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# Accepted Manuscript

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**Title page****Scottish consensus statement on the role of FeNO in adult asthma**

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#### **Author Contributions**

All of the authors who were present at the meeting had an input into writing the paper. Dr Kuo and Dr Lipworth wrote the first draft of the manuscript. Dr Kuo, Dr Lipworth, Dr Spears, Dr Haughney, Dr Smith, Dr Miller, Dr Bradshaw, Dr Murray and Dr Williamson were responsible for the review and final version the manuscript.

#### **Competing interests**

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**Abstract**

FeNO is the only available point of care test to assess type-2 inflammation in asthma. In making a diagnosis of asthma, FeNO should be used together with blood eosinophils and spirometry, alongside a history. Raised FeNO in conjunction with blood eosinophilia are treatable traits of type 2 inflammation in asthma, which in turn may guide personalised management. A FeNO suppression test can be used to assess adherence and device use with ICS therapy. Furthermore FeNO may be used to provide feedback to patients in response to ICS, especially when spirometry is normal. FeNO may facilitate appropriate referral to secondary care for more definitive specialist investigations. In summary, FeNO is cost effective in the diagnosis and management of asthma and should be incorporated into primary care as part of routine clinical practice.

## Introduction

Asthma is characterised by the presence of reversible airway obstruction and airway hyper-responsiveness (AHR) usually resulting from type-2 (T2) inflammation<sup>1</sup> (Figure 1). Assessment of asthma control is conventionally based on a combination of symptoms, exacerbations, reliever use and pulmonary function tests. However, in many patients these parameters are often disconnected from the underlying airway inflammatory process<sup>2</sup>. Optimising suppression of T2 inflammation by using sputum eosinophils to adjust the inhaled corticosteroid (ICS) dose has shown to reduce frequency of asthma exacerbation<sup>3</sup>. Indeed the same has been shown for suppression of AHR<sup>4,5</sup>. However, using induced sputum to guide treatment decisions is not feasible for routine clinical practice in either primary or secondary care. The fraction of exhaled breath nitric oxide (FeNO) is a well-recognised non-invasive point of care surrogate test for T2 airway inflammation<sup>6</sup>.

Although both FeNO and eosinophils are part of the T2 inflammatory cascade, the two biomarkers are regulated by different inflammatory pathways<sup>7-9</sup>. The activation of the T2 inflammatory cascade produces a variety of cytokines including interleukin-13 (IL-13) which in turn induces nitric oxide synthase in bronchial epithelium<sup>10</sup>. The FeNO level is related to bronchial eosinophilic inflammation<sup>11</sup> as well as to AHR<sup>12</sup>.

The purpose of the present article is to produce a brief Scottish consensus statement on the role and the utility of FeNO in adult asthma. This paper was prepared in collaboration after a meeting of all authors to discuss the relevant literature and way forwards on the role of FeNO testing, including in primary care, where its use has thus far been minimal.

### FeNO as an aide to asthma diagnosis

Asthma is a clinical diagnosis, supported where possible by evidence of reversible airflow obstruction and/or airway inflammation. As such FeNO alone cannot be used to diagnose asthma. Recent asthma guidelines incorporated FeNO ( $\geq 40$ ppb) as a starting for the diagnostic algorithm, in conjunction with a

comprehensive clinical history suggestive of asthma as well as evidence of airflow obstruction ideally using spirometry<sup>13</sup>, or where this is not available in primary care using peak expiratory flow. However, elevated FeNO levels may be especially useful at ruling in asthma in patients with a suggestive history who have normal spirometry and no bronchodilator response, as reversibility testing with salbutamol is only informative in patients with an abnormal FEV1 where there is room for improvement. Hence measuring airway calibre using spirometry and T2 inflammation using FeNO could be viewed as being relatively disconnected. Pointedly, FeNO has a higher sensitivity and specificity than measuring airway calibre using the specialist test impulse oscillometry in distinguishing preschool children with probable asthma<sup>14</sup>. The presence of blood eosinophilia (>300 cells/ $\mu$ l) may be used to identify activity of T2 inflammation, although it may be normal in patients with raised sputum eosinophils. While FeNO alone provides sufficient accuracy for detecting T2 inflammation, the combination of FeNO and blood eosinophils further improves the strength of identifying T2 related inflammation in asthma<sup>15</sup>. By the same token a normal FeNO level in a patient who has stopped pre-existing ICS may be useful for undiagnosing asthma, especially when a normal value is obtained in conjunction with a negative bronchial challenge test<sup>16</sup>.

FeNO has a steep dose response curve to budesonide reaching a plateau effect beyond 400 $\mu$ g<sup>17</sup>. On the other hand, eosinophilic cationic protein (ECP) a marker of eosinophil activation, reaches a plateau at 800 $\mu$ g, while AHR requires 1600 $\mu$ g to achieve maximal suppression. Lung function measurement with spirometry (FEV1) is rather distant from the underlying T2 inflammation with no further improvement above 400 $\mu$ g of budesonide<sup>17</sup>. Therefore, FeNO stands out as the only available non-invasive point of care test that is able to provide an objective assessment of airway inflammation in asthma.

It is also important to consider the patient's smoking status when interpreting the results as this can suppress FeNO levels<sup>18</sup>. FeNO levels can be elevated for other reasons such as concomitant allergic rhinitis<sup>19</sup> and nasal polyposis<sup>20</sup>. For these reasons, FeNO should be used in conjunction with blood



eosinophils and spirometry, alongside a history suggesting asthma. We suggest pragmatic cut off values for FeNO of >40ppb and >25ppb to support a diagnosis of asthma in adult patients who are ICS naïve or taking ICS respectively.

### **FeNO to guide ICS treatment and assess adherence**

ICS are the mainstay of treatment for the T2 inflammatory component of persistent asthma. A better understanding of T2 inflammation has helped clinicians to personalise asthma treatment, which in turn results in improved symptoms, exacerbations and asthma control over and above standard of care. Anderson *et al.*<sup>21</sup> demonstrated rapid improvements in FeNO with near maximal suppression after 7 days on fluticasone propionate 100µg/day in steroid-naïve patients. It also took approximately 5 days to wash out the effect of ICS, with FeNO returning to baseline after this point. As well as producing dose related suppression of FeNO with ICS, the asthma control questionnaire (ACQ) score showed significant improvements exceeding the minimal clinically important difference of 0.5 with mean absolute values in keeping with optimal control (<0.75)<sup>21</sup>. In regards to T2 inflammation, a medium dose of ICS suppresses both FeNO and blood eosinophils respectively as well as improving AHR<sup>22,23</sup>. Hence, elevated FeNO may be useful to rule in asthma in patients who have stopped their pre-existing ICS.

Following a month of treatment, fluticasone propionate 200µg/day produced 45% FeNO suppression from baseline in moderate persistent asthma, and a 77% reduction in sputum eosinophils, although the variability was much higher with the latter<sup>24</sup>. In regards to the effect of medium dose ICS treatment in ICS naïve patients, the improvement in ACQ was significant and almost clinically relevant, with mean change of 0.49 in patients who had a high FeNO (≥50 ppb) at baseline<sup>25</sup>. As a result of these findings and other work a recent meta-analysis<sup>26</sup> concluded that exacerbations were reduced by 40% in patients where FeNO was incorporated into asthma management when compared to standard care.

Non-adherence to ICS treatment is a common contributing factor to poor asthma control. FeNO has a role in monitoring response to ICS and provides an objective clinical point of care test to identify non-

adherence. McNichol *et al.*<sup>27</sup> showed a relatively greater reduction in FeNO in non-adherent patients following 7 days of directly observed ICS treatment, as compared to a group of known adherent patients. A further study from the same group in severe uncontrolled asthma patients using the combination of remote FeNO and electronic inhaler monitoring showed that suppression of FeNO was similar after 1 and 4 weeks of ICS treatment, with concomitant suppression of blood eosinophils and improvements in FEV1 and ACQ<sup>28</sup>. This 'FeNO suppression test' can be therefore used to monitor the adherence to ICS, perhaps by bringing patients back to the clinic at regular intervals after educational input perhaps along with electronic inhaler monitoring. Moreover, the FeNO suppression test might be useful to identify non adherent patients on high dose ICS/LABA before considering expensive treatment with biologics.

#### **FeNO and biologic therapy**

With increasing use of biologic therapy in asthma we believe it is important for primary care physicians to have a basic understanding of the potential role of FeNO in the management of severe asthma. Current asthma guidelines advocate that biologic agents should be considered for poorly controlled frequently exacerbating patients including those who require maintenance oral corticosteroids<sup>29-31</sup>. Thus it is important to consider which biomarkers can be employed to target T2 inflammation with appropriate biologics including anti-IgE (omalizumab), anti-IL 5 (mepolizumab, reslizumab or benralizumab) or anti-IL4/13 (dupilumab). In other words can biomarkers including FeNO be used to personalise biologic therapy. A key point to bear in mind is that FeNO is mediated by IL-13 signalling while eosinophils are mediated by IL-5.

The EXTRA study<sup>32</sup> evaluated the additional benefit of omalizumab in reducing future asthma exacerbations in uncontrolled severe persistent allergic asthma despite treatment with ICS/LABA. Use of omalizumab was associated with 25% relative overall reduction in asthma exacerbations compared to placebo<sup>32</sup>. A pre-specified post hoc analysis showed that a greater reduction in asthma exacerbations

was seen in the high FeNO group (>19.5 ppb) with a mean reduction of 53% compared to 16% in the low FeNO group (<19.5ppb)<sup>32</sup>. Therefore, use of FeNO may help to identify the patients who are likely to benefit most from treatment with omalizumab.

Mepolizumab which blocks IL-5 signalling reduces exacerbations compared to placebo in patients with severe eosinophilic asthma despite there being no concomitant effect on FeNO, in keeping with the known effects of IL-5 on eosinophils but not FeNO<sup>33</sup>.

Dupilumab acts by blocking the IL-4 receptor  $\alpha$  and hence inhibits signalling of both IL-4 and IL-13, which are key drivers of T2 inflammation. Dupilumab was found to optimally reduce exacerbations and improve FEV1 in patients who exhibited both FeNO>25ppb and blood eosinophils > 150 cell/ul<sup>34</sup>. Furthermore, dupilumab produced significant reductions in FeNO levels on top of pre-existing medium to high dose ICS, in keeping with the known effects of IL-13 on FeNO. Therefore, FeNO is a reliable T2 biomarker for predicting improvements in airway calibre and reduction in asthma exacerbation mediated by blocking IL-4/13. In another study in oral corticosteroid dependent severe asthma, FeNO was significantly reduced even in association with tapering down the dose of oral glucocorticoid while patients were receiving dupilumab treatment comparing to placebo<sup>35</sup>.

A randomised placebo-controlled trial that evaluated the effect of anti-IL 13 therapy with tralokinumab<sup>36</sup> showed significant reduction in FeNO despite there being no significant reduction on blood, bronchial mucosal or sputum eosinophils<sup>36</sup>. This again showed the disconnection between IL-13 mediated effects on FeNO and eosinophils.

### **Health economics of FeNO**

Asthma diagnosis based on FeNO measurement with NIOX MINO is less costly and more accurate than standard diagnostic methods. Utilising of FeNO measurement in asthma diagnosis cost £43 less per patient as compared with standard diagnostic tests such as spirometry<sup>37</sup>. This resulted in annual cost-

savings of £341 and 0.06 quality-adjusted life-years gained for patients with mild to severe asthma and £554 and 0.004 quality-adjusted life-years gained for those with moderate to severe asthma<sup>37</sup>. A primary care study showed that a FeNO driven strategy for asthma control achieves the highest probability of cost effectiveness in terms of willingness to pay to achieve a quality of life adjusted year<sup>38</sup>.

### **Conclusions (Box 1)**

FeNO is the only non-invasive point of care test to assess type 2 inflammation in asthma. FeNO appears to be a cost effective way of making an asthma diagnosis and in achieving better control with ICS therapy. FeNO and blood eosinophils should be used together as treatable traits of type 2 inflammation in asthma to guide informed management decisions on a personalised basis. The use of FeNO will continue to evolve in a primary care setting and will depend on availability and accessibility within different regions. A hub and spoke approach linking several practices with a FeNO machine might be a cost effective way forward for primary care to more widely adopt this test.

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### **Figure legend**

Schematic diagram showing the inter-relationship between type-2 (T2) biomarkers, lung function and asthma control.

**Box 1****Panel consensus on utility of FeNO**

In making a diagnosis of asthma, FeNO should be used in conjunction with blood eosinophils and spirometry, alongside a history suggesting asthma.

Raised FeNO in conjunction with blood eosinophilia should be regarded as treatable traits of type 2 inflammation in asthma, which in turn may be used to guide personalised management decisions.

ICS should be stopped for at least 1 week in order to obviate a false negative test for asthma when using FeNO.

We suggest pragmatic cut off values for FeNO of >40ppb and >25ppb to support a diagnosis of asthma in adult patients who are ICS naïve or taking ICS respectively.

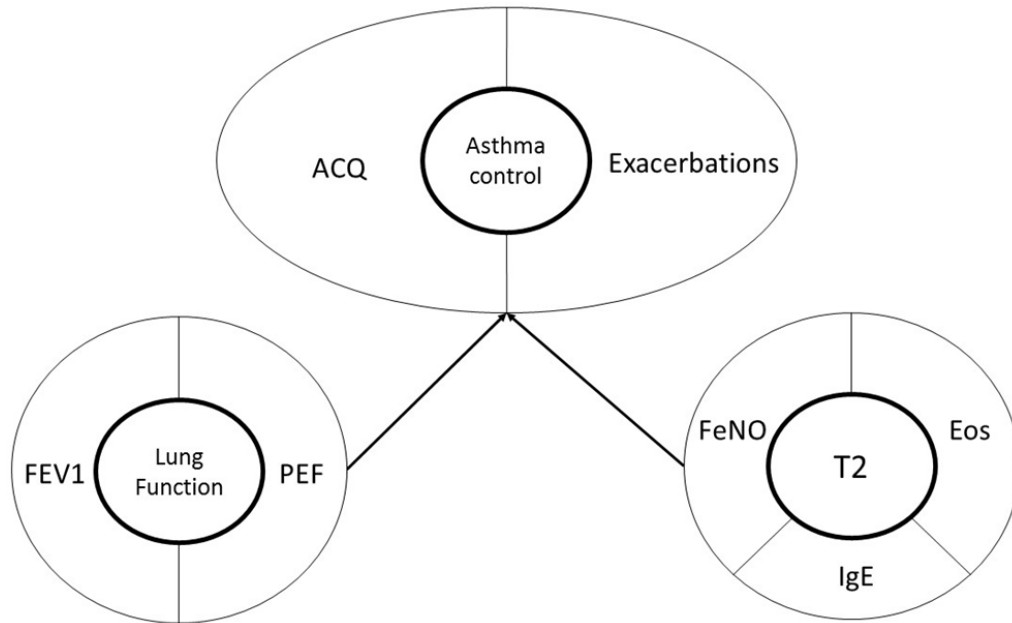
Serial FeNO measures, the so called FeNO suppression test, can be used to help assess adherence and device use with ICS therapy.

FeNO may be useful as a tool to provide feedback and reassurance to patients in response to ICS, especially in cases where spirometry is normal.

FeNO may be used to facilitate appropriate referral to secondary care for more definitive specialist investigations such as bronchial challenge testing.

FeNO is cost effective in the diagnosis and management of asthma and should be incorporated into primary care as part of routine clinical practice.

Figure 1



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**Highlights:**

- FeNO is the only available point of care test to assess type-2 inflammation in asthma
- Raised FeNO with blood eosinophilia should be regarded as treatable traits of type 2 inflammation

**Declaration of interests**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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