

# FeNO Testing For Asthma Diagnosis - A PCRS Consensus

**FeNO Testing For Asthma Diagnosis - A PCRS Consensus was commissioned to set out the PCRS position on the role of FeNO testing within the context of asthma diagnosis.**



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## PCRS position on FeNO testing for asthma diagnosis

The fractional exhaled nitric oxide (FeNO) test measures the level of NO in the exhaled breath and provides an indication of eosinophilic inflammation in the lungs. For the diagnosis of asthma, the British Thoracic Society (BTS) and the Scottish Intercollegiate Guidelines (SIGN) position FeNO testing after the objective evaluation of airways obstruction and alongside other potential tests for inflammation such as determination of blood eosinophil levels, IgE skin-prick test to detect atopy, and tests for variability (reversibility, peak expiratory flow [PEF] charting and challenge tests).<sup>1</sup> Patients with a history and clinical characteristics that support a high probability of asthma and who have had an objective measure of reversible airways obstruction do not need FeNO before progressing to a trial of treatment.<sup>1</sup> Additional objective evidence including FeNO is recommended as an optional investigation as a test for eosinophilic asthma for those considered to have an intermediate probability of asthma.<sup>1</sup> The current PCRS position aligns with the guidance issued by BTS/SIGN. This article reviews the evidence base and clinical guidelines upon which the PCRS position is based.

## Background

Asthma is a heterogeneous condition characterized by respiratory symptoms (wheeze, cough, breathlessness, chest tightness and pain) associated with variable airflow obstruction, hyper-responsiveness and often an underlying inflammation. There is no single defining feature or symptom of asthma, however variability is at its

core, so diagnosis is achieved through a holistic evaluation of patient symptoms over time alongside repeated physiologic evaluation of lung function, and assessment of response to trials of treatment. Pathologic evaluations including tests for eosinophilic airway inflammation, and other investigations, may sometimes be needed.

Nitric oxide (NO) is produced in the lungs and so can be detected in the exhaled breath and elevated exhaled NO levels are thought to be related to eosinophilic lung inflammation.<sup>2</sup> Fractional exhaled NO (FeNO) testing is quantitative, noninvasive, simple and safe and elevated FeNO may be supportive of a diagnosis of asthma in untreated individuals presenting with respiratory symptoms.<sup>3</sup> However, while suggestive, a positive FeNO test is not conclusive evidence of asthma. Indeed, eosinophilic lung inflammation has been suggested to be a contributing factor to asthma in approximately 50% of cases, with the remaining 50% of cases not showing evidence of eosinophilic lung inflammation.<sup>4,5</sup>

There has been considerable discussion in recent years regarding the relevance of FeNO testing in the diagnostic workup of patients presenting with respiratory symptoms for whom a diagnosis of asthma is suspected. Here we review the current recommendations for the role of FeNO testing in the diagnosis of asthma and explore the benefits, limitations and challenges of utilising this test in the primary care setting.

## How is FeNO testing conducted?

The FeNO test measures the level of NO in the exhaled breath. FeNO testing is conducted using a handheld device into which the patient blows

for 10 seconds at 60 litres a minute. A shorter test is available for children. The result is provided within approximately 1 minute with a FeNO level  $\geq 35$  ppb as a positive test in children and a level  $\geq 40$  ppb as a positive test in adults.<sup>6</sup>

## What are the current recommendations for FeNO testing for asthma diagnosis?

### NICE

In November 2017 the National Institute for Health and Care Excellence (NICE) issued guidance for the diagnosis, monitoring and management of asthma.<sup>6</sup> The guidance focuses on objective testing for the diagnosis of asthma and suggests FeNO evaluation be considered as an objective test alongside spirometry and peak expiratory flow (PEF) at initial presentation if equipment is available, and as part of the diagnostic algorithm for both children over 5 and adults with respiratory symptoms suggestive of asthma (Box 1).

### BTS/SIGN

The 2016 BTS/SIGN guidance takes a pragmatic approach to asthma diagnosis and recommends that for patients with a high probability of asthma, a trial of treatment is appropriate.<sup>1</sup> The guideline incorporates FeNO testing as part of the diagnostic algorithm only for patients with an intermediate probability of asthma where further evidence is required (Box 2). Unlike the current NICE guidance, the principle investigation is to test for airway obstruction and bronchodilator reversibility on spirometry. FeNO testing is positioned after spirometric evaluation as an optional investigation to test for eosinophilic inflammation along side determination of blood eosinophil level, IgE skin-prick test for detection of atopy, and tests for variability (reversibility, PEF charting and challenge tests)<sup>1</sup> if the results of spirometric evaluation are not clear. **A positive FeNO increases the probability of asthma but a negative test does not exclude a diagnosis of asthma.**

### Box 1: NICE guidance for the role of FeNO is the evaluation and diagnosis of asthma in children over 5 and adults<sup>6</sup>

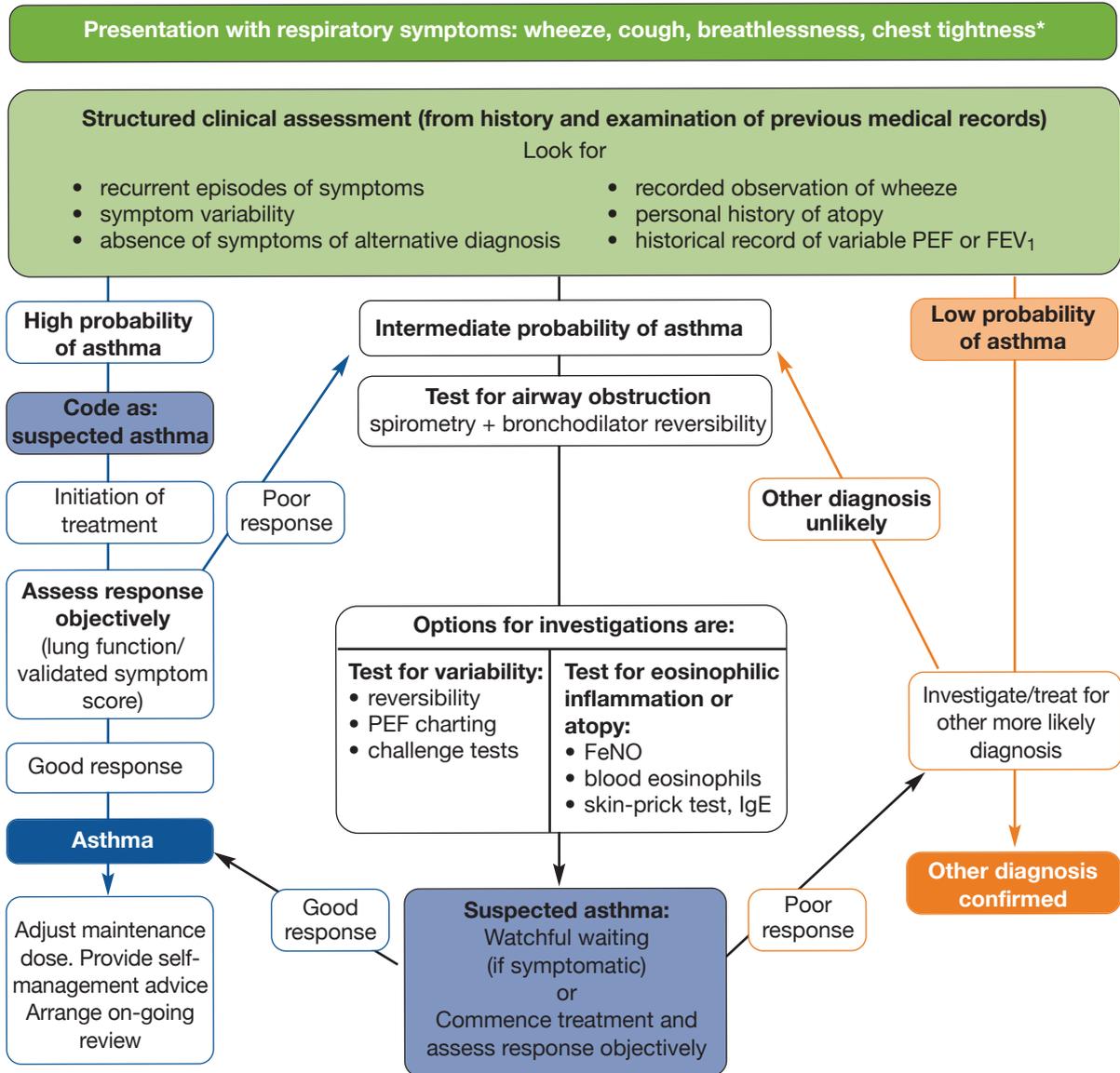
#### FeNO in the diagnosis of asthma in children

- Consider a FeNO test in children and young people (aged 5-16 years) if there is diagnostic uncertainty after initial assessment and they have either:
  - Normal spirometry or
  - Obstructive spirometry with a negative bronchodilator reversibility test. **Regard a FeNO level of  $\geq 35$  ppb as a positive test**
- Suspect asthma in children and young people (aged 5-16 years) if they have **symptoms suggestive of asthma** and:
  - A FeNO level  $\geq 35$  ppb with normal spirometry and negative peak flow variability or
  - A FeNO level  $\geq 35$  ppb with obstructive spirometry but negative bronchodilator reversibility and no variability in peak flow or
  - Normal spirometry, a FeNO level  $\leq 34$  ppb and a positive peak flow variability
- Diagnose asthma in children and young people (aged 5-16 years) if they have **symptoms suggestive of asthma** and:
  - A FeNO  $\geq 35$  ppb with normal spirometry and negative peak flow variability or
  - Obstructive spirometry and positive bronchodilator reversibility

#### FeNO in the diagnosis of asthma in adults

- Offer a FeNO test to adults (aged  $>17$  years) if a diagnosis of asthma is being considered. **Regard a FeNO level of  $\geq 40$  ppb as a positive test**
- Suspect asthma in adults (aged  $>17$ ) with **symptoms suggestive of asthma**, obstructive spirometry and:
  - Negative bronchodilator reversibility, and either a FeNO level  $\geq 40$  ppb, or a FeNO levels between 25 and 39 ppb and positive peak flow variability, or
  - Positive bronchodilator reversibility, a FeNO level between 25 and 39 ppb and negative peak flow variability
- Diagnose asthma in adults ( $>17$  years) if they have symptoms suggestive of asthma and:
  - A FeNO  $\geq 40$  ppb with either positive bronchodilator reversibility or positive peak flow variability or bronchial hyperreactivity or
  - A FeNO between 25 and 39 ppb and a positive bronchial challenge test or
  - Positive bronchodilator reversibility and positive peak flow variability irrespective of FeNO level

Box 2: The BTS/SIGN diagnostic algorithm for patients presenting with respiratory symptoms<sup>1</sup>



\* In children under 5 years and others unable to undertake spirometry in whom there is a high or intermediate probability of asthma, the options are monitored initiation of treatment or watchful waiting according to the assessed probability of asthma

**Benefits of FeNO testing as part of the diagnostic workup for asthma**

Reliance on physiologic measures of lung function is a point-in-time measure and as such if patients are asymptomatic on the day they attend for testing the results may be negative. A negative result may also be delivered if the test did not achieve optimal quality due to operational or patient factors. FeNO is an objective measure of eosinophilic lung inflammation which is likely to persist even in the absence of overt respiratory symptoms on a given day.<sup>7-9</sup>

At present, data on the cost-effectiveness of FeNO testing in the primary care setting is limited but early indications suggest this may be favourable.<sup>10</sup> Although an initial investment in equipment and training is required with ongoing consumable costs, there may be cost savings associated with correct diagnosis, reduced referrals to secondary care and reductions in emergency primary care and accident and emergency visits.<sup>11-14</sup>

While not currently recommended in clinical practice guidelines, evidence suggests FeNO testing may also be informative for the ongoing monitoring of patients with asthma with poor

## Box 3: Confounding factors that may result in an increased or decreased FeNO level<sup>1</sup>

### Confounding factors that may INCREASE FeNO levels

- FeNO levels may be higher than population norms in:
- Men, tall individuals and those consuming a diet high in nitrates
- FeNO levels may be elevated in:
- Patients with allergic rhinitis exposed to an allergen even in the absence of respiratory symptoms
  - Patients with active rhinovirus infection

### Confounding factors that may DECREASE FeNO levels

- FeNO levels may be lower than population norms in:
- Children (a lower reference range must be used)
- FeNO levels may be reduced in:
- Cigarette smokers
  - Patients recently treated with inhaled or oral corticosteroids

control, providing an objective measure of steroid responsiveness and providing an alert of persistent lung inflammation even in the absence of evidence of airway obstruction.<sup>9,15</sup> Changes in FeNO levels may be useful to guide step up and step down of anti-inflammatory medication and may prompt an evaluation of adherence and inhaler technique. Having an objective test result may facilitate opening up a conversation about adherence and inhaler technique that may be otherwise difficult to approach or forgotten.

### Challenges and limitations of FeNO testing

There is some overlap between FeNO levels among individuals with and without asthma.<sup>3</sup> An evaluation of the results of eight studies among adults within the secondary care setting suggested that around 1 in 5 individuals with a positive FeNO test will not have asthma (false positive) and around 1 in 5 people with a negative FeNO test will have asthma (false negatives).<sup>1</sup> Data are lacking for primary care populations. However, as a general rule, a FeNO level  $\geq 40$  ppb is regarded as positive in adults with a level of  $\geq 35$  ppb regarded as positive in children.<sup>1</sup>

A variety of factors not related to the pathology of asthma can result in increased and decreased levels of FeNO, confounding the utility of this test in supporting a diagnosis of asthma (Box 3).

Understanding these potentially confounding factors and the potential for false positive and false negative results is essential to the proper utilization of FeNO testing as part of the diagnostic workup of patients presenting with respiratory symptoms.

In the general practice setting cost may be a barrier to the routine use of FeNO testing as part of the work up of patients presenting with respiratory symptoms suggestive of asthma. The introduction of Primary Care Networks and new ways of working with larger populations offers opportunity in primary care beyond practice level. FeNO is not currently widely available in the UK and if this test is to be a required component of the diagnostic workup primary care networks will be required to invest in the

necessary equipment, training (usually provided by the manufacturer of the equipment required) and consumables or rely on referrals to secondary care. Routine FeNO testing for all patients with asthma may not be a practical approach for all primary care practices at this time. The NICE 2017 guideline recommends a FeNO test for all adults presenting with acute respiratory symptoms suggestive of asthma if equipment is available and if testing will not compromise treatment of the acute episode. However, treatment can be initiated for patients who are acutely unwell at presentation if waiting for objective tests may compromise treatment of the acute episode. Objective tests should then be carried out once the acute symptoms have been controlled. Referral to secondary care may be made in cases of diagnostic uncertainty. An alternative to investment in FeNO testing by individual primary care practices may be a locality-based approach whereby primary care practices in a given locality or Primary Care Network pool resources to invest in a FeNO testing service. This approach is currently being trialled in the UK.<sup>6,16</sup>

### Conclusions

FeNO testing is a quantitative, non-invasive, simple and safe test making it suitable for use in the primary care setting with appropriate training of health care professional with responsibility for delivering and interpreting the results.<sup>3</sup> The benefits to patients are that they do not need to be referred to secondary care for additional testing as a positive FeNO test alongside respiratory symptoms and lung function tests suggestive of asthma supports a diagnosis. However, concerns remain over the necessity for FeNO testing in every asthma diagnosis and its cost-effectiveness, and it has been suggested the FeNO testing is more appropriately placed in diagnostic centres within the community, intermediate or secondary care setting. Given the current limitations of extending FeNO testing to all patients presenting with symptoms suggestive of asthma, the current PCRS position aligns with the guidance issued by BTS/SIGN namely the use of

FeNO testing as an optional investigation to test for eosinophilic inflammation where there is diagnostic uncertainty.

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