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Review

The role of objective tests to support a diagnosis of asthma in children

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Educational aims

The reader will be able:

- To describe the difficulties in diagnosing asthma in children and the resulting high rate of misdiagnosis.
- To highlight the impact of over- and under-diagnosis in children.
- To explain the recently published NICE guidance on asthma diagnosis and how it affects children.
- To describe the feasibility and practical implications of performing the objective tests recommended by NICE in healthcare settings including primary care.

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ABSTRACT

In many healthcare settings asthma in children is a clinical diagnosis based on parental reported symptoms. These include intermittent episodes of wheezing, breathlessness and periodic nocturnal dry cough. Increased symptoms often coincide with colds. Confirming a diagnosis of asthma in children can be difficult and recent reports highlight that misdiagnosis, including over- and under-diagnosis of asthma are common. Recent UK National Institute of Health and Care Excellence guidelines recommend diagnostic algorithms for children from five years and adults to support a clinical suspicion of asthma. Spirometry, bronchodilator reversibility and fractional exhaled nitric oxide testing are the first line tests to diagnose asthma in children. The introduction of these tests across all healthcare settings has the potential to reduce misdiagnosis, improve asthma management and reduce healthcare spending for asthma.

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INTRODUCTION

Asthma is a chronic airways disease characterised by reversible airflow obstruction that is completely or partially reversible following inhalation of short acting beta-2-agonists. Eosinophilic airway inflammation is frequently a feature of allergic asthma [1]. Airway obstruction in children is often triggered by viral respira-

tory tract infections (e.g. the common cold), exercise and environmental conditions, such as cold air, but also specific allergic triggers which include grasses, pollens and animal fur. The risk of developing asthma is multi-factorial with genetic and environmental factors playing key roles [2].

Asthma affects over 300 million people worldwide [3] and in contrast to other lung diseases, the prevalence of asthma is considerably higher in children compared to adults [4]. In fact asthma is the most common chronic condition in children and the UK has one of the highest childhood asthma rates in the world (ISAAC study) with approximately 1.1 million children, the equivalent of 1 in 12 children, diagnosed with the condition [5]. Asthma has a considerable impact on a child's quality of life [6].

In many healthcare settings asthma in children is a clinical diagnosis based on parental reported symptoms including episodes

Abbreviations: FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; ATS, American Thoracic Society; ERS, European Respiratory Society; BTS, British Thoracic Society; NICE, National Institute for Health and Clinical Excellence.

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of shortness of breath; often in conjunction with colds, intermittent episodes of wheezing, chest tightness and periodic nocturnal dry cough.

Making a diagnosis of asthma in pre-schoolers is controversial as objective tests are difficult to perform in this age group. Diagnostic difficulties and the management approach to children with preschool wheezing has been recently reviewed as part of an ERS Task Force report and will not be discussed further here [7].

ASTHMA MISDIAGNOSIS

A symptom based approach to the diagnosis of asthma carries a significant risk of misdiagnosis, resulting in over- and under-treatment of asthma, poor symptom control, and in delayed start to asthma treatment [8]. Asthma over- as well as under-diagnosis are now recognised as common problems reported from North America [9,10], Europe [11] and the UK [12,13]. This is perhaps not surprising because respiratory symptoms in children are frequently non-specific and getting to the correct diagnosis is complicated by the fact that children experience frequent episodes of colds [14], some of which can be prolonged with clinical symptoms very similar to those present in true asthma. In addition, the majority of children with isolated dry cough do not have asthma [15]. To complicate matters further parents often report symptoms of wheezing in their children that on closer examination turns out to be something else [16].

Over diagnosis

A clinical diagnosis of asthma that is not supported by lung function testing may lead to over treatment of asthma, the prescription of inappropriate treatments [17] and unnecessary medicinal side effects. This also has cost implications because a substantial amount of the UK asthma budget is spent on corticosteroid inhaler medication [18]. Importantly, a lack of spirometry testing has been identified as an independent risk factor for asthma misdiagnosis [19]. Persistent on-going morbidity due to the wrong diagnosis is an additional complication. In one adult study, which employed objective lung function tests including spirometry and bronchoprovocation tests to confirm or reject a pre-existing asthma diagnosis, a greater proportion of adults in whom asthma was excluded were found to be on regular asthma medications compared with those who had asthma confirmed; suggesting that over-diagnosis may also lead to over treatment, presumably because symptoms do not go away when patients are given asthma medications incorrectly and thus continue on the wrong treatment indefinitely [11].

Researchers conducting a community based study in Canada investigated 154 children aged 9 to 12 years, including 102 with doctor diagnosed asthma and 52 age-matched children with respiratory symptoms but no asthma diagnosis. Bronchodilator reversibility and methacholine challenge tests were used as gold standard objective tests to diagnose asthma. The authors reported that 45% of cases were over-diagnosed and 10% of symptomatic controls were under-diagnosed with asthma, highlighting the importance of objective testing [20].

A 2016 Dutch study reported that 53% of children in a large primary care cohort were likely to have been misdiagnosed as having asthma [21]. Though the children from this study did not undergo a rigorous protocol of objective testing, with diagnosis excluded on the basis of electronically recorded symptom history and medication usage, a previous UK epidemiological study also found no evidence of bronchial hyperresponsiveness in 50% of children with GP diagnosed asthma, providing objective support for the Dutch study [22].

The problem is not confined to children. A prospective study of 90 adults, aged 18–70 years with physician-labelled asthma, found that up to 41% did not meet criteria for the diagnosis for asthma, based on a positive history and one of the following; documented reversible airflow obstruction; defined as an increase in FEV₁ (L) of 12% or greater or diurnal variation on PEFR of 20% or greater, or airway hyper-responsiveness; defined as 20% fall in FEV₁ following methacholine challenge compared with baseline of (PC₂₀) of 8 mg/ml or less during provocation testing [17].

Under diagnosis

The International Study of Asthma and Allergies in childhood (ISAAC) reported that one-third of children aged between 12 and 14 years in Great Britain with frequent night time wheezing had no diagnosis of asthma [13]. Getting the diagnosis right clearly matters, as the early detection of asthma might improve the long term prognosis of asthma patients.

A random sample of adults aged 25–70 years in the Netherlands were screened for respiratory symptoms and underwent lung function testing. Of 1155 participants, 7% (*n* = 86) demonstrated airflow obstruction and had symptoms of asthma. Of these only 34% (*n* = 29) had consulted the GP. Importantly, of those patients with airflow obstruction only 79% were recorded as having asthma, thus indicating an under-diagnosis by the GP in 21% of cases [23].

ASTHMA DIAGNOSIS AND OBJECTIVE TESTING

There is considerable controversy on how a diagnosis of asthma should best be confirmed. The absence of a generally accepted gold-standard diagnostic criteria means that it is difficult to make unequivocal evidence-based recommendations on how to make a diagnosis of asthma in children or adults. However, recent published guidelines (GINA, 2017 [3], NAEPP, 2007 [24], BTS, 2016 [25], NICE, 2017 [26]) are generally in agreement that a diagnosis based on symptom history alone is inadequate. Spirometry is the recommended first line objective test in most internationally recognised asthma guidelines.

A clinical suspicion of asthma should therefore be supported by objective tests to help confirm the diagnosis and to ascertain the degree of lung function deficit. Both the US National Asthma Education and Prevention Program (NAEPP, 2007) expert review panel report and latest Global Initiative for Asthma (GINA, 2017) guidelines recommend that a diagnosis of asthma should be made on the basis of episodic symptoms consistent with asthma, exclusion of an alternative diagnosis and objective evidence of airflow obstruction with short acting beta-2agonist reversibility. Use of spirometry and reversibility testing is recommended from 5 years.

The British Thoracic Society (BTS) guideline recommends that diagnosis is based on clinical history including cough, wheeze, breathlessness and chest tightness and the success of a trial of treatment [25]. There is however no evidence for the use of a trial of treatment to confirm a diagnosis of asthma. Spirometry is recommended where diagnostic uncertainty remains but in primary care this is rarely done.

Recent NICE guideline for asthma diagnosis and monitoring (NICE, 2017) advocates stricter criteria for diagnosis, stating that not only should an asthma diagnosis not be made based on symptoms alone, but also the diagnosis should not be based on any single test. The proposed paediatric diagnostic algorithm, which applies across all health sectors, specifies the use of spirometry ± reversibility testing, fraction of exhaled nitric oxide (FeNO) measurements and peak expiratory flow (PEF) variability monitoring over 2–4 weeks as the recommended diagnostic tests (Fig. 1). The 2018 NICE asthma quality standards support the use of

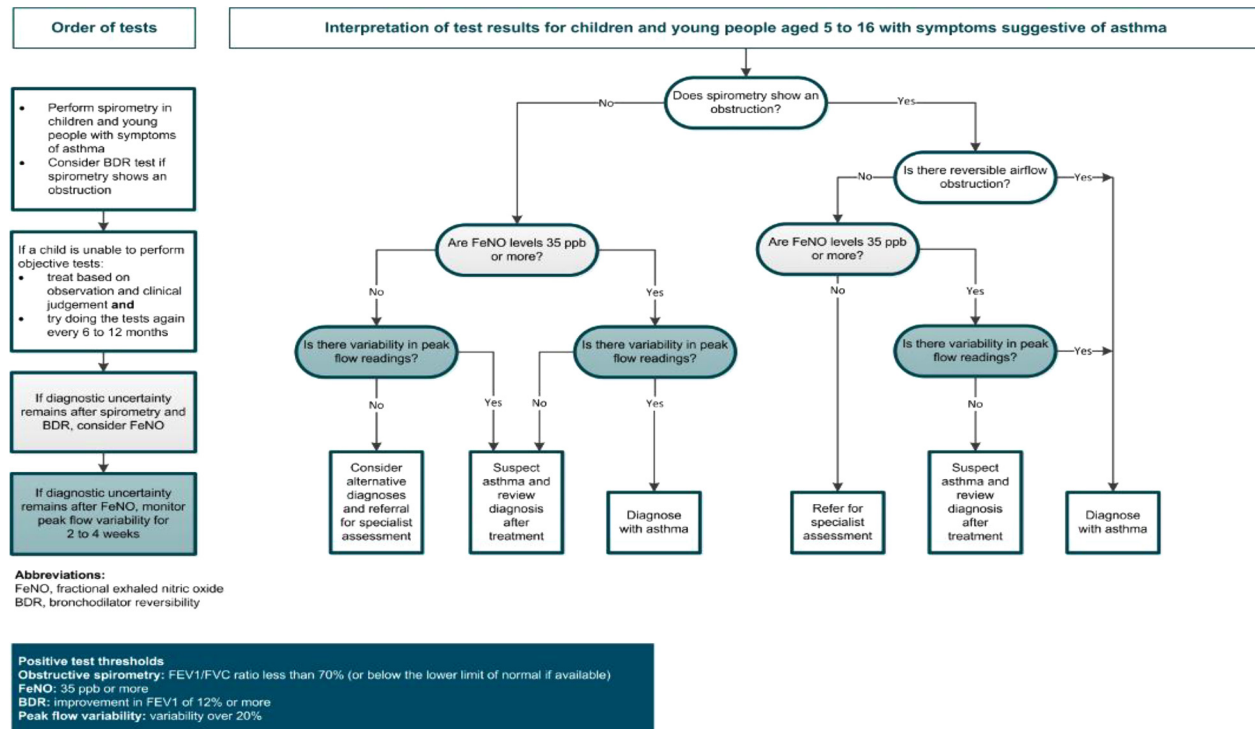


Fig. 1. NICE diagnostic algorithm for children aged 5–16 years. The figure has been reproduced with permission from NICE UK.

objective tests to diagnose asthma from 5 years of age as one of their five quality standards [27]. These are not currently supported by the British Thoracic Society or the Primary Care Respiratory Society highlighting the controversy surrounding objective testing.

SPIROMETRY

Spirometry is a non-invasive physiological test which measures the volume and flow rate of air during inhalation and exhalation. The most commonly reported parameters are FEV₁ (forced expiratory volume in 1 s) and FVC (forced vital capacity) and the ratio of FEV₁ to FVC (FEV₁/FVC). All parameters are measured during a forced expiratory manoeuvre – a subject inhales to total lung capacity and forcefully expires down to residual volume.

The FEV₁ represents the volume of air (litres) expired in the first second and the FVC (litres) is the total volume of air expired from the start of the manoeuvre to the end. A reduced FEV₁ to FVC ratio indicates obstruction, as it represents a prolonged expiratory time secondary to narrowed/obstructed airways. A standardised procedure for performing spirometry has been published jointly by the European Respiratory Society (ERS) and American Thoracic Society (ATS) [28]. Depending on the equipment used, the primary recorded signal may be flow or volume, with extrapolation of the remaining parameter.

Spirometry testing requires good patient participation but with appropriate encouragement and guidance from trained healthcare professionals this can be achieved in the majority of children from 5 years onwards [29]. Likewise the accuracy of interpretation relies on the quality and standardisation of training the operator has received.

Diagnostic accuracy of spirometry

Patients presenting to their doctor when they are well often have normal spirometry and the key is to perform lung function testing when they are symptomatic, which in the current health

care setting is not always possible. A normal spirogram in a patient when they are asymptomatic cannot rule out asthma [30,31]. Even in children with severe persistent asthma, as defined by NAEPP (NAEPP, 2007), up to a half may have normal FEV₁ to FVC ratios [32].

The diagnostic accuracy of spirometry in asthma has recently been reviewed in a NICE document (NICE, 2017). Using a definition for obstruction as either a FEV₁/FVC < 70% or FEV₁ predicted < 80%, NICE identified only one paediatric study.

Sivan et al. performed spirometry in 150 children with non-specific respiratory symptoms before following their progress over 18 months [33]. A diagnosis of asthma was made, during the follow up period, based on either a suggestive clinical history or documented variability of FEV₁ ≥ 15% over time or in response to bronchodilation. Using this criteria, they reported the diagnostic accuracy of FEV₁% predicted < 80% at time of recruitment as having a sensitivity of 52% and specificity of 72%.

What about bronchodilator reversibility?

Performing spirometry pre- and post- inhalation of bronchodilator medicine is a test of bronchial lability, a hallmark of asthma, which can readily be performed in the clinic setting without the need for additional specialist equipment. Reversible airflow obstruction is identified by an improvement of 12% or more in the FEV₁ (L) 15 min following administration of a short-acting bronchodilator through a spacer and a positive test supports a diagnosis of asthma [34].

In children, the validity of the 12% cut-off has been questioned by previous paediatric studies which have reported the mean change in FEV₁ (L) post-bronchodilator to be 2.2–2.7% from baseline in healthy children [35,36]; compared with 8.6–10.7% in those with a history of asthma. A lower cut-off of 9% has been proposed, which differentiates between health and disease with a sensitivity of 43–50% and specificity of 78–86% [35–38].

Global lung initiative

Along similar lines, it is now almost impossible to discuss spirometric cut-offs including children without mention of the excellent work done by the Global lung initiative (GLI). Measuring spirometry in tens of thousands of healthy individuals' all-age multi-ethnic reference values for spirometry have been published [39]. There is no evidence for a cut-off of 70% for FEV₁/FVC and using this value in clinical practice results in substantial underestimation of the number of children with obstructed spirometry. The gold standard for evaluation of spirometry results is the use of lower limits of normal as proposed by the GLI.

Training and support

The necessary resources and funding to provide equipment and nurse time are needed to meet the criteria of quality assured spirometry. The key factor is in the provision of adequate educational opportunities and time to support nurses in spirometry training, as well as to address the potential increase in costs for practices. Designed programmes to deliver virtual spirometry training in primary care are rarely used, but have shown increased spirometry quality and improved recognition of asthma severity levels [40].

The Association for Respiratory Technology and Physiology (ARTP) are the guardians of quality spirometry in the UK. Together with the British Thoracic Society, the ARTP delivers certified training for nurses, physiotherapists and doctors in the theoretical and practical knowledge of spirometry, offering an accreditation system to ensure that tests are performed and interpreted to internationally acceptable standards. In order to maintain certification, individuals need to demonstrate that they are regularly performing and/or interpreting spirometry and recertify every three years.

FRACTIONAL EXHALED NITRIC OXIDE

The inducible form of nitric oxide (NO) is expressed predominantly in inflammatory and epithelial cells, and activated by inflammatory cytokines during inflammation. The major determinant of increased NO concentration in the exhaled breath of asthmatics is increased epithelial NO expression [41] consequent to allergic airway inflammation.

Fractional exhaled nitric oxide (FeNO) measurements have been recommended to support a diagnosis of asthma [25,26,42], and as an objective marker of disease severity and compliance with therapy.

Several asthma guidelines have referred to the use of FeNO as a marker of allergic airway inflammation and its role in supporting a diagnosis of asthma (BTS, 2016, NAEPP, 2007, GINA, 2017), without providing clear guidance on how it should influence clinical decision making, or when it should be used. The recent NICE asthma guideline (NICE, 2017) includes FeNO within its proposed algorithm for asthma diagnosis in children and adults. Current NICE recommendations state that a FeNO test should be offered to children aged 5–16 years with suspected asthma if they have normal spirometry or obstructive spirometry with negative bronchodilator reversibility. A FeNO level of 35 ppb or more in children should be interpreted as a positive result [26]. A negative result does not of course exclude a diagnosis of asthma.

In a recent review, which included eight studies in children evaluating the accuracy of FeNO in asthma diagnosis, the pooled estimates for sensitivity and specificity were 79% (95% CI 64–89%) and 81% (95% CI 66–90%) respectively, using thresholds for FeNO ranging from 19 to 25 ppb [43]. It should be noted however, that not all studies included in this review used another objective

testing as the reference standard to confirm asthma, i.e. physician diagnosis was used instead. Nevertheless, the optimal threshold reported in all these studies were lower than the 35 ppb suggested in the proposed NICE diagnostic algorithm. The 35 ppb cut-off is supported by an ATS clinical practice guideline [42].

FeNO measurement should be interpreted in the context of age, gender, allergic profile and the presence of any current symptoms in children [44]. FeNO results are also confounded by the presence of allergic rhinitis as the presence of this is associated with higher FeNO levels in exhaled breath [45].

FeNO values are moderately associated with sputum eosinophils and serum IgE levels [46]. As a result FeNO levels are associated with corticosteroid responsive asthma and may have a role in the monitoring of treatment response and adherence to inhaled corticosteroids [47]. Other factors that contribute to FeNO variability are smoking, which lowers FeNO levels, and respiratory infections which raise level of FeNO in children with both upper and lower respiratory tract infections [46–48].

TRIAL OF TREATMENT

A trial of treatment in patients under investigation for asthma has been suggested in existing asthma guidelines (BTS 2016, GINA 2016); using clinical response to treatment as evidence to help support a diagnosis of asthma. This approach is often taken in UK primary care.

There is no evidence to support a trial of treatment in the diagnosis of asthma. Especially in children this approach is fraught with uncertainty. Important questions on what a trial of treatment should look like, what an appropriate starting dose of preventer treatment should be, whether or not to use inhaled corticosteroids and which patients are suitable for a therapeutic trial remain unanswered [49]. A pragmatic approach that has been suggested is to offer a trial of inhaled corticosteroids for 8–12 weeks, whilst assessing its effects on daytime and nocturnal symptoms, frequency of asthma attacks, and whether there is deterioration when it is stopped [50]. This rigorous approach is rarely used in primary care and many children, especially those of early school age, have lingering respiratory symptoms following viral respiratory tract infections or episodes of prolonged non-specific dry cough [48]. Symptoms may improve during the trial of treatment as a result of the natural history of the underlying condition rather than as a genuine response to therapy and the child is then often misdiagnosed as having asthma. Based on current evidence this approach cannot be recommended.

However, in children who exhibit seasonal variation in their symptoms, repeated therapeutic trials may be needed to demonstrate positive symptom response to treatment [51].

SERIAL PEAK FLOW MONITORING

The peak expiratory flow rate (PEFR) is a readily available objective lung function measure of the fastest flow rate of exhaled air during forced expiration in litres per minute. PEFR is widely used in the diagnosis and monitoring of asthma in primary care but the test is of limited value as it only measures one parameter and the measurement is very effort dependent. There is no evidence to support single peak flow measurements in the diagnosis or monitoring of asthma in children or adults. There is limited evidence for peak flow diaries. Variations of 20% in flow rates during a two week observation period with twice daily measurements are suggestive of asthma [52,53]. Serial peak flow monitoring is currently recommended as a confirmatory test for occupational asthma in adults. Serial peak flow recordings are more difficult to interpret in children and peak flow diaries are often not completed,

not returned or unreliable after the monitoring period. Studies have demonstrated up to 25% of peak flow entries being incorrectly recorded, with mean differences between written and electronic recorded peak flows ranging from -72 to 34 litres per minute per patient [54].

AIRWAY AND BLOOD EOSINOPHILIA

The measurement of airway and blood eosinophils as diagnostic and monitoring tools tend to be reserved for children attending specialist clinics. Sputum eosinophils >2% support a diagnosis of asthma. Sputum eosinophilia can guide the management of adults with severe asthma [55] but this has not been confirmed in children [56]. Blood eosinophils counts rarely reflect airway eosinophilia even in children with severe asthma [57]. Blood eosinophils are used in the adult severe asthma population to direct treatment with the anti-interleukin-5 monoclonal antibody mepolizumab [58].

IDENTIFYING ATOPIC DISEASE

There is limited evidence to support the use of allergy testing in the diagnosis of asthma, but skin prick testing or IgE blood tests may be useful in identifying specific allergic triggers of airway inflammation, in particular aeroallergens, such as house dust mite, grass and tree pollen, animal fur and mould spores. Measuring total serum IgE can help identify children with allergic asthma, who if non-responsive to high dose inhaled or oral corticosteroids may be suitable for a trial of the monoclonal anti-IgE antibody, omalizumab.

CHALLENGE TESTING

Direct bronchial challenge tests using inhaled histamine, or methacholine, or indirect challenge testing using exercise or inhaled mannitol may be useful to support a diagnosis of asthma. The most common challenge test involves inhaling methacholine, a non-selective muscarinic receptor agonist, to induce bronchoconstriction. Incremental doses are inhaled until there is a fall in the patient's FEV₁ of at least 20% from the baseline value (PC20). A PC20 value of 8 mg/ml or less is generally regarded as a positive test. There is currently insufficient evidence to support large scale challenge testing in children under investigation for asthma [26], as the diagnostic accuracy of bronchial challenge tests with histamine or methacholine is unclear and the tests are uncomfortable and unsuitable for younger children. If direct challenge testing is used, methacholine is likely to be better tolerated in children as histamine can cause throat irritation. Direct challenge tests are not performed within a primary care setting. The tests carry a small risk of bronchospasm response to the methacholine and histamine and test sites require facilities for resuscitation.

Indirect bronchial provocation testing is done more commonly in children in the UK, in the form of an exercise test. Physical challenges require cooperation but are useful to identify any exercise induced symptoms, where the patient is asked to perform a 6-min treadmill run, with speed and slope adjusted to ensure a heart rate >85% predicted maximum [59]. However, although an exercise test in a child who is able to run is generally well accepted and currently the most commonly used test, its diagnostic accuracy remains uncertain [60].

ADDITIONAL TESTING

Additional testing may be indicated in children where the diagnosis of asthma remains in doubt after objective tests have been

completed. Chest radiography may identify other potential diagnoses such as chest infections, retained foreign body or other rare lung diseases. A barium swallow may be useful to identify any swallowing dysfunction or large airway compromise due to for example vascular rings. Impedance or pH studies can identify the presence of gastroesophageal reflux that could lead to aspiration and a sweat chloride test may help to rule out cystic fibrosis. If the diagnosis remains uncertain, referral to a specialist respiratory clinic should be considered for further evaluation.

IN SUMMARY

Diagnosing asthma can be difficult and misdiagnosis is common. There is no widely accepted gold standard diagnostic test therefore no single test in isolation can be used to diagnose the condition. Recent UK NICE guidelines recommend a diagnostic algorithm to be used in adults and children five years and older in whom a diagnosis of asthma is suspected. Spirometry, reversibility and FeNO testing are first line tests in the diagnostic algorithm. The introduction of these objective tests across all healthcare settings has the potential to reduce misdiagnosis, improve asthma management and reduce healthcare spending for asthma.

DIRECTIONS FOR FUTURE RESEARCH

Further research is needed to establish barriers to implementation of spirometry and FeNO testing for diagnosis and monitoring of asthma in children in general practice. The usefulness of spirometry testing for asthma monitoring in primary care needs to be firmly established. Research is also urgently needed to be able to reach consensus on appropriate spirometry cut-off values for bronchodilator reversibility in children. We need to better understand the UK health economic impact of objective testing in all healthcare settings. And finally, the clinical and cost effectiveness of using electronic monitoring systems and tele-healthcare to improve asthma control also need to be explored further.

SUGGESTED AREAS IN WHICH RESEARCH COULD BE FOCUSED

- **Diagnosis:** To establish in children aged 5–16 years what is the acceptability and diagnostic accuracy of challenge testing including exercise challenge and direct bronchial challenge with histamine or methacholine.
- **Health economics:** To better understand the UK health economic impact of introducing objective tests to diagnose asthma in all healthcare settings.
- **Monitoring:** To study the clinical and cost effectiveness of using electronic monitoring systems to improve adherence with regular inhaled maintenance therapy.
- **Monitoring:** To study the clinical and cost effectiveness of using tele-healthcare to improve asthma control in children with asthma.

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