparable between different protocols and devices, the latter is the preferred method [69]. No studies using histamine challenge fulfilling inclusion criteria were identified by the literature searches.

Some parents/carers and patients have concerns about challenge tests due to the risk of creating a potentially severe asthma response. Health professionals should be mindful of these concerns when explaining the risks and benefits of challenge testing.

#### Review of evidence directly addressing PICO 8

Three studies directly addressed the PICO question and were included in the quantitative analysis (supplementary table S22) [35, 70, 71]. Histamine for bronchial challenge was not tested in any of the studies fulfilling the inclusion criteria.

We were unable to pool the accuracy data for these studies, because sensitivity and specificity differed too much between studies, and therefore calculated the absolute effects of tests using the range of results. Sensitivity and specificity ranged from 0.66 to 0.91 and from 0.63 to 0.82, respectively (supplementary table S23).

#### Justification of recommendation

Direct bronchial testing is time consuming, requires a specialist setting and tests can be unpleasant for children. Therefore, children referred for direct bronchial challenge testing require careful selection. However, the task force agreed that direct bronchial challenge testing should be offered to children where diagnostic uncertainty remains after repeated first-line tests have not confirmed the diagnosis, the child remains symptomatic and other diagnoses have been considered (supplementary table S24). The task force emphasises the importance of interpreting direct challenge testing as part of a wider clinical assessment. A positive challenge test may be present in the absence of asthma.

#### Key unanswered questions and future research needs

We need clinical studies to answer the question as to which children benefit most from direct bronchial challenge testing in order to make recommendations on the most appropriate referrals.

*PICO 9. In children aged 5–16 years under investigation for asthma, should indirect bronchial challenge testing including exercise and mannitol be used to diagnose asthma?*

#### Recommendation

- The task force recommends an indirect bronchial challenge test using a treadmill or a bicycle in children aged 5–16 years under investigation for asthma with exercise-related symptoms where asthma

diagnosis could not be confirmed with first-line objective tests (conditional recommendation for the intervention, moderate quality of evidence).

#### Remarks

- A fall in FEV<sub>1</sub> of >10% from baseline should be taken as a positive test.
- A mannitol challenge can be considered as an alternative to exercise challenge. However, due to its limited availability in most countries, and the fact that children often find the test unpleasant, mannitol challenge should be best avoided in favour of other challenge tests.

#### Background

Indirect bronchial challenge tests trigger airway obstruction *via* endogenous pathways that are involved in the pathophysiology of asthma [72]. Therefore, they are considered to be more specific for asthma compared to direct challenge tests, but may be less sensitive at detecting AHR. Several methods exist for indirect bronchial challenge testing including exercise, eucapnic voluntary hyperpnoea, cold air challenge and the inhalation of osmotic substances such as hypertonic saline, mannitol or adenosine monophosphate. An ERS task force has revised the recommendations for indirect bronchial challenge testing [73].

Exercise testing using a cycle ergometer or a motorised treadmill is the preferred test [73, 74]. Exercise-induced bronchoconstriction is defined as a decrease in FEV<sub>1</sub>  $\geq$ 10% from baseline, but some studies use the criterion of 15%, which results in a higher specificity [73, 75].

The mannitol challenge test is performed with the alcohol sugar mannitol, an osmotic agent, using a dry-powder inhaler device. Increasing doses of mannitol are inhaled and FEV<sub>1</sub> is measured repeatedly between the inhalation steps [76]. The test is considered positive if there is a fall of  $\geq$ 15% in FEV<sub>1</sub> from baseline in response to the cumulative total dose or a 10% decrease between two consecutive doses of mannitol [77].

As described earlier, some parents/carers and patients have concerns around challenge testing and potential adverse events.

#### Review of evidence directly addressing the question

We only found studies using either exercise challenge testing or the mannitol challenge test that fulfilled our inclusion criteria. Three studies directly answered the review question and were included in the quantitative analysis (supplementary table S25) [35, 70, 71]. All three studies provided accuracy data for indirect bronchial challenge tests using either exercise or mannitol.

ANDERSON *et al.* [70] provided data for mannitol inhalation in children as a subsample of a larger study in adults. ZACZENIUK *et al.* [71] reported the diagnostic accuracy of exercise testing by treadmill, as did DE JONG *et al.* [35], who also included bicycle testing. We were not able to pool the accuracy data of these studies because of the range of the results. ZACZENIUK *et al.* [71] defined a positive test by a  $\geq$ 10% decrease in FEV<sub>1</sub> and reported a sensitivity of 0.77 and a specificity of 0.68, with DE JONG *et al.* [35] reporting sensitivity and specificity data for  $\geq$ 10% and  $\geq$ 12% FEV<sub>1</sub> cut-off. Sensitivity was 0.47 and 0.37, respectively, and specificity was 0.77 for both cut-offs (supplementary table S26).

We were unable to pool the mannitol challenge test data due to the range of values. For mannitol challenge testing, ANDERSON *et al.* [70] reported a sensitivity of 0.63 and specificity of 0.81, and DE JONG *et al.* [35] reported a sensitivity and specificity of 0.39 and 0.97, respectively (supplementary table S27).

#### Justification of recommendation

Indirect bronchial testing is time consuming, and formal tests require a specialist setting. Children referred for indirect direct bronchial challenge testing require careful selection. However, a positive indirect bronchial challenge test confirms the diagnosis of asthma with a moderate sensitivity and high specificity. Based on the evidence (supplementary table S28), the task force agreed that indirect challenge testing during the diagnostic work-up with treadmill or bicycle is recommended in children where the diagnosis could not be confirmed using first-line diagnostic tests and particularly for children with exercise-induced symptoms.

The task force emphasises the importance of interpreting indirect challenge testing as part of a wider clinical assessment. A positive challenge test may be present in the absence of asthma.

### Key unanswered questions and future research needs

There is uncertainty regarding the best approach with respect to challenge testing in children and it is unclear whether indirect or direct challenge tests should be prioritised in the asthma diagnostic pathway. Younger children especially were under-represented in the selected studies and should be included in future studies.

### Development of the diagnostic algorithm

The task force agreed on the recommended diagnostic tests and a draft diagnostic algorithm during a meeting of the whole task force based on the results of the literature reviews, the recommendations for each PICO question and the Evidence to Decision framework.

The task force used a modified Delphi process to decide on the hierarchy of the diagnostic tests.

Using the Delphi process described in the methods section, the task force members agreed that no single test on its own is currently sufficient to confirm the diagnosis of asthma. The task force agreed that two positive, evidence-based tests are required to confirm the diagnosis in children aged 5–16 years. Spirometry, BDR testing and  $F_{eNO}$  are the most widely available objective tests performed in patients under investigation for asthma. Major international asthma guidelines variously recommended these as first-line tests. In addition, the tests are noninvasive, the equipment is portable, feasible in all healthcare settings, and have high acceptability by children and families [41]. The evidence supporting the proposed objective tests was frequently sparse and in some places relied on a single research publication fulfilling inclusion criteria. In addition, there is no study that tested a hierarchy of tests to diagnose asthma in children or adults. No test was recommended for which there was no evidence. This means that a “trial of preventer medication” is not included as a diagnostic test. While it has been included as a step in the algorithm, the diagnosis of asthma depends entirely on a significant improvement in lung function after the trial of treatment. No studies were found investigating BDR as a test for asthma. However, there is substantial indirect evidence. Variable airflow obstruction is universally accepted as the key feature of asthma and most studies included in this task force report used the presence of BDR as a reference standard to measure other tests against. This approach is pragmatic and there is no evidence underpinning it. The diagnostic algorithm is shown in the figure 1.

### Application of the algorithm

This algorithm applies to all children and adolescents presenting with symptoms of asthma, irrespective of whether they are treatment-naïve or had a prior diagnosis of asthma and are currently on treatment including ICS.

Where children are symptomatic despite ICS treatment, the algorithm can be applied because in children with current symptoms but normal lung function and a normal  $F_{eNO}$  value alternative diagnoses should be considered. Asymptomatic children on ICS should be reviewed at regular intervals (6–12-monthly) and treatment stepped down. If symptoms recur, the algorithm should be applied to confirm the diagnosis of asthma.

The algorithm is valid across the paediatric age group of 5–16 years. We did not conduct separate reviews for children age 5–11 years and adolescents (12–16 years), because most included studies had recruited children across school age and adolescence and did not stratify their analyses by age. The whole task force agreed that the algorithm applies to children from age 5 to 16 years. Future studies could test whether the algorithm can be refined by adapting it to different age groups, although every diversification will have to be gauged against the increasing complexity of its use in clinical practice.

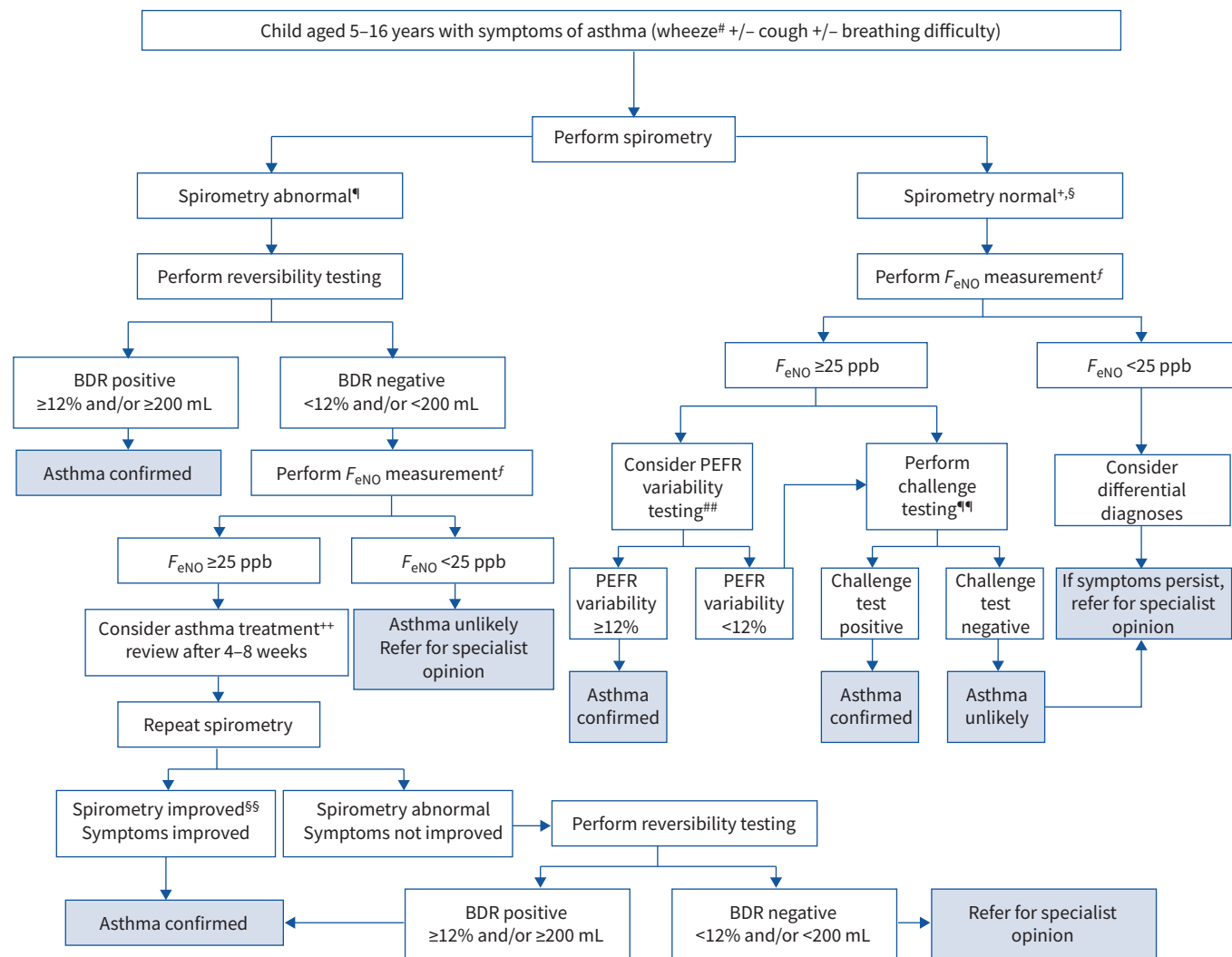
## Discussion

This document presents the first European evidence-based clinical practice guidelines for the diagnosis of asthma in children. We reviewed the literature for the past 40 years and found adequate evidence to support our recommendations in some areas, but limited or no data in others.

### Key recommendations

The task force recommends diagnosis of asthma in children only when at least two objective test results are abnormal. The task force recommends that spirometry, BDR and  $F_{eNO}$  are first-line tests in the asthma diagnostic pathway. In addition, the task force recommends against trials of treatment where an improvement of symptoms alone after a period of empiric asthma preventer medication is used to confirm the diagnosis.





**FIGURE 1** Asthma diagnostic algorithm for children and young people aged 5–16 years presenting in primary, secondary and tertiary care. This algorithm is based on the recommendations stemming from the Population, Intervention, Comparator and Outcome (PICO) questions; the hierarchy of the recommendations was decided using a Delphi process. There is no gold-standard test to confirm the diagnosis of asthma and no single abnormal test by itself is sufficient to make the diagnosis. If initial tests (spirometry, bronchodilator reversibility (BDR) and exhaled nitric oxide fraction ( $F_{eNO}$ )) fail to confirm the diagnosis, watchful waiting can be considered in children with normal spirometry with repeat testing especially at a time when the child presents with symptoms of asthma. PEFR: peak expiratory flow rate. #: reported wheeze has better sensitivity and specificity for the diagnosis of asthma compared to symptoms cough and breathing difficulty, which are rather nonspecific. †: forced expiratory volume in 1 s ( $FEV_1$ ) or  $FEV_1$ /forced vital capacity (FVC) less than lower limit of normal (LLN) and/or <80% predicted. Abnormal spirometry in a child presenting with symptoms of asthma does not confirm a diagnosis of asthma. ‡:  $FEV_1$  and  $FEV_1$ /FVC  $\geq$ LLN and/or  $\geq$ 80% pred. Normal spirometry in a child presenting with symptoms of asthma does not exclude a diagnosis of asthma. §: BDR testing can be considered if there is a strong clinical suspicion of asthma despite normal spirometry. f: the task force is aware that  $F_{eNO}$  should ideally be performed before spirometry, and in many clinics both tests are performed together. ###: peak expiratory flow variability could be used instead of challenge testing in healthcare settings where challenge testing is unavailable, but this would be an inferior choice. ¶¶: direct bronchial challenge testing with methacholine or indirect bronchial challenge testing using treadmill or bicycle or both (direct and indirect bronchial challenge testing) should be performed in children where asthma diagnosis could not be confirmed with other objective tests. \*\*: asthma treatment using anti-inflammatory therapy with inhaled corticosteroids according to current national and international guidelines. Depending on the severity of symptoms therapy should be started at Global Initiative for Asthma (GINA) step 2 or 3. If starting treatment, demonstrate and check inhaler technique and prescribe age-appropriate spacer devices unless breath-activated devices are prescribed age-appropriately. §§: task force recommendation based on clinical experience; indirect (but no direct) evidence that an improvement in  $FEV_1$  >7% may be considered significant [43]. Reduce treatment after 6–12-month periods of disease stability, as suggested by GINA 2020 [18].

We are not aware of any national or international guidelines that focus entirely on the diagnosis of asthma in children. The most widely cited asthma guidelines make statements or recommendations for diagnosis while focusing on the management of asthma, and cover children and adults in one document. The

guideline development is different between all major asthma guidelines, resulting in considerable variability of recommendations. These are summarised in table 3.

Our guidelines differ from the GINA strategy document and the BTS/SIGN guidelines in that neither proposes a clear diagnostic pathway for either sequence or timing of investigations. The BTS/SIGN guideline [19] does not recommend any tests for the routine diagnosis of asthma. Neither guideline recommends  $F_{eNO}$  testing to diagnose asthma. NICE recently developed asthma guidelines using GRADE methodology and systematic literature searches similar to our approach [20]. These guidelines included a diagnostic algorithm for children aged 5–16 years presenting with symptoms of asthma. Key differences between this and the UK NICE guideline include 1) downgrading of the use of PEFR variability testing because the evidence to support this test in children is not strong. The cut-off for PEFR variability testing is also different based on the available evidence (12% *versus* 20%); 2) the  $F_{eNO}$  cut-off is lower (25 ppb *versus* 35 ppb) based on recent evidence that was not available to NICE; 3) challenge testing in children was not recommended by NICE based on insufficient evidence. The task force recommends challenge testing in children as part of the diagnostic algorithm due to new evidence not available to NICE [35] and two studies not identified by the NICE searches [71, 76].

The task force strongly recommends the use of LLN derived from the GLI [78] as the reference standard for spirometry cut-off values. We have included fixed cut-offs only as a close approximation to be used in exceptional circumstances where LLN are not available either due to the spirometry equipment not displaying LLN values or where there are no GLI data due to the ethnicity of the patient.

We have included fixed cut-off values for other tests including BDR,  $F_{eNO}$ , PEFR variability and challenge testing. These cut-offs are based on the evidence available to the task force and the research papers included in the quantitative analysis for each PICO. We used the Youden index for pooled data where more than one research paper was available. The task force is aware that these cut-offs represent arbitrary thresholds and that the likelihood that a child has asthma increases with decreasing FEV<sub>1</sub>, increasing BDR, increasing PEFR variability, increasing  $F_{eNO}$ , and greater bronchial hyperresponsiveness.

We did not include children aged <5 years in these guidelines, because diagnostic tests for asthma on young children are rarely performed and there is insufficient evidence to support an evidence-based diagnostic algorithm. We recognise that many children aged <5 years are treated for asthma-like symptoms and families don't understand why asthma can't be diagnosed sooner but their child has to take asthma treatment. We refer readers to a recent ERS task force report on the management of children with preschool wheeze [79].

There are no randomised controlled trials that used diagnostic tests to diagnose asthma, and the proposed diagnostic algorithm is based on pragmatic decisions including access to test equipment, clinicians' familiarity with the tests and acceptability by children and families. All these factors and decisions are clearly documented in the Evidence to Decision tables in the supplementary material. In addition, we have not undertaken a health economic analysis because this was beyond the scope of this task force. Because of this lack of evidence to support a diagnostic sequence, every diagnostic algorithm will be open to criticism. A recent study from Switzerland confirms the limited use of individual tests and applying the NICE and GINA algorithm retrospectively to a series of diagnostic tests showed variable sensitivity and specificity between the NICE and GINA algorithms [80]. The task force is aware that diagnostic algorithms involving multiple tests are challenging especially in the primary care setting. Moreover, spirometry is frequently normal in patients with asthma during stable disease [40, 41]. Where this is the case and if the child is relatively asymptomatic a "watchful waiting" approach can be considered. Repeat spirometry testing should then be performed with comparison of test results over time. Spirometry testing is likely to be most useful when the child is symptomatic, especially when wheezing is present, and a comparison is made with spirometry obtained during disease stability as suggested by the BTS/SIGN asthma guidelines [19].

We have highlighted areas of research need in the individual PICO sections. Future studies require careful planning with respect to study designs to improve the evidence base of paediatric asthma diagnosis and focus on affordable and scalable tests to diagnose asthma. Better strategies to diagnose childhood asthma in primary care are of particular importance in order to avoid large numbers of secondary and tertiary care referrals for asthma diagnostic tests, in particular challenge tests. More research is urgently needed in this area.

Invariably, regional differences exist in Europe in relation to asthma incidence and severity, availability of tests and the approach to asthma diagnosis. Given the resources and timeframe of this clinical practice

guideline it was not possible to evaluate all the tests described in the literature for the diagnosis of asthma, but instead we focused on the most commonly used tests and approaches. The ERS task force clinical practice guidelines closely align to other major international asthma guidelines [18–20]. All recommend some form of spirometry testing in patients with suspected asthma, usually from 5 years of age. Where this guideline differs is in the recommendation of a diagnostic algorithm that should ultimately allow us to diagnose or refute the diagnosis of asthma in all children presenting with relevant respiratory symptoms.

In summary, we present the first European guidelines for the diagnosis of asthma in children aged 5–16 years. The task force recommends spirometry, BDR and  $F_{eNO}$  as first-line tests to diagnose asthma in children and that asthma be diagnosed only when two test results are abnormal.

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The guidelines published by the European Respiratory Society (ERS) incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Health professionals are encouraged to take the guidelines into account in their clinical practice. However, the recommendations issued by this guideline may not be appropriate for use in all situations. It is the individual responsibility of health professionals to consult other sources of relevant information, to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary, and to verify rules and regulations applicable to drugs and devices at the time of prescription.

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