Key points

- For individuals aged ≥12 years, F_{ENO} is not recommended by all guidelines as a test to diagnose asthma (recommended only by the UK National Institute for Health and Care Excellence guideline for asthma symptoms, which are likely to respond to corticosteroid treatment).
- F_{ENO} may be used in conjunction with other investigations to diagnose asthma in 5–16-year-olds where there is diagnostic uncertainty, but further evidence is required.
- F_{ENO} is not recommended as a routine test to monitor all patients with asthma or to titrate asthma treatment.
- F_{ENO} is not recommended for routine clinical testing in adults with COPD.
- F_{ENO} may be useful to identify patients with COPD who could benefit from the use of inhaled corticosteroids (asthma–COPD overlap).

Educational aims

- To understand what factors other than asthma and COPD affect F_{ENO}
- To understand the current controversies in the application of F_{ENO} to diagnosis and management of asthma in children
- To understand the current controversies in the application of F_{ENO} to diagnosis and management of asthma and COPD in adults

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Review

Clinical utility of exhaled nitric oxide fraction in the management of asthma and COPD

Exhaled nitric oxide fraction (F_{ENO}) values can be easily measured using portable analysers and are a surrogate marker of airway eosinophilia. F_{ENO} may be useful in diagnosing and monitoring conditions characterised by airway eosinophilia, *i.e.* asthma and possibly COPD. Many factors other than asthma and COPD affect F_{ENO}, especially atopy, which is associated with elevated F_{ENO}. One guideline recommends that F_{ENO} should be used as part of the diagnostic pathway for asthma diagnosis in adults and children aged >5 years. The role of F_{ENO} in monitoring asthma is even less clear, and most guidelines do not recommend its use outside of specialist asthma clinics. Currently, F_{ENO} is not recommended for diagnosis or monitoring of COPD. Although F_{ENO} is starting to find a place in the management of asthma in children and adults, considerably more research is required before the potential of F_{ENO} as an objective measurement in asthma and COPD can be realised.

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30 years ago, it was realised that nitric oxide was protean and regulates almost every bodily function, including neuronal function important in laying down memories and regulating the tone of muscles in the walls of the coronary artery. Subsequent research into the role of nitric oxide in various diseases was associated with a rapid increase the nitric oxide literature [1]. Nitric oxide is produced by nitric oxide synthetase (NOS), which is a family of enzymes [1]. Briefly, NOS can be considered as having two isoforms: constitutive (cNOS), which constantly produces relatively small quantities of nitric oxide; and inducible (iNOS), which responds to various stimuli and is able to quickly produce large quantities of nitric oxide. iNOS is considered more important than cNOS to various diseases, including those of the respiratory system.

Why might exhaled nitric oxide fraction be a useful marker of respiratory disease?

In the respiratory tract, nitric oxide is produced by a variety of structural and inflammatory cells, including eosinophils, macrophages, epithelial cells and smooth muscle cells [2]. During inflammation, the concentration of nitric oxide increases in the lungs and nitric oxide can be measured in the exhaled breath as the exhaled nitric oxide fraction (F_{ENO}). Elevated F_{ENO} levels generally reflect eosinophilic airway inflammation [2] and patients likely to benefit from corticosteroids [2]; monitoring levels of eosinophilic airway inflammation using F_{ENO} as a noninvasive surrogate should theoretically aid clinical management [2, 3]. In the current era,

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in which we aspire to personalised medicine [4], F_{ENO} may be crucial to categorising asthma pheno/endotypes, although these is remain to be determined. This review explores the current thinking of how F_{ENO} should be applied in the respiratory clinical setting, and focuses on the potential role of F_{ENO} in diagnosing and monitoring asthma and COPD.

Currently, in the clinical setting, eosinophilia can be defined in blood, lower airway cells (from sputum or bronchoalveolar lavage) and F_{ENO} levels [5]. As recently highlighted, these measures do not always correlate in children, especially in young children [5]. In children with stable asthma, induced sputum eosinophil counts vary over time and have a variable relationship with F_{ENO} levels, with discordant values in 25% of paired sputum–F_{ENO} measurements [6]. Furthermore, induced sputum-based phenotypes [7] vary considerably in the same individual over time in mild–moderate and severe asthma in children. Nevertheless, measuring F_{ENO} levels is increasingly available and advocated. As it adds an additional cost of ~US$8.50 per test (which equates to ~US$17.00 per occasion, excluding the cost of labour) above current universal practice [2], evidence for its application in routine clinical practice requires evaluation.

How is F_{ENO} measured?

Nasal and exhaled breath nitric oxide can be measured using widely available nitric oxide analysers. Nasal nitric oxide is not used for asthma or COPD-related diagnosis or monitoring and hence, this article is restricted to F_{ENO}.

Like other lung function tests, standardised methods of measuring F_{ENO} need to be adhered to for reliable results [2]. The online test is simple, requiring the individual to exhale to reach an acceptable plateau with online visual feedback and tests are performed at least twice to achieve results within 10% of each other [2]. With the wide availability of portable F_{ENO} analysers, the offline method, where breath was collected in a bag and then, at a later stage, taken to a machine and analysed, is now not used in the clinical setting

F_{ENO} levels provided by nitric oxide analysers are not equivalent, with differences as large as 30% [8]. A study comparing F_{ENO} levels measured by NIOX VERO (Aerocrine AB, Solna, Sweden) described significantly lower values than that measured with the NOA280i (Sievers Instruments, Boulder, CO, USA), where the median values were 29 parts per billion (ppb) and 41 ppb respectively [8], *i.e.* the portable NIOX values were 30% lower than the standard chemiluminescence stationary electrochemical analyser; and between portable F_{ENO} analysers, there was variability among devices (limits of agreement is up to 10 ppb) [9]. Portable F_{ENO} analysers have cartridges which need changing after a preset number of measurements are made, and different cartridges can deliver slightly different F_{ENO} concentrations when the same patient uses the same analyser.

Factors other than asthma that affect F_{ENO}

F_{ENO} levels are affected by various external factors [2] (*e.g.* nitric oxide analyser variability, air pollutants, season and ambient nitric oxide). In addition to the external factors, clinicians need to be cognisant of the many factors that influence these levels above and beyond clinical disease when using and/or interpreting studies involving F_{ENO} and its levels in patients [10]. Atopy is an important factor that is associated with elevated F_{ENO} independent of asthma. Other factors include ethnicity, height, age, recent dietary intake, exercise and tobacco exposure. Inhaled corticosteroids (ICS) and leukotriene receptor antagonists both lower F_{ENO} [2]. Interestingly, age is the only factor that many guidelines suggest should be considered when interpreting F_{ENO} [2, 9].

Interpretation of F_{ENO}

F_{ENO} can be interpreted in at one of at least three ways:

- As a percentage of the predicted value for the population, but this is not a preferred method [2], in part due to a lack of data and in part due to the many factors (previously discussed) that may affect F_{ENO} independent of asthma.
- As a single "one-size fits all" cut-off value, and this is currently the preferred value [2] although there are some limitations to this including the low values in people with nonatopic asthma and individuals with values close to a single cut-off may find their treatment varies as F_{ENO} values fall just above or just below the threshold concentration.
- As a use percentage change from a previous value, and this may have merit for monitoring of asthma over time [2].

Currently, F_{ENO} results are classified as either normal, intermediate or abnormal positive for diagnostic of eosinophilic airway inflammation (note that this is not diagnostic of asthma). F_{ENO} values below the reference (cut-offs) indicate a likely absence of eosinophilic inflammation and a lower likelihood of response to corticosteroids [2]. Importantly, these statements are acknowledged to be based on low-quality evidence [2] and several guidelines interpret the available literature in different ways an recommend different cut-offs in adults and children [2, 9, 11, 12] (table 1).

Table 1 *A summary of the recommended F_{ENO} cut-off values for use in asthma diagnosis and management from international guidelines*

	Age range for children years	Healthy values ppb		Intermediate values ppb		Elevated values ppb		Recommended role of F_{ENO} in diagnosing asthma	Recommended role of F_{ENO} in diagnosing asthma
		Children	Adults	Children	Adults	Children	Adults		
ATS (2011) [2]	<12	<20	<25	20–35	25–50	>35	>50	F_{ENO} may be used to support the diagnosis of asthma in situations in which objective evidence is needed.	The use of F_{ENO} in monitoring airway inflammation in patients with asthma is recommended
National Institute for Health and Care Excellence (2017) [9]	5–16	Not stated	Not stated	Not stated	Not stated	>35	>40	Diagnose asthma if patients have symptoms suggestive of asthma, an elevated F_{ENO}, positive peak flow variability or obstructive spirometry, and positive bronchodilator reversibility	Do not routinely use F_{ENO} use to monitor asthma control
GINA (2019) [11]	6–11	Not stated	Not stated	Not stated	Not stated	>50	>50	F_{ENO} has not been established for ruling in or ruling out a diagnosis of asthma	F_{ENO}-guided treatment is not recommended for the general population There may be a role for F_{ENO} in a severe asthma clinic; cut-offs of 20, 25 and 50 ppb may have a role in stratifying treatment
British Thoracic Society/Scottish Intercollegiate Guidelines (2019) [12]	5–16					>35	>40	Use measurement of F_{ENO} (if available) to find evidence of eosinophilic inflammation A positive test increases the probability of asthma but a negative test does not exclude asthma	Except in specialist asthma clinics, the routine use of F_{ENO} testing to monitor asthma in adults or children is not recommended

Exhaled nitric oxide in childhood asthma

Feasibility

F_{ENO} can be measured using commercially available equipment in most children aged ≥6 years and values are reproducible over a 24-h period [13]. Unfortunately, at present, although the challenge of diagnosing asthma and the overall burden of asthma symptoms is in children aged 5 years and younger, F_{ENO} cannot be measured outside of research setting in this age group.

F_{ENO} and asthma diagnosis

Epidemiological papers published since 1997 [14] that have described elevated F_{ENO} in children with asthma compared individuals with established asthma to controls. Although these studies provided proof of the concept that F_{ENO} may be useful in diagnosing asthma, they do not provide valid cut-off F_{ENO} values for asthma diagnosis. Comparing differences in F_{ENO} between groups who have "typical" asthma and controls does not help in the clinical encounter with a child who may have asthma. The absence of a gold standard diagnostic test for asthma also gives researchers a challenge in establishing the role of F_{ENO} in diagnosing asthma.

There have been at least four studies that measured F_{ENO} in children being considered for a diagnosis of asthma as part of observational, "real-life" asthma diagnosis programmes in hospital clinics [15–18]. These studies identified F_{ENO} cut offs of between 16 and 22 ppb as having the best combination of sensitivity and specificity for a later asthma diagnosis. An important confounder for interpreting F_{ENO} in the context of asthma diagnosis is prior asthma treatment since both ICS [19] and leukotriene receptor antagonists [20] reduce F_{ENO} by up to one third. The study with the highest cut-off was the only one to include only steroid-naïve children [16], whereas other studies included 11% [18] to 33% [15] on ICS or children who had their ICS withheld for 4 weeks [17].

As previously described, there is uncertainty about which precise cut-off value should be applied to asthma diagnosis in children but despite their limitations, these four studies would support a cut off value of 15–20 ppb for diagnosing asthma. A key question for clinicians to consider after having taken a history and then measuring F_{ENO} is whether they believe an asthma diagnosis is likely or not; if the history suggests that asthma is likely then a F_{ENO} value >15 ppb could be supportive of a diagnosis and if asthma seems unlikely, then a F_{ENO} value <20 ppb would be helpful in excluding an asthma diagnosis. Two European Respiratory Society task forces are currently exploring, from different perspectives, the role of F_{ENO} in diagnosing childhood asthma and, collectively, will bring more clarity to clinicians in this area.

F_{ENO} and monitoring childhood asthma

In principle, F_{ENO} offers everything that an objective test should have for monitoring asthma in children since it has the following characteristics:

- sensitivity to symptoms
- sensitivity to treatment
- a known biomarker for airway eosinophilia
- reproducibility
- results are available almost immediately
- apparatus is portable and affordable

Not surprisingly, at least eight clinical trials [10] have evaluated the role of F_{ENO} in guiding treatment to reduce asthma exacerbations and improve asthma control. There were important differences between these trials in several aspects, as described elsewhere [10], summarised in table 2 and discussed here.

- Inclusion criteria: atopy is a key determinant of F_{ENO} and four trials selected only participants who were atopic; by including a mix of participants, it is not surprising that the results were heterogeneous.
- Primary outcomes: the primary outcome determines a study sample size, and such outcomes include exacerbations, control (as evidenced by a symptom score) and change in lung function; the presence of different primary outcomes makes it hard to directly compare results between studies.
- Population size: this varied between 47 and 546 with a median of 88 participants; many trials are likely to have been underpowered and reported false-negative findings.
- F_{ENO} values used to trigger treatment changes: the trials were published between 2005 and 2015, and during this decade, our understanding of F_{ENO} changed. It was increasingly recognised that F_{ENO} behaves differently to percentage of predicted forced expiratory volume in 1 s (FEV_1); for example, F_{ENO} is much more variable than FEV_1 % pred and worse asthma outcomes are associated with increasing F_{ENO} but falling FEV_1 % pred. The earlier studies used a single F_{ENO} value to trigger changes in treatment whereas some later studies had a "sliding scale" and used two or more values, and one had different values for nonatopic and atopic children. The pioneering trials may have been too simplistic when applying F_{ENO} to treatment.
- Inclusion of FEV_1: three trials used a cut-off of FEV_1 <80% pred to influence treatment decisions in addition to rising F_{ENO} values. This means that decision making in these trials was not solely influenced by F_{ENO}.

Table 2 *Characteristics of trials that have used F_{ENO} to guide treatment in children with asthma*

First author [ref.]	Primary outcome(s)	Mean age# years	Participants	Atopy as inclusion criterion?	FEV_1 <80% pred also used in treatment algorithm?	F_{ENO} cut-off(s) used ppb	What did the trial find? (F_{ENO} treatment compared to standard care)
Fritsch [21]	FEV_1	11.5	47	Yes	Yes	20	Higher midexpiratory flow, higher dose of ICS
Peirsman [22]	Symptom-free days	11	99	Yes	Yes	20	Reduced exacerbations, increased LTRA and ICS dose No difference in primary outcome
Petsky [23]	Exacerbations	10	63	No	No	10 for nonatopic, 12 with one PSPT, 20 for >1 PSPT	Reduced exacerbation, increased ICS dose
Pijnenburg [24]	Cumulative ICS dose	12	84	No	No	30	Reduced F_{ENO} and bronchial hyperresponsiveness No increase in ICS dose
Pike [25]	ICS dose and exacerbation frequency	11	90	No	No	≤15 and ≥25	No differences in outcomes
Szefler [26]	Days with asthma symptoms	14	546	Yes	Yes	20, 30 and 40	Reduced exacerbations, increased ICS dose No difference in primary outcome.
Verini [27]	Exacerbations, symptom score, treatment	12	64	No	No	12	Reduced exacerbations, improved symptom score, less asthma treatment
Voorend-van Bergen [28]	Proportion of symptom-free days	10	181¶	Yes	No	20 and 50	Increased asthma control but not the primary outcome

PSPT: positive skin-prick test; LTRA: leukotriene receptor antagonist. #: where mean age is given for children in separate arms of trial, an approximate overall mean age is given; ¶: not including 91 randomised to a web-based intervention.

- Treatment changes made: studies had different treatment steps triggered by different F_{ENO} cut-offs. Some studies only changed ICS dose and different dose changes were applied.

Despite these considerable differences, these trials collectively provide evidence that asthma treatment guided by F_{ENO} reduces the risk of asthma attacks [10, 29] and the mechanism for this might be due to an increased in ICS [10]. There is no evidence that asthma control (a primary outcome in many studies) was improved in these trials [29], and it is increasingly recognised that there are different factors driving asthma control compared to exacerbations [30]. Despite providing proof of the concept that F_{ENO} has a role in managing childhood asthma, the differences between the trials mean that there is considerable uncertainty as to how F_{ENO} can be applied to clinical practice.

The answer to question "when should F_{ENO} trigger a change in asthma treatment?" is still far from clear, and probably depends on whether the outcome is asthma control or exacerbations. A very cautious recommendation in the American Thoracic Society (ATS) guideline states "We suggest using the following values to determine a significant increase in F_{ENO}: greater than 20% for values over 50 ppb or more than 10 ppb for values lower than 50 ppb from one visit to the next" [2].

At present, F_{ENO} is considered a useful tool in diagnosing asthma in children (or symptoms that are responsive to treatment with corticosteroids) [2, 9]. In the absence of robust evidence that links a certain change in F_{ENO} to a certain change in treatment to an improved asthma outcome (exacerbation or control), F_{ENO} is not recommended for monitoring asthma in all children [9, 12]. Looking forward, the absence of evidence for the potential benefit of F_{ENO} to diagnose and monitor asthma needs to be addressed by our community. We are hopefully about to step into an era where objective measurements such as FEV1 and F_{ENO} are used to stratify treatment (perhaps alongside objective measurements of treatment adherence) with the goal of improving symptoms, reducing exacerbation and reducing treatment.

Exhaled nitric oxide in adult respiratory medicine

F_{ENO} in adults with asthma

The ATS guideline outlines potential uses for F_{ENO} in adults with asthma, including identifying eosinophilic airway inflammation, predicting responsiveness to ICS, monitoring airway inflammation and detecting nonadherence to ICS [2]. Since the publication of these guidelines in 2011, additional studies have shed further light on the utility of F_{ENO} testing in clinical practice.

Is F_{ENO} useful for the diagnosis of asthma in adults?

Asthma remains a clinical diagnosis in adults supported by evidence of variable airflow limitation, so supplementary testing may be useful for increasing the diagnostic probability of asthma in people who present with variable respiratory symptoms. In a systematic review of the use of F_{ENO} for the diagnosis of asthma in adults, F_{ENO} ≥40 ppb had a sensitivity of only 41% but a high specificity of 93%, with likelihood ratio for a positive test (high F_{ENO}) of 6.18 (95% CI 3.64–10.47) [31]. Overall, there was evidence for moderate accuracy for the diagnosis of asthma in adults (*i.e.* a high F_{ENO} can rule in asthma but may not be able to rule out asthma).

F_{ENO} and asthma phenotypes

Elevated F_{ENO} correlates with the presence of specific asthma phenotypes. Consequently, F_{ENO} testing may be useful to characterise treatable traits in asthma.

Sputum eosinophilia

Eosinophilic airway inflammation is an asthma phenotype that is more likely to be steroid responsive. Biomarkers to predict sputum eosinophilia were evaluated in a study of 336 adults with asthma in the Netherlands. The area under the curve for F_{ENO} was 0.82, compared with 0.83 for blood eosinophils and 0.69 for total serum IgE. Hence, F_{ENO} and blood eosinophils were similar in accuracy (and more accurate than IgE) for predicting sputum eosinophilia. Furthermore, in a prospective study of 144 adult patients with asthma in Denmark, high F_{ENO} (>50 ppb) had moderate positive predictive value (77%) for sputum eosinophilia of >3%, although one-third of patients with sputum eosinophilia >3% had intermediate F_{ENO} values (25–50 ppb) [32].

Cough-variant asthma

This asthma phenotype is represented by chronic cough, rather than wheeze or breathlessness, and often characterised by type 2 inflammation. F_{ENO} has moderate, but not high, accuracy for detection of cough-variant asthma.

Nonspecific respiratory symptoms

In primary care, patients may present with symptoms resembling asthma but not meet the clinical criteria for asthma and not have a previous diagnosis of asthma, presenting a diagnostic challenge. F_{ENO} could add to the diagnostic testing for these patients. In a randomised controlled trial (RCT) in the UK and Singapore, 517 patients with nonspecific respiratory symptoms, but without a prior history of asthma or bronchodilator reversibility, were randomised to inhaled beclomethasone *versus* placebo for 4 weeks [33]. In the per-protocol analysis (214 patients), those with a greater baseline F_{ENO} had a higher improvement in asthma symptoms when on inhaled steroids, compared to the placebo group, as well as reduced cough and improved FEV1. As a simple and noninvasive tool, F_{ENO} measurement may be helpful for clinical decision making in primary care about whether to trial an ICS in patients with asthma-like symptoms who do not initially meet bronchodilator reversibility and other criteria.

Is F_{ENO} useful for the management of asthma in adults?

Current asthma clinical guidelines recommend assessment and monitoring of symptoms, exacerbations and lung function tests to optimise asthma management in individual patients. Whether routinely adding measurements of type 2 inflammation is beneficial, beyond clinical and physiological assessment, is still a matter of intense debate.

A Cochrane systematic review examined the benefits of tailored asthma management using F_{ENO} levels for adults with asthma, compared with symptom- or guideline-based approaches [34]. Seven studies of 1700 patients were reviewed. Meta-analysis demonstrated a reduction in the number of patients with one or more exacerbations in the F_{ENO}-guided approach (OR 0.60, 95% CI 0.43–0.84; moderate quality of evidence), translating to a number needed to treat to benefit over 52 weeks of 12 (95% CI 8–32). In contrast, there were no differences in other outcomes such as rates of hospitalisation, symptom scores, F_{ENO} levels or ICS dose. The authors' conclusions were that widespread F_{ENO} use for adults with asthma could not be recommended; however, this approach may be useful in patients with more frequent exacerbations. Management based on sputum analysis of airway eosinophilia similarly reduces exacerbations but does not improve asthma control or spirometric measures.

Role of F_{ENO} in patients with severe asthma

F_{ENO} testing may have a useful role in severe asthma clinics, where additional asthma phenotyping is helpful for risk stratification and tailored management. In a study of 132 adults with severe allergic asthma in Italy, patients with $F_{ENO} \geq 30$ ppb had worse asthma symptoms and quality of life, and higher rates of hospital admission, than patients with $F_{ENO} < 30$ ppb [35].

Oral corticosteroid (OCS)-dependent patients with severe asthma require further treatment choices for better asthma control. The question arises as to how responsive biomarkers are in these patients, especially given chronic OCS use. F_{ENO} responds to a 7-day course of oral prednisolone, and then this and other biomarkers (blood eosinophils, periostin, interleukin (IL)-5 and IL-13) return to baseline by 1 month after an oral steroid burst.

F_{ENO} may be responsive to treatment with some biologic agents in severe asthma.

Omalizumab

In a subgroup analysis (n=394) of an RCT, patients receiving the anti-IgE monoclonal antibody omalizumab had a small reduction of F_{ENO} (mean change −4 ppb) compared to those receiving placebo [36], but reduction in exacerbation rates was much greater in the high-F_{ENO} group receiving omalizumab than in the low-F_{ENO} group [37]. F_{ENO} levels (high (≥25 ppb) *versus* low (<25 ppb)) do not appear to predict responders to omalizumab.

Mepolizumab

There was no statistically significant change in F_{ENO} with use of mepolizumab, an anti-IL-5 monoclonal antibody for severe eosinophilic asthma, despite a substantial reduction in blood eosinophil counts.

Lebrikizumab

Use of lebrikizumab, an anti-IL-13 monoclonal antibody, reduced F_{ENO} by 19% at week 12, compared to a reduction of 10% with placebo [38], consistent with the role of IL-13 in nitric oxide production in the airways.

Dupilumab

Dupilumab, an anti-IL-4 and anti-IL-13 monoclonal antibody, reduces F_{ENO}, compared to placebo, and a greater reduction in exacerbations occurs with baseline $F_{ENO} \geq 25$ than <25 ppb.

Clinical recommendations regarding F_{ENO} in adults with asthma

The 2017 UK National Institute for Health and Care Excellence guidelines for asthma recommend use of F_{ENO} testing in adults with asthma [9]. In contrast, the 2019 Global Strategy for Asthma Management and Prevention [11] from the Global Initiative for Asthma (GINA) does not currently recommend F_{ENO}-guided treatment for all adults with asthma. The GINA strategy notes that elevated F_{ENO} can be used to guide initiation of ICS in adults with asthma, but that ICS should not necessarily be withheld in patients with suspected asthma despite a low initial F_{ENO} measurement. The GINA strategy also suggests that F_{ENO} can be used in adult patients with moderate to severe asthma, in experienced severe asthma centres, as a potential biomarker to predict response to certain biologics.

Self-assessment questions

1) In adult patients with asthma, which one of the following statements is true?
   a. A low F_{ENO} level can rule out asthma.
   b. All adult patients with asthma and sputum eosinophilia have high F_{ENO} >50 ppb.
   c. All biologic agents for asthma significantly reduce F_{ENO} levels.
   d. F_{ENO} testing in adults with asthma leads to a reduction in rates of hospitalisation.
   e. Patients with nonspecific respiratory symptoms and high F_{ENO} may show clinical response to ICS.
2) In patients with COPD, for which of the following could F_{ENO} testing potentially be useful for?
   a. Detecting type I inflammation in COPD airways.
   b. Diagnosing severe emphysema.
   c. Diagnosing viral exacerbations.
   d. Identifying great likelihood of asthma–COPD overlap.
   e. Predicting response to long-acting bronchodilators.
3) Increased F_{ENO} levels occur in all the following situations except?
   a. Child with allergic rhinitis
   b. Post-exertion.
   c. Diagnosing respiratory viral exacerbations.
   d. During an infection.
   e. African Americans.
4) In children, for which of the following is F_{ENO} clinically useful?
   a. Screening for asthma
   b. Definitive diagnoses of asthma
   c. Predicting risk of future exacerbation
   d. Predicting airway obstruction
   e. Monitoring asthma in a small subset of children with asthma

Future developments

Further definition of the clinical utility of F_{ENO} in a range of mild, moderate and severe asthma phenotypes should be undertaken in large prospective studies. In addition, characterisation of interacting clinical and biological factors on F_{ENO} levels should be undertaken, including the role of the lung microbiome in influencing F_{ENO}. Comparative studies are needed to test novel molecular biomarkers such as sputum gene expression as predictors of asthma outcomes [39] compared to F_{ENO} and other inflammatory markers. Remote, web-based monitoring of suppression of F_{ENO} with ICS treatment may improve adherence issues in patients with severe asthma.

F_{ENO} in adults with COPD

Role of F_{ENO} in patients with COPD

Some patients with COPD may have type 2 inflammation, which increases during exacerbations. Furthermore, increased blood eosinophils may predict ICS-responsiveness in patients with COPD; hence, there has been some interest in using F_{ENO} to characterise COPD phenotypes.

COPD versus non-COPD controls

Patients with COPD may have a mildly elevated F_{ENO} compared to non-COPD, healthy controls.

Frequent exacerbators

F_{ENO} was used to predict frequency of exacerbations in 226 stable COPD patients in Spain. Patients with F_{ENO} consistently ≥20 ppb over a 12-month period had a greater risk of exacerbations [40].

Exacerbations

In a study of 163 patients during a COPD exacerbation, elevated F_{ENO} was associated with higher sputum and blood eosinophil levels, although the sensitivity and specificity of F_{ENO} were relatively low for sputum eosinophilia (sensitivity 65% and specificity 56% for sputum eosinophilia with F_{ENO} ≥17.5 ppb) [41].

Hospitalisations

In a cohort study of 50 patients hospitalised with a COPD exacerbation, patients with asthma–COPD overlap had higher F_{ENO} levels than other COPD phenotypes. F_{ENO} correlated with blood eosinophils at admission, but not when measured at discharge or stability [42].

Response to ICS treatment

A systematic review of five studies of 171 patients with COPD found a decrease in F_{ENO} in patients treated with ICS, predominantly in former smokers [43]. COPD patients with high F_{ENO} (defined as ≥25 ppb), when given ICS/long-acting β2-agonists, had the greatest reduction in F_{ENO} and largest improvement in COPD Assessment Test score, compared to those receiving long-acting muscarinic antagonists or low-F_{ENO} patients [44].

Asthma–COPD overlap

Patients with COPD may have features of asthma such bronchodilator reversibility and eosinophilia. In 80 patients with severe COPD (Global Initiative for Chronic Obstructive Lung Disease grade 4, group D) in Germany, 33% had F_{ENO} ≥22.5 ppb [45]. In a study of 121 patients with COPD in Japan, F_{ENO} was higher in patients with features of asthma–COPD overlap (median 24.5 ppb) than in patients with COPD (median 16.0 ppb) [46]. When combined with blood eosinophil count, a F_{ENO} level of ≥25 ppb, when combined with blood eosinophil count ≥250 per µL, had 96% specificity for asthma–COPD overlap.

Clinical recommendations regarding F_{ENO} in COPD

F_{ENO} testing is not routinely recommended in international or national clinical guidelines for patients with COPD alone. However, COPD patients may, at times, have some features of asthma, or some patients may have coexisting asthma and COPD (asthma–COPD overlap), when F_{ENO} may be more useful to identify a potential asthma component, as a treatable trait.

Future F_{ENO} research in adults and children

There is currently an absence of evidence for clinicians to confidently apply F_{ENO} into routine clinical practice. There are many chronic noncommunicable diseases where there is a "standalone" test for diagnosis and monitoring (*e.g.* blood pressure for hypertension and blood glucose for diabetes) but currently, F_{ENO} is not likely to be a standalone test for airway disease. Instead, F_{ENO} is likely to be part of an overall evaluation of symptoms and objective measurements for the diagnosis and stratification of treatment for airway disease.

Suggested answers

1) e.
2) d.
3) d.
4) e.

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Conflict of interest

S.W. Turner has received apparatus at no cost from Circassia (and formerly Aerocrine) for measuring nitric oxide in three research studies. A.B. Chang reports grants from National Health and Medical Research Council, Australia related to the submitted work (multiple grants relating to cough, bronchiectasis and PBB). Other grants and interests from GSK (member of a data monitoring committee relating to an unlicensed vaccine), Up to Date (author of sections on paediatric cough) and BMJ Evidence Centre (author of two chapters on paediatric asthma with monies received (to Institution)) are outside the submitted work. I.A. Yang has nothing to disclose.

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