THE SCIENTIFIC DATA BEHIND FENO TESTING

Lovemedical
Cardiopulmonary Diagnostics

FeNO by
NIOX®

FeNO is the ideal biomarker to assess airway inflammation[1]

FeNO stands for fractional exhaled nitric oxide and is used to accurately measure the level of inflammation in the airways.[1]
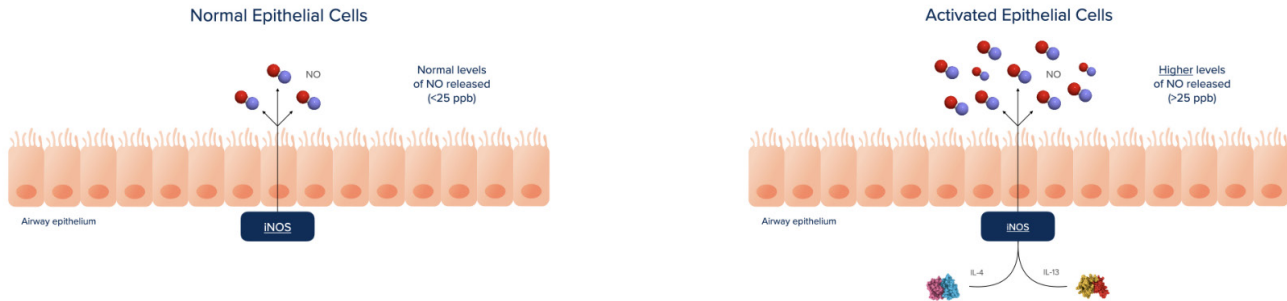
FeNO testing can help improve asthma patient outcomes in one quick test, right at the point-of-care.[2]
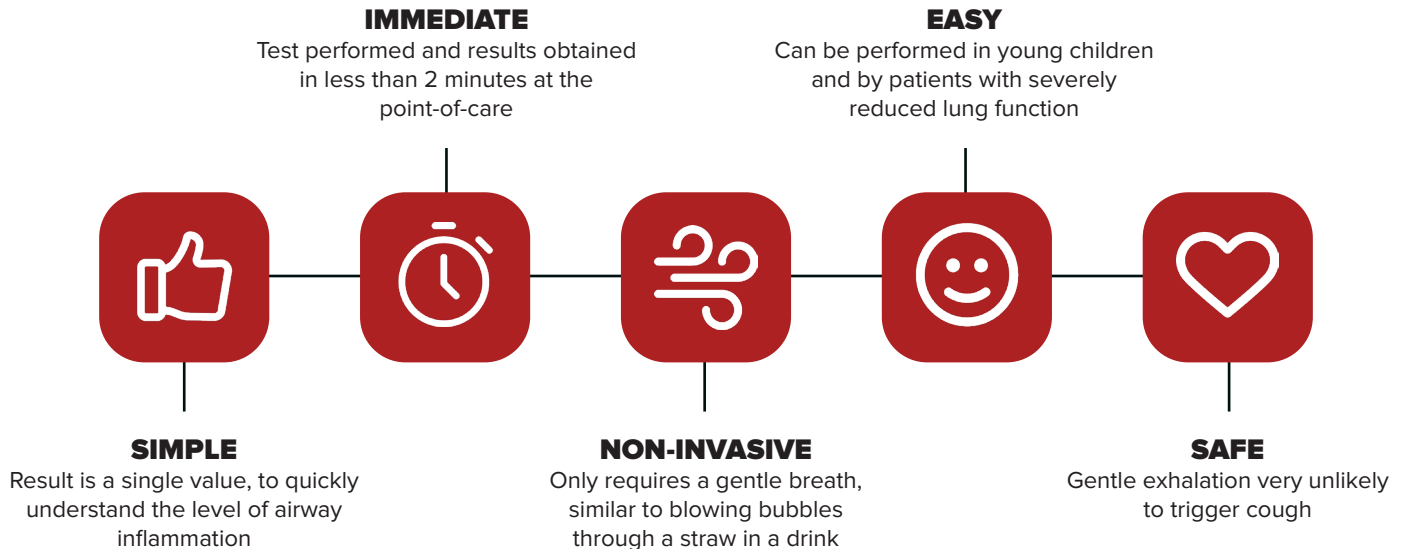
The science behind FeNO

Airway epithelial cells produce nitric oxide (NO). When Type 2 inflammation (the type of inflammation responsible for up to 93% of asthma cases[3]) is present in the airways, interleukins 4 and 13, or IL-4 and IL-13, upregulate the activity of the iNOS (inducible Nitric Oxide Synthase) enzyme, which produces NO in the airway.[4] Levels of exhaled NO are increased, giving healthcare professionals an objective measure of airway inflammation.[5]

In addition, FeNO levels are significantly reduced by corticosteroids, both inhaled (ICS) and oral (OCS), as corticosteroids act by suppressing a wide range of inflammatory pathways.[5]

Normal Epithelial Cells — NO — Normal levels of NO released (<25 ppb) — Airway epithelium — iNOS

Activated Epithelial Cells — NO — Higher levels of NO released (>25 ppb) — Airway epithelium — iNOS — IL-4 — IL-13

The most convenient biomarker of airway inflammation

FeNO testing may be performed by young children and in patients with severely reduced lung function.[6-7] Most national and international guidelines recommend FeNO testing to help achieve more accurate diagnoses and better asthma management.[2,8-12]

IMMEDIATE
Test performed and results obtained in less than 2 minutes at the point-of-care

EASY
Can be performed in young children and by patients with severely reduced lung function

SIMPLE
Result is a single value, to quickly understand the level of airway inflammation

NON-INVASIVE
Only requires a gentle breath, similar to blowing bubbles through a straw in a drink

SAFE
Gentle exhalation very unlikely to trigger cough

"FeNO brings us **one step closer** to the precision medicine we all talk about."

Dr Priya Ilangovan

More accurate diagnosis

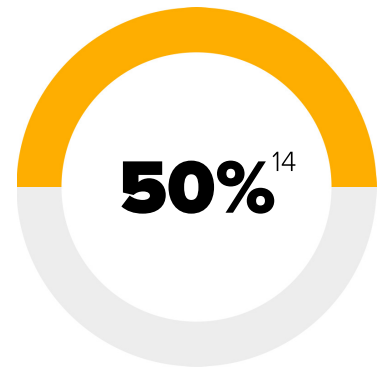Visualise the data behind FeNO for asthma diagnosis

UP TO
18% [7]
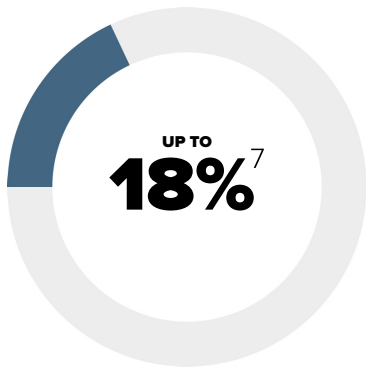
Prevalence
of asthma

33% [13]
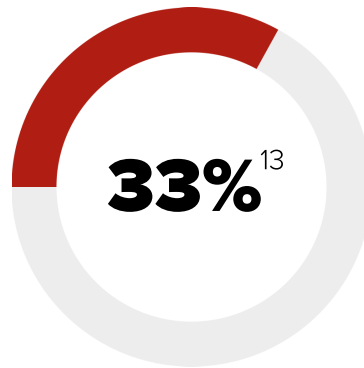
Overdiagnosis
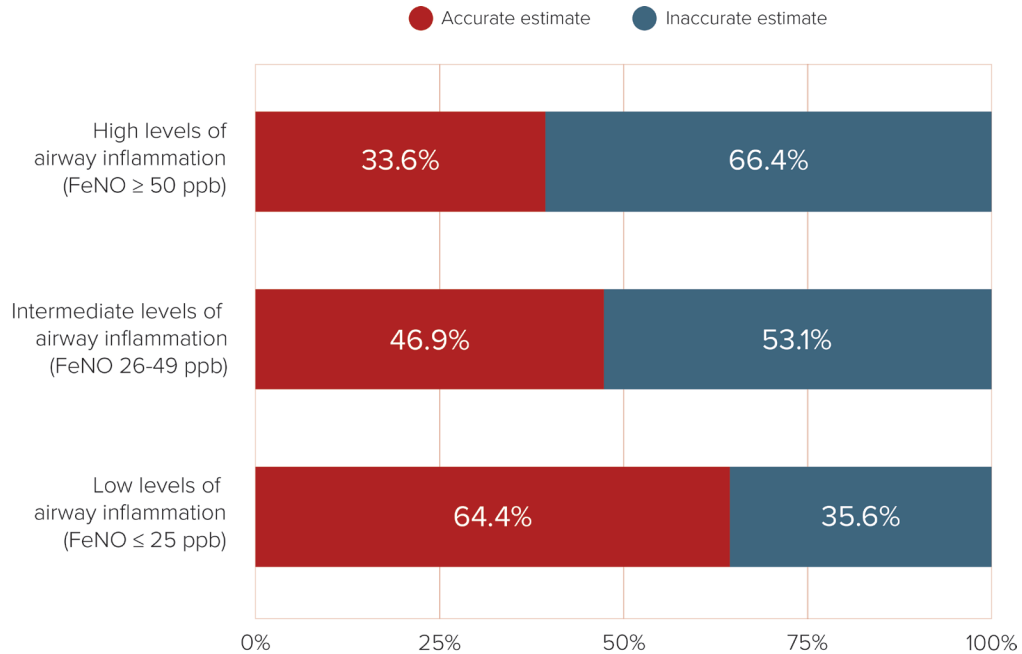(wrong diagnosis)

50% [14]

Underdiagnosis
(missed diagnosis)

The burden of misdiagnosis in asthma

Asthma has been recognised as an inflammatory condition for decades, but asthma diagnosis usually relies on clinical history and lung function tests. Airway obstruction and symptoms can vary over time and in intensity, and they may not be present at all, especially in mild asthma cases or in children.[7]

Misdiagnosis can have severe consequences, such as unnecessary treatment, inappropriate use of healthcare resources, poor quality of life, and an increased risk of exacerbations and mortality.[12]

Concordance between clinical assessment and actual levels of airway inflammation

Accurate estimate   Inaccurate estimate

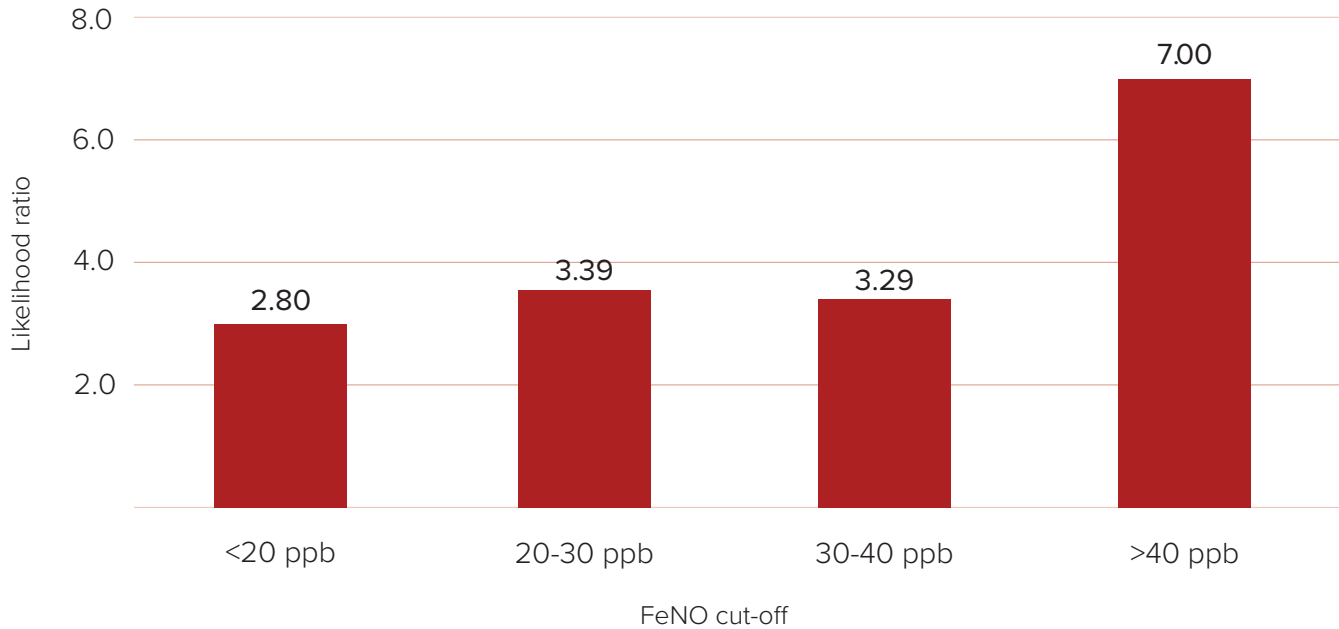|	Accurate estimate	Inaccurate estimate
High levels of airway inflammation (FeNO ≥ 50 ppb)	33.6%	66.4%
Intermediate levels of airway inflammation (FeNO 26-49 ppb)	46.9%	53.1%
Low levels of airway inflammation (FeNO ≤ 25 ppb)	64.4%	35.6%

0%   25%   50%   75%   100%

Airway inflammation should not be guessed

In a real-world study of 7,901 patients, physicians were asked to evaluate the level of airway inflammation in each individual using conventional methods. FeNO testing was then performed to assess accurate levels of airway inflammation.[15]

Clinical assessment was concordant with FeNO measurement in only 56% of cases, and in as little as 34% of cases for patients with high inflammation, showing that airway inflammation tends to be underestimated.[15]

> "The increased identification of patients with high levels of airway inflammation that is not apparent from clinical assessment or spirometry is a striking finding from this survey."[15]

Likelihood ratio for a positive asthma test

Bar chart showing Likelihood ratio (y-axis) versus FeNO cut-off (x-axis).

FeNO cut-off	Likelihood ratio
<20 ppb	2.80
20-30 ppb	3.39
30-40 ppb	3.29
>40 ppb	7.00

Adapted from:
Wang Z et al. Agency for Healthcare Research and Quality (AHRQ). The clinical utility of fractional exhaled nitric oxide (FeNO) in asthma management. Comparative Effectiveness Reviews, 197. 2017.

A diagnosis of asthma is 7x more likely when FeNO >40 ppb[16]

The Agency for Healthcare Research and Quality (AHRQ) in the US conducted a systematic review of 175 studies, with 43 of those studies addressing the diagnostic accuracy of FeNO measurement.

Statistical analysis of these 43 studies showed the higher the FeNO value, the more likely an asthma diagnosis, with odds ratios ranging from 2.8 to 7.0, depending on the cut-off point.[16]

> "Depending on the FeNO cut-off, the likelihood of having asthma in people aged 5 years and older increases from 2.8 to 7.0 times given a positive FeNO test result."[16]

FeNO measurements provide superior accuracy compared with the majority of other predictors[17]
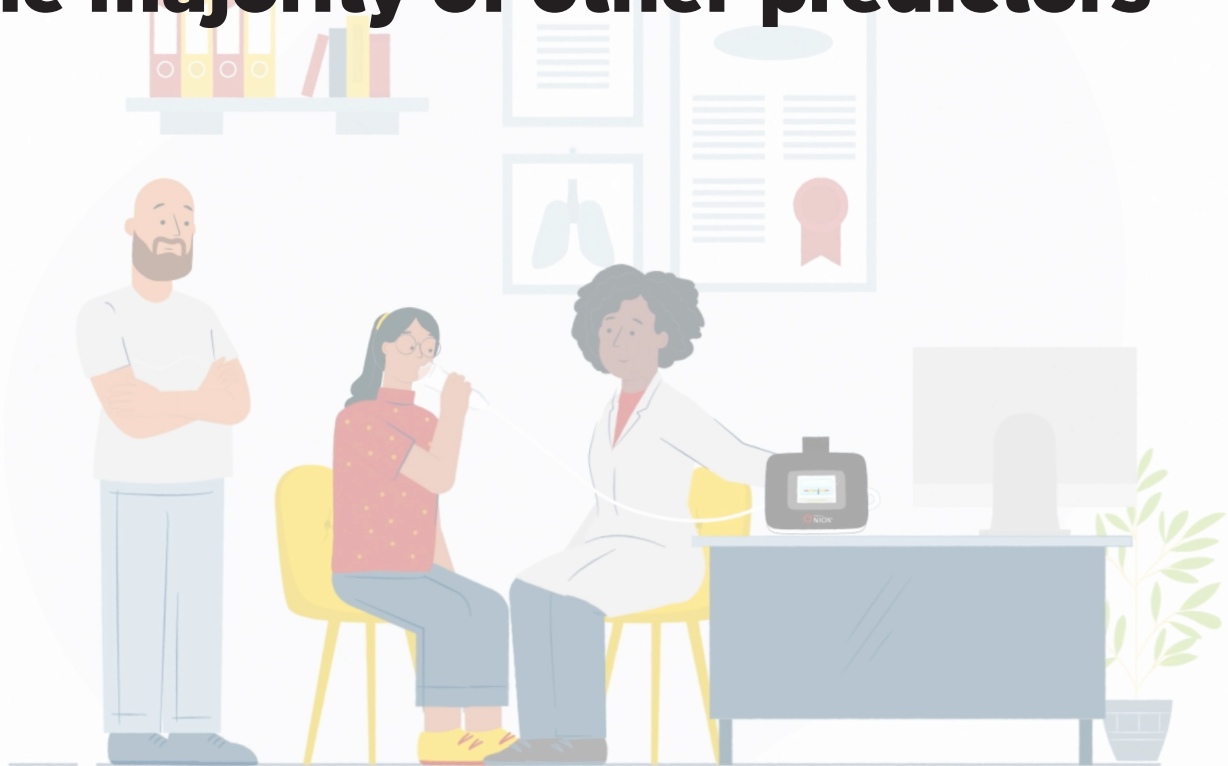
FeNO can predict ICS responsiveness better than lung function tests[17]

It is now widely recognised that FeNO levels forecast corticosteroid responsiveness. One study by Smith et al. compared the predictive accuracy of FeNO versus conventional tests (peak flow, spirometry, bronchodilator response, airway hyperresponsiveness). Steroid response was significantly greater in the high FeNO group, and predictive values for FeNO were significantly greater than almost all other baseline tests.[17]

> "Measuring FeNO is potentially very useful in this regard given that it correlates well with eosinophilic airway inflammation."[17]

Transform your asthma care with FeNO-guided asthma management

50%

Up to 50% fewer exacerbations with FeNO testing[18]

A Cochrane review included 16 trials in a meta-analysis to compare outcomes between a FeNO-based asthma management strategy and standard care. In both adults and children, the number of participants with exacerbations in the FeNO-guided management group was significantly lower. Interestingly, the number needed to treat to avoid one exacerbation over 52 weeks was 12 (95% CI 8-32) in adults and 9 (95% CI 6-15) in children.[18]

"Use of FENO to guide anti-inflammatory treatment within primary care significantly reduced the exacerbation rate and improved asthma symptom control."[19]

Exacerbation rate in subjects with ≤ 1 exacerbation

	Low FeNO (≤ 25ppb) / Low PBE	Medium FeNO (> 25 - < 50ppb) / Med PBE	High FeNO (≥ 50ppb) / High PBE
Estimated annualised exacerbation rate (95% CI)	**0.556** (0.353 - 0.877)	**1.138** (0.761 - 1.701)	**1.777** (1.245 - 2.536)
Risk ratio	n/a	**2.05**	**3.2**
P value	n/a	**0.0164**	**0.0008**

Adapted from:
Busse WW et al. Baseline FeNO as a prognostic biomarker for subsequent severe asthma exacerbations in patients with uncontrolled, moderate-to-severe asthma receiving placebo in the LIBERTY ASTHMA QUEST study: a post-hoc analysis. Lancet Respir Med. 2021;9(10):1165-1173.
PBE = peripheral blood eosinophil count

The risk of exacerbation is up to 3.2x greater with high FeNO levels[20]

A post-hoc analysis of a phase 3, double-blind study was recently conducted on 620 patients to assess the prognostic value of Type 2 biomarkers (FeNO and blood eosinophils) and exacerbation history for subsequent exacerbations. Results showed patients with higher baseline FeNO and/or eosinophils had a greater exacerbation rate, supporting the value of FeNO as a prognostic biomarker.[20]

> "FeNO provides important prognostic information on the risk of future severe exacerbations over and above that of blood eosinophil count, and independently of standard clinical baseline characteristics."[20]

1,000 people worldwide die from asthma every day[21]

2 in 3 deaths could be avoided with better asthma care[22]

Lung function decline is **2x** faster in patients with frequent exacerbations[23]

Reducing exacerbations is a priority

Uncontrolled asthma, defined by frequent exacerbations and/or poor symptom control, can have serious consequences for patients.[11]

Exacerbations can occur in all patients, even those with mild asthma, or whose asthma seems controlled. Modifiable risk factors for exacerbations include high inflammation levels, reduced lung function, poor adherence or high SABA usage.[7]

A tailored approach to managing personal risk factors is essential to improve patient outcomes.[8] FeNO testing has been proven to be a helpful tool when personalising asthma care for each individual.[18]
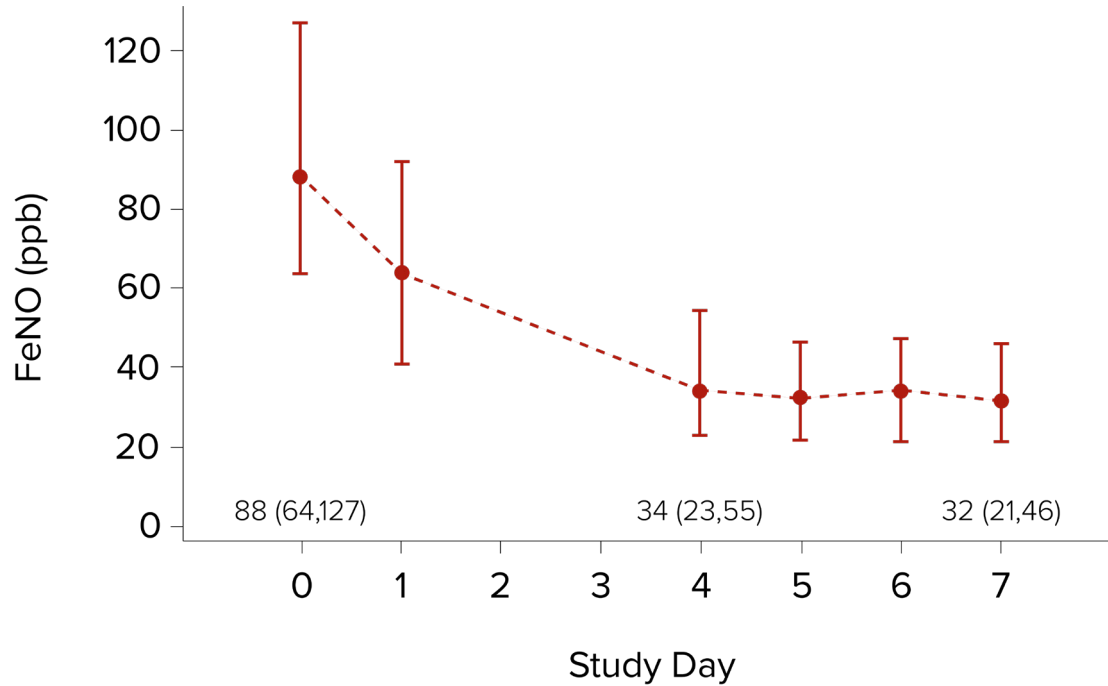
Mean dose of ICS
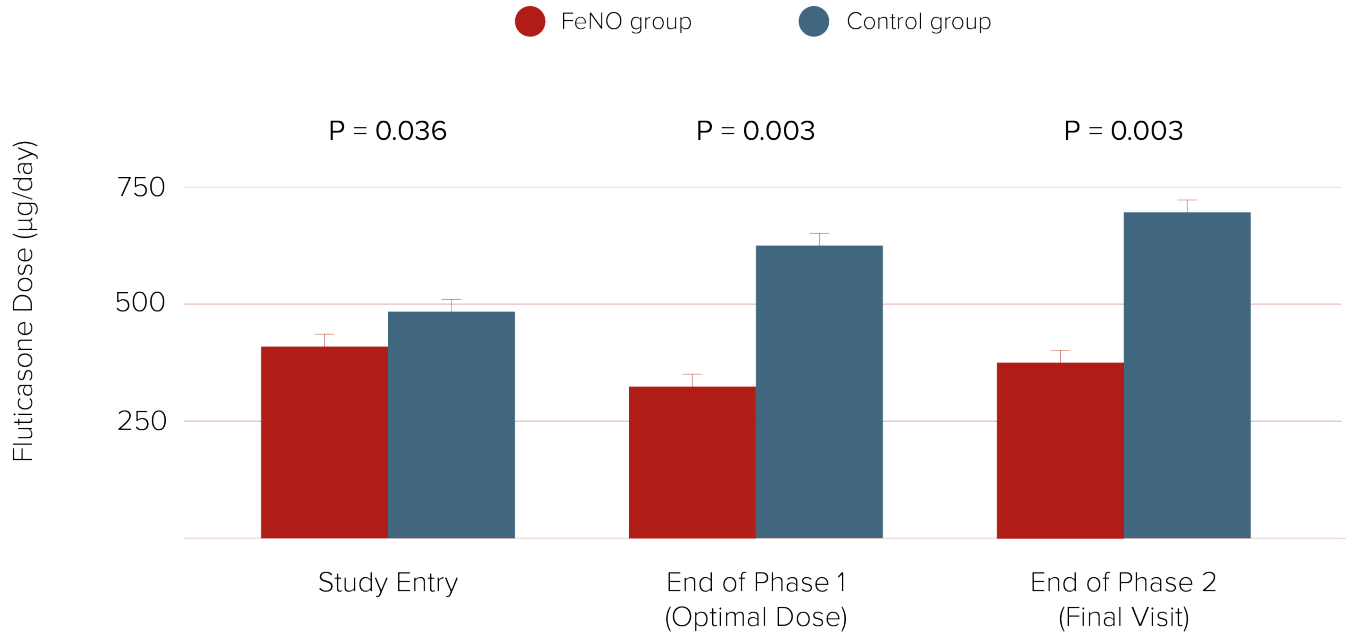
Adapted from:
Smith AD et al. Exhaled nitric oxide: a predictor of steroid response. Am J Respir Crit Care Med. 2005;172(4):453-9.

Optimising therapy

Studies have shown that performing FeNO testing directly alters treatment decisions, especially ICS titration.[15,24] In a single-blind, placebo-controlled trial, the optimal ICS dose was determined using FeNO testing and reviewed every two months: a cut-off of 35 ppb was applied to guide changes to dosage. Regular FeNO testing resulted in a 40% lower ICS dose (p=0.003) with no increase in exacerbations or prednisolone use.[24] Identifying the lowest effective ICS dose can help minimise the potential long-term side-effects associated with steroids, more likely when higher doses are used.[25]

"With the use of FeNO measurements, maintenance doses of inhaled corticosteroids may be significantly reduced without compromising asthma control."[25]

FeNO levels in subjects under directly observed ICS treatment over 7 days

Heaney LG et al. Medical Research Council UK Refractory Asthma Stratification Programme (RASP-UK). Remotely monitored therapy and nitric oxide suppression identifies nonadherence in severe asthma. Am J Respir Crit Care Med. 2019;199(4):454-464.

Uncovering non-adherence

Therapy adherence is notoriously low in asthma with up to 80% of patients not taking their medication as prescribed.[26] Those patients usually have higher FeNO levels, indicating a lack of control of airway inflammation due to missed doses of anti-inflammatory treatment.[27]

In a real-world study of 250 subjects, FeNO levels reduced by up to 50% in as little as four days, with maximal suppression seen after seven days, when patients had good adherence (defined as > 70% of doses appropriately taken). FeNO testing can therefore help identify patients who may either miss doses or have poor inhaler technique.[28]

"An attractive proposition is to move away from imperfect surrogate measures of adherence (eg, patient self-report, physician impression, prescription records) to using an ICS-responsive biomarker (FeNO)."[28]

Selecting the right
biologic

Tezepelumab (anti-TLSP)

Better response when FeNO is higher[7]

Dupilumab (anti-IL-4)

FeNO > 25 ppb[29]

Omalizumab (anti-IgE)

FeNO > 20 ppb[7]

FeNO testing helps select the most appropriate biologic in severe asthma[7]

Severe asthma is usually defined as uncontrolled asthma despite adherence to maximal therapy and affects up to 10% of asthmatics.[7] In the last few years, biologic treatments have been used as an effective means of improving asthma control and reducing exacerbations in severe asthma patients.[2,4]

Most biologics target Type 2 inflammation pathways. FeNO testing is recommended by GINA, ERS and ATS to assess the Type 2 phenotype and predict a good response to certain biologics.[7,29]

In addition, it has been shown that FeNO and blood eosinophil count have a cumulative value in phenotyping asthma. FeNO and blood eosinophils relate to different parts of the Type 2 inflammatory cascade and measuring both biomarkers could help sub-stratify Type 2 inflammation based on the predominant mechanism.[30]

The gold standard

Introducing NIOX VERO®, the gold standard FeNO device

Accurate. Reliable. Straightforward.

With millions of tests completed worldwide, NIOX® is trusted by thousands of healthcare professionals as the device of choice for clinical use and global research.[31]

FeNO testing with NIOX® is safe and easy to perform.[32] Patients simply inhale and exhale to produce a FeNO result. Performing a test is like blowing bubbles through a straw in a drink. Our three engaging visual and audio guides help patients achieve the perfect exhalation flow rate to ensure an accurate and reliable result every time.

NIOX® is suitable for patients as young as four.[33]

Behind the world's most used FeNO guidelines

FeNO levels are interpreted worldwide with cut-off points from American Thoracic Society (ATS) guidelines. Those cut-off points were derived from studies where 83% of patients used NIOX® technology to measure their FeNO levels.[5,31]

See how FeNO levels work with our interactive online interpretation tool

niox.com/interpreting-feno

Take action at the point-of-care

Quicker than making a cup of coffee, FeNO results with NIOX® are available in less than two minutes.

FeNO testing with NIOX® is a non-aerosol-generating procedure, making it ideal for year-round asthma diagnosis and management.[34]

Taking a FeNO test is as simple as inhaling and exhaling: no blood, sweat or tears required.

View NIOX® on your desk today via our augmented reality experience

niox.com/ar

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