Circassia White Paper

Evidence Supporting the Clinical Value of Measuring Exhaled Nitric Oxide (FeNO) in the Diagnosis and Management of Asthma

Circassia Pharmaceuticals Inc.

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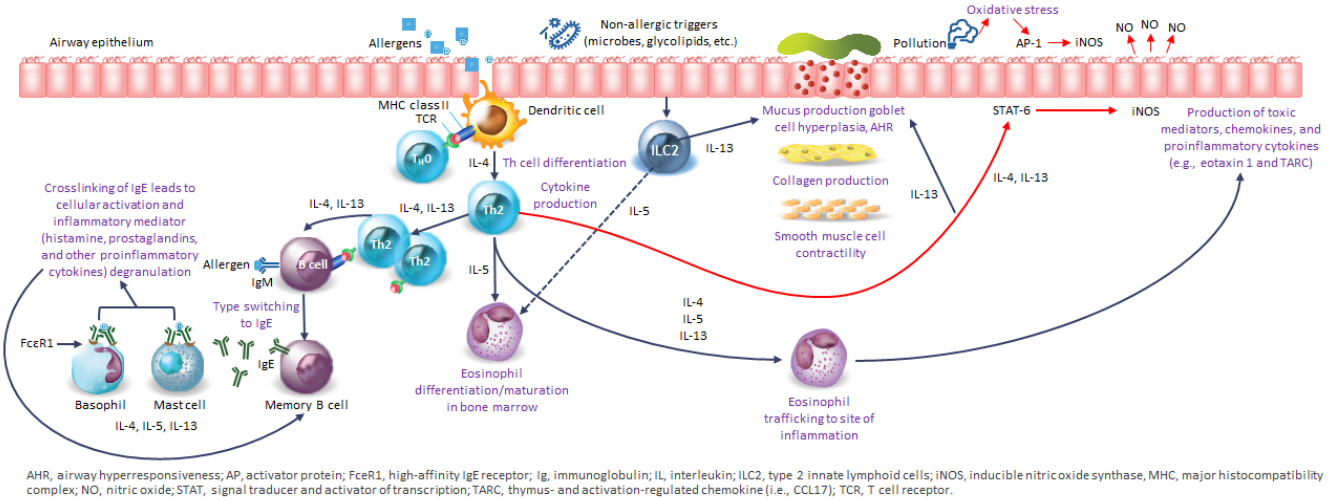
Executive Summary

This white paper summarizes Circassia's view of currently available peer-reviewed evidence of the clinical value of measuring and monitoring fractional exhaled nitric oxide (FeNO) to aid in the diagnosis and management of asthma. The clinical benefits of measuring and monitoring FeNO in asthma are increasingly recognized and FeNO monitoring is currently recommended by national asthma guidelines and international strategies, including the Global Strategy for Asthma Management and Prevention. Studies have demonstrated that clinicians will often alter their treatment strategy when FeNO results are known. Measurement of FeNO can:

- Help identify asthma patients with T2 airway inflammation,
- Help identify asthma patients who may respond favorably to steroid therapy,
- Help optimize steroid therapy in asthma by identifying patients that may need to step up or step down in dosing,
- Help identify asthma patients who are non-compliant with steroid therapy,
- Help reduce the likelihood of exacerbations in patients at risk for future events (compared to traditional monitoring), and
- Help identify severe asthma patients who will benefit most from treatment with certain biologic agents (dupilumab and omalizumab), when use of these agents is deemed appropriate.

FeNO and NIOX® Device Technology

Type 1 and type 2 immune responses are regulated by subpopulations of CD4+ T cells known as T helper 1 (Th1) and Th2 cells, respectively. Th1 cells secrete interleukin (IL)-2, interferon-γ, lymphotoxin-α, and stimulate type-1 immunity characterized by phagocytic activity, while Th2 cells secrete IL-4, IL-5, IL-13, and stimulate type-2 (T2) immunity characterized by high antibody titers and elevated eosinophil production (Fahy 2015, Godar 2018). Airway T2 immune responses are associated with atopic diseases such as allergy and asthma and are mediated by eosinophils, mast cells, basophils, Th2 cells, group-2 innate lymphoid cells (ILC2s) and IgE-producing B-cells (Figure 1) (Fahy 2015, Godar 2018).



AHR, airway hyperresponsiveness; AP, activator protein; FceR1, high-affinity IgE receptor; Ig, immunoglobulin; IL, interleukin; ILC2, type 2 innate lymphoid cells; iNOS, inducible nitric oxide synthase, MHC, major histocompatibility complex; NO, nitric oxide; STAT, signal traducer and activator of transcription; TARC, thymus- and activation-regulated chemokine (i.e., CCL17); TCR, T cell receptor.

Figure 1: T2 inflammation in asthma

Today FeNO is a well-established, validated, and specific biomarker for T2-driven airway inflammation in asthma, that is supported by almost 30 years of research. Scientists at the Karolinska Institute in Stockholm first discovered that nitric oxide (NO) is exhaled from human lungs in 1991 (Gustafsson

1991). Shortly thereafter, the role of exhaled NO in airway inflammation and asthma pathophysiology was described (Kharitonov 1996, Lundberg 1996). Airway inflammation is driven by the activation of antigen-specific Th2 cells that produce a variety of inflammatory cytokines. Of these inflammatory cytokines, IL-4 and IL-13 have been shown to induce gene transcription to produce the enzyme inducible nitric oxide synthase (iNOS) in the epithelial cells of the airway which then release NO in expired breath (Ekroos 2002, Chibana 2008, Fahy 2015, Godar 2018).

The first device for measuring FeNO was developed by the same innovative researchers at the Karolinska Institute and utilized a chemiluminescence-based methodology developed according to standardized specifications (Kharitonov 1997). The researchers formed the company Aerocrine to commercialize the device. The first Aerocrine NIOX® device was launched in Europe in 2000 and in the US in 2003. The chemiluminescence method is still considered the "gold standard" since it is the most sensitive and precise means for measuring FeNO; however, due to its complexity it was primarily used for research purposes.

A second-generation device that was easier and more convenient to use in the clinic (NIOX MINO®) was subsequently developed and launched in Europe in 2004 and in the US in 2008. NIOX MINO was the first device for measuring FeNO that could be performed at the point-of-care. This milestone allowed, physicians to utilize FeNO results at the time when treatment decisions are being made. Coinciding with the introduction of NIOX MINO, the first CPT code (*95012 Nitric oxide expired gas determination*) was assigned to support billing and reimbursement of FeNO assessments.

The third generation of the device (NIOX VERO®) was launched in 2013 (Europe) and 2014 (US) and offers significant advantages in terms of ease of use and portability. It provides results of a FeNO measurement in approximately one minute, following a 10-second exhalation (Maniscalco 2016). Aerocrine was acquired by Circassia in 2015 and further advancements to the NIOX VERO device are being planned. In addition to clinical use, NIOX VERO is currently utilized in clinical trials for registration of asthma treatments.

Guideline Recommendations for Clinical Use of FeNO Monitoring

Asthma management is influenced by guidelines that were initially created to emphasize the importance of treating the inflammatory nature of the disease to improve patient outcomes (NHLBI 1991). International and country-specific asthma strategies and guidelines now include recommendations for measuring FeNO (GINA 2019a, SIGN158 2019, Hong 2018, Buhl 2017, Plaza Moral 2016). The inclusion of FeNO is in response to mounting evidence supporting its role in the diagnosis and management of asthma. The first clinical guideline to include FeNO monitoring was published by the American Thoracic Society (ATS) in September 2011 (Dweik 2011). This guideline provided evidence-based recommendations for the use and interpretation of FeNO measurements in clinical practice and included many of the same reasons for measuring FeNO that are mentioned in the executive summary of this white paper. The ATS guideline was formally endorsed and supported by the American College of Allergy, Asthma and Immunology (ACAAI) and the American Academy of Allergy, Asthma and Immunology (AAAAI) in February 2012 (Zitt 2012).

Subsequent reports support the measurement of FeNO in asthma. The United States Department of Health and Human Services (HHS) Agency for Healthcare Research and Quality (AHRQ) published an extensive evidence-based review of FeNO that also supports its use in the diagnosis and management of asthma (Wang 2017). The National Institute for Health and Care Excellence (NICE) recommends FeNO to help diagnose and manage asthma in adults and children (NICE 2017). In 2019 the Global Initiative for Asthma (GINA) published its annual report with recommendations for FeNO measurements (GINA 2019a). GINA also includes recommendations for FeNO monitoring specific to treatment with biologics in the updated Pocket Guide for Difficult to Treat and Severe Asthma (GINA 2019b).

The Clinical Utility of FeNO in Diagnosing Asthma

FeNO Helps Identify Patients with T2 Airway Inflammation

Asthma is one of the most common chronic diseases, affecting over three hundred million people worldwide with an incidence of 8-10% across major countries (Mazurek 2018, Fletcher 2015). It is a disease of chronic airway inflammation characterized by variable and recurring airflow obstruction and symptoms. Airway inflammation plays a central role in the pathogenesis of asthma, leading to bronchoconstriction, bronchial hyperresponsiveness, and edema, which can manifest as symptoms of cough, wheezing, breathlessness, and chest tightness (NHLBI 1991, NHLBI 2007, GINA 2019a).

According to national and international guidelines, patients should be diagnosed with asthma using a variety of clinical tools including patient and family history, physical examination, symptoms, and lung function tests such as spirometry (NHLBI 2007, NICE 2017, GINA 2019a). While spirometry is considered a very important and objective clinical tool for supporting a diagnosis of asthma, its usefulness is limited to the measurement and interpretation of airflow limitation and lung capacity. None of the aforementioned tools directly measure the airway inflammation that defines our current understanding of asthma; however, the current ATS guideline strongly recommends use of FeNO in the diagnosis of asthma driven by T2 airway inflammation (Dweik 2011).

Incorporating biomarkers into the patient's clinical evaluation can uncover untreated airway inflammation and assist the clinician in properly classifying the patient's asthma and facilitating individualized drug therapy (Fajt 2015, Bush 2016, Pavord 2017). Though some consider evaluation of induced sputum eosinophils as the "gold standard" for detecting T2 airway inflammation, this test is difficult to perform, the experience can be uncomfortable for patients, results are not immediately available, and its use is mostly limited to specialized research centers.

FeNO measurement has been directly compared with other diagnostic procedures for asthma including induced sputum eosinophils, spirometry, and bronchial challenge testing. FeNO has high sensitivity and specificity and correlates well with induced sputum eosinophils (Sivan 2009) and bronchial challenge testing with a variety of stimuli (Smith 2004, Schleich 2012, Attanasi 2016). In a comparative meta-analysis of a variety of tests for diagnosing asthma (i.e., spirometry, bronchial challenge, and/or bronchial reversibility, FeNO), FeNO was found to have performed well to the extent that the authors considered whether FeNO might render bronchoprovocation testing superfluous (Karrasch 2017).

In addition, FeNO has been shown to be equivalent to peripheral blood eosinophils as a surrogate for predicting sputum eosinophils (Wagener 2015). While the combination of peripheral blood eosinophils and FeNO further improves the sensitivity and specificity of detecting airway inflammation to a minor degree (Westerhof 2015), FeNO alone provides sufficient accuracy of detecting T2 airway inflammation and is available for use at the point of care to assist in clinical decision-making (Wagener 2015).

In an analysis of 43 studies with a total of 13,747 patients, it was concluded that the likelihood of people 5 years of age and older having asthma increases by 2.8 to 7.0 times (depending on the FeNO level) with a positive FeNO test result (Wang 2017). Since FeNO testing is relatively inexpensive compared to other procedures (e.g., spirometry), it is not surprising that it was found to be cost-effective (Price 2009). However, use of FeNO alone in the diagnosis of asthma has been criticized since it is not a measure of airway obstruction. More recently FeNO has been evaluated as part of a diagnostic algorithm in adults (17 years of age and older) that incorporates the contribution of both airway inflammation and obstruction (Figure 2) (NICE 2017). Using the algorithm, the initial use of FeNO and spirometry (with bronchodilator reversibility testing) followed by other tests was shown to be the most accurate and cost-effective method for diagnosing asthma (NICE 2017).

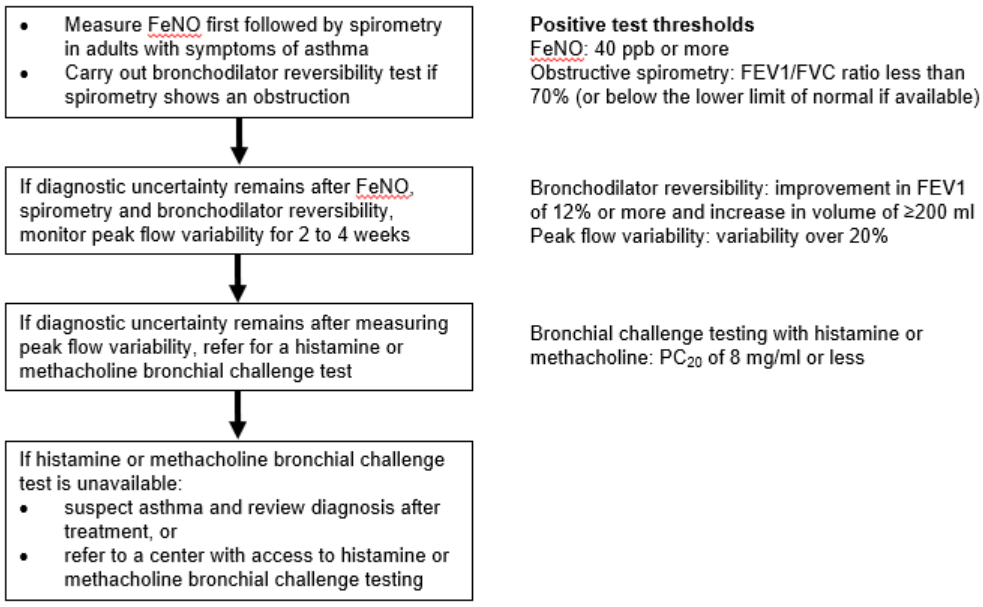


Figure 2: Recommended order of objective tests for diagnosing asthma (adapted from NICE 2017)

Implications for clinicians: Measuring FeNO can aid in the diagnosis of asthma by helping to identify patients with ongoing T2 airway inflammation. FeNO provides sufficient accuracy and is available for use at the point of care.

The Clinical Utility of FeNO in Managing Asthma

Asthma is typically variable in most patients and fluctuations in symptoms and airway inflammation are to be expected. This underscores the need for periodic re-assessment of patients and longitudinal monitoring of patient data, including biomarkers. The variability of clinical tools (e.g., patient questionnaires, spirometry, and bronchodilator reversibility) and biomarkers (e.g., FeNO, induced sputum for eosinophils and neutrophils) has been assessed over a 12-month period. Less variability was seen in measures of spirometry but moderate to high variability in other characteristics (e.g., bronchodilator reversibility, symptom scores and FeNO >35 parts per billion [ppb]). The authors concluded that higher variability was most likely related to seasonal variations in climate, allergen exposure, medication changes, and acute exacerbations, and emphasized the importance of longitudinal monitoring of indices that are more specific for T2 asthma inflammation (i.e., FeNO) (Silkoff 2016).

One of the first reports describing the value of longitudinal monitoring of FeNO was published by Jones et al. in 2001. This study demonstrated that the change in FeNO had a very high predictive value for loss of asthma control (80-90%) and correlated with changes in peak flow, forced expiratory volume in one second (FEV_1), and other clinical indices (Jones 2001). This report was followed by a landmark study published in the New England Journal of Medicine that compared patient monitoring with and without FeNO (Smith 2005a). This study demonstrated that FeNO monitoring significantly improves patient outcomes and helps optimize drug therapy (Smith 2005a). The importance of monitoring FeNO over time was further explored in a real-world investigation by Michils et al. These investigators found little benefit to a single FeNO measurement by itself, but when combined with serial assessments, the change in FeNO concentration provides the greatest predictive value for asthma control (Michils 2008).

The 2011 ATS guideline for FeNO monitoring defines specific thresholds of FeNO concentrations for helping clinicians to interpret the result (Dweik 2011). This is mainly for asthma patients who have not yet had a FeNO measurement. During treatment guided by FeNO monitoring, the ATS guidelines

provide direction on how to interpret the change in FeNO concentration over time. An increase in FeNO greater than 20% for values >50 ppb or more than 10 ppb for values <50 ppb from one visit to the next would indicate a significant change. A reduction of at least 20% for FeNO values >50 ppb or more than 10 ppb for values <50 ppb would indicate a significant response to anti-inflammatory therapy (Dweik 2011).

FeNO Helps Identify Patients Who May Respond Favorably to Steroids

Inhaled corticosteroid (ICS) therapy has been and continues to be the mainstay of asthma treatment since the first guidelines highlighted the importance of treating the inflammatory component of the disease (NHLBI 1991). More recently, the need for understanding the phenotype (observable characteristics) and endotype (pathophysiologic mechanism) of asthma has become important, since it helps clinicians individualize treatment. Patients with the T2-high endotype have increased airway inflammation associated with eosinophils, compared to the T2-low endotype that is associated with more neutrophilic or paucigranulocytic inflammation (Fajt 2015, Samitas 2017).

While the majority of asthma patients demonstrate T2 airway inflammation and respond to steroid treatment, a portion of patients have asthma that is not characteristic of T2 inflammation and thus respond to ICS to a much lesser degree. Up to 75% of steroid-naïve patients have primarily T2-driven asthma and respond to ICS (Bradding 2008). However, it has been reported that up to 45% of asthmatic patients do not benefit from ICS therapy (Spahn 2016). Measurement of FeNO can identify patients with T2-driven airway inflammation and help predict those that will respond to ICS therapy (Price 2013).

FeNO was used to evaluate ICS response in another study by Smith et al. (Smith 2005b). Patients presenting with nonspecific respiratory symptoms who were referred to a respiratory specialist for treatment were examined. Steroid response was evaluated in 52 patients using spirometry (i.e., FEV_1, peak flow, bronchodilator response), bronchial challenge, and FeNO. Baseline FeNO provided greater sensitivity and negative predictive values than each of the other predictors. More specifically, a baseline FeNO >47 ppb predicted steroid response better than any other test. Optimum predictive accuracy was provided using the cut point of 47 ppb (Smith 2005b).

A large study in primary care investigated FeNO for predicting response to ICS treatment in difficult to manage patients with undiagnosed, non-specific respiratory symptoms (Price 2018). In 294 patients, a higher baseline FeNO was associated with an increased likelihood of a positive response for Asthma Control Questionnaire score (ACQ7, a 7-item questionnaire on asthma control using a 7-point scale), severity of cough, FEV_1, and a global evaluation of treatment effectiveness. In addition, the baseline FeNO was a better predictor of clinical improvement in cough than peripheral blood eosinophils, and neither FEV_1 nor clinical opinion of asthma were associated with a response to ICS treatment (Price 2018).

Recent studies have also demonstrated response (or lack of response) to ICS in patients with mild asthma not currently receiving anti-inflammatory therapy and with low levels of T2 biomarkers. Use of T2 biomarkers, such as FeNO and eosinophils, can help clinicians determine the likelihood of patients responding to an initial trial of ICS. In a large NIH-funded trial of 295 adolescents and adults with mild persistent asthma randomized to mometasone or tiotropium according to sputum eosinophil count, those with increased FeNO and/or peripheral blood eosinophils were more likely to respond to mometasone than tiotropium (Lazarus 2019). Similar data were presented recently from a large study of 180 steroid-naive adults with suspected asthma who presented with a FeNO <27 ppb and were randomized to ICS or placebo. Responses to ICS and placebo were equivalent as measured by ACQ7 and spirometry (Sutherland 2019).

While other studies in children and adults have demonstrated that patients who initially present with an increased FeNO value will be more likely to have a positive response to ICS, patients who have a lower FeNO value are less likely to respond to ICS therapy (Price 2013, Lazarus 2019). Thus, FeNO measurement helps predict the likelihood of steroid responsiveness more consistently than spirometry, bronchodilator response, peak flow variation, or bronchial hyperresponsiveness to methacholine (Knuffman 2009, Szefler 2002).

Implications for clinicians: Measuring FeNO can aid in the management of asthma by helping to identify patients who may respond favorably to steroid therapy. In studies, FeNO was a better predictor of steroid responsiveness compared to spirometry, bronchodilator response, peak flow variation, and bronchial hyperresponsiveness.

FeNO Helps to Optimize the Dose of Inhaled Steroids

Current asthma guidelines recommend periodic clinical re-assessment of patients and adjustment of medications by either stepping-up or stepping-down therapy accordingly. (NHLBI 2007, NICE 2017, GINA 2019a, GINA 2019b). The benefit of periodically re-assessing airway inflammation using FeNO in chronic asthma was demonstrated in the landmark study by Smith et al. (Smith 2005a). Two groups of patients were evaluated: one used traditional monitoring (symptoms, spirometry, etc.) and the other included a FeNO-based approach. After 12 months, the dose of ICS (fluticasone) was 370 µg/day in the FeNO group and 641 µg/day in the traditional monitoring group (p=0.003). More importantly, asthma control was better in the FeNO group with 45.6% less exacerbations (not statistically significant; Figure 3) and a greater proportion achieving "total control" of their asthma. Exposure to high doses of ICS was also reduced in this study by using the FeNO-based strategy to step patients down (Figure 3). At the end of the study 48% of the standard care group were receiving 1,000 µg/day of fluticasone compared to just 20% in the FeNO group (Smith 2005a).

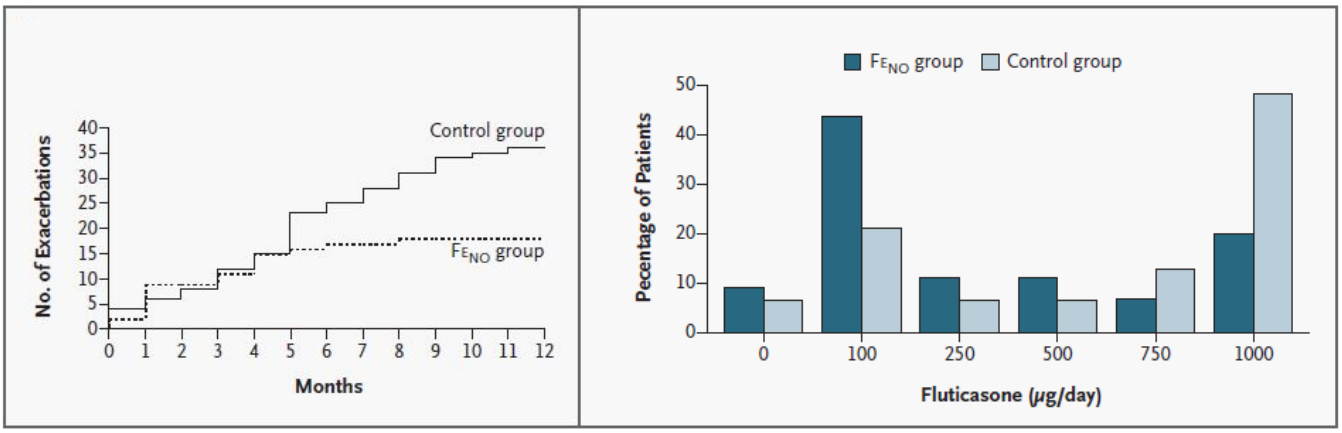


Figure 3: Left panel, cumulative number of exacerbations during ICS dose titration period (p=0.27 between groups); Right panel, distribution of ICS dose at end of study (p=0.008 between groups) (adapted from Smith 2005a)

The use of steroids in pediatric patients with asthma can be concerning to both clinicians and parents. Steroid withdrawal is sometimes difficult and can sometimes result in serious exacerbations if patients are not monitored carefully. One of the first studies to demonstrate the value of FeNO during withdrawal of steroid therapy was conducted in the Netherlands and published in 2005 (Pijnenburg 2005). Pijnenburg et al. studied 40 children during frequent visits over 24 weeks following discontinuation of ICS. An increased FeNO concentration 2 and 4 weeks after discontinuation of steroids was a predictor of asthma relapse, with an elevated measurement at 4 weeks having the best combination of sensitivity (71%) and specificity (93%) (Pijnenburg 2005). These results were recently substantiated by another study using similar methodology. Forty-two asymptomatic children with well-controlled asthma receiving low-dose ICS were evaluated following steroid withdrawal to assess loss of

asthma control (Chang 2019). FeNO together with the Asthma Control Test (ACT) and spirometry were used to assess asthma control. Increased FeNO, but not FEV_1, was significantly associated with increased odds for loss of asthma control (Chang 2019).

Historically, the dose-response curve for the clinical efficacy of ICS in asthma has been considered relatively flat, meaning that the efficacy response to ICS plateaus early with minimal or no further therapeutic response at higher doses (Szefler 2002). While studies show clinical benefit with ICS, it has been difficult to demonstrate significant differences between doses, with most benefit obtained at lower doses (Barnes 2010). The relatively flat efficacy dose-response curve of ICS (based on changes in lung function) without using specific and sensitive measures of airway inflammation has led many patients to receive higher than necessary ICS doses (Beasley 2019). Higher doses of ICS may put patients at risk for systemic adverse effects, such as slowed growth velocity in children, reduction in bone density, cataracts, adrenal insufficiency, and increased risk of diabetes (Skoner 2016, Carr 2016, Choi 2017, Nguyen 2003, Suissa 2010).

Lipworth and colleagues re-evaluated the efficacy dose-response curve for ICS with the addition of markers of airway inflammation (Anderson 2017). In their study the authors confirmed that improvements in symptoms and lung function were only seen with lower doses of ICS. However, when measures of inflammation such as FeNO, eosinophilic cationic protein, and blood eosinophils were incorporated, a clear efficacy dose-response curve covering low to high doses of ICS was detected (Anderson 2017). This study confirmed earlier findings from Nolte et al. who used FeNO as a primary endpoint to compare the dose response to mometasone (Nolte 2013).

Real-world evidence also supports monitoring FeNO to guide treatment decisions when managing patients with asthma. LaForce et al. demonstrated that without knowledge of patients' FeNO, clinicians did not recognize the presence of significant airway inflammation in 50% of patients (LaForce 2014). Measurement of FeNO substantially altered treatment decisions in more than one-third of subjects, with medications stepped up in 20% and stepped down 16% of the patients studied (LaForce 2014). This experience was expanded to real-world survey of FeNO in almost 8,000 patients at over 300 asthma clinics in the US (Hanania 2018). Using traditional office-based clinical assessment tools to detect the presence of airway inflammation, FeNO >50 ppb was recognized in only one-third of the patients (Table 1). However, once clinicians were aware of an elevated FeNO (>50 ppb), anti-inflammatory treatment was then stepped up in 96% of patients (Hanania 2018).

Level of inflammation	Clinical assessment, n/N (%)	FeNO assessment, n/N (%)	Agreement, n/N (%)
Low	4,247/7,901 (53.8)	5,083/7,901 (64.3)	3,271/5,083 (64.4)
Intermediate	2,749/7,901 (34.8)	1,802/7,901 (22.8)	845/1,802 (46.9)
High	905/7,901 (11.5)	1,016/7,901 (12.9)	341/1,016 (33.6)

Table 1: Clinical assessment and FeNO measurement to assess airway inflammation (adapted from Hanania 2018)

Implications for clinicians: Measuring FeNO can aid in the management of asthma by helping to optimize steroid therapy by identifying patients who may need to step up or step down their steroid dosing. Individualized therapy can help to maximize therapeutic benefits while reducing the likelihood of steroid adverse effects.

FeNO Helps Identify Non-Adherence to Inhaled Steroids

Inhaled steroid treatment is widely considered to be the cornerstone therapy for the control of asthma symptoms (NHLBI 2007, GINA 2019a); however, adherence to asthma medication regimens tends to be very poor, with reported rates of non-adherence ranging from 30 to 70 percent (Lindsay 2013). Many factors are associated with non-adherence to asthma therapy, including difficulties with inhaler

devices, complex regimens, side effects, cost of medication, dislike of medication, and distant pharmacies (Bender 2004).

Medication non-adherence is a major reason for poor asthma control, asthma-related emergency department visits, inpatient hospitalizations, persistent eosinophilic inflammation, and increased oral steroid use (Murphy 2012, Williams 2004). Up to three-fourths of the total costs associated with asthma may be due to poor asthma control (Apter 2015). Guidelines and consensus statements on the diagnosis and assessment of patients with difficult-to-treat asthma stress the importance of identifying and addressing non-adherence to medications in this population (Bousquet 2010, Bel 2011).

Inducible nitric oxide synthase (iNOS) is expressed by airway epithelial cells and is very sensitive to the effect of corticosteroids (Kharitonov 1996). Therefore, FeNO should be a useful tool to determine if patients have been using their inhaled or oral steroid medications. Indeed, good adherence to prescribed asthma therapy has been associated with better disease control and lower FeNO concentrations (Klok 2014).

A 2002 study investigated the effect of budesonide on changes in FeNO and spirometry (Beck-Ripp 2002). Fifty-four pediatric and adolescent patients were followed for 8 weeks during treatment with budesonide or placebo following a 4-week washout period. A significant relationship between budesonide dosing and reductions in FeNO levels was seen, while no relationship was observed with FEV_1. Interestingly, the reduction in FeNO levels was positively correlated to budesonide compliance (Beck-Ripp 2002).

Delgado-Corcoran et al. investigated the relationship of FeNO and asthma control and medication adherence in 30 pediatric and adolescent patients who were followed periodically for 2.5 years using NHLBI guidelines (Delgado-Corcoran 2004). FeNO levels correlated to improved asthma control and were significantly reduced in subjects with good compliance to steroids compared with patients with poor and moderate compliance. FEV_1 levels were not substantially different between compliance groups (Delgado-Corcoran 2004).

A study by McNicholl et al. demonstrated that the dynamic effect of ICS on FeNO may be used as an accurate discriminator of non-adherence to ICS in adults using a “FeNO Suppression Test” (McNicholl 2012). Twenty-one patients received 7 days of direct observed administration of ICS treatment (DOICS). Those patients with a history of poor adherence as measured by ICS prescription refills <50%, experienced a significantly greater reduction in FeNO following 7 days of DOICS as compared to the group of adherent patients who had >80% history of ICS refills (reduced to 47±21% vs. 79±26% of baseline, respectively; p=0.003, mean±standard deviation) (McNicholl 2012).

In another study investigating FeNO as a surrogate marker of medication adherence, Kaminsky et al. evaluated 27 children who attended a summer camp for asthma (Kaminsky 2008). Throughout the one-week duration of the camp, children were administered their usual medications brought from home in an observed manner. While the duration of the summer camp was too short to see an effect on asthma outcomes, there was a significant decrease in FeNO (-45%, p<0.0001) that was attributed to improved adherence via directly observed administration (Kaminsky 2008).

Heaney et al. examined the feasibility and utility of measuring FeNO in routine clinical care within a UK severe asthma center (Heaney 2019). Using a remote monitoring system, testing in 201 patients with difficult-to-control asthma demonstrated that measuring FeNO is effective in identifying non-adherence to ICS/LABA treatment. Peripheral blood eosinophils were also reduced, but in a small proportion of patients eosinophils remained elevated despite reductions of FeNO and improved lung function. This suggests that peripheral blood eosinophils may not be as responsive to ICS, as compared to FeNO (Heaney 2019).

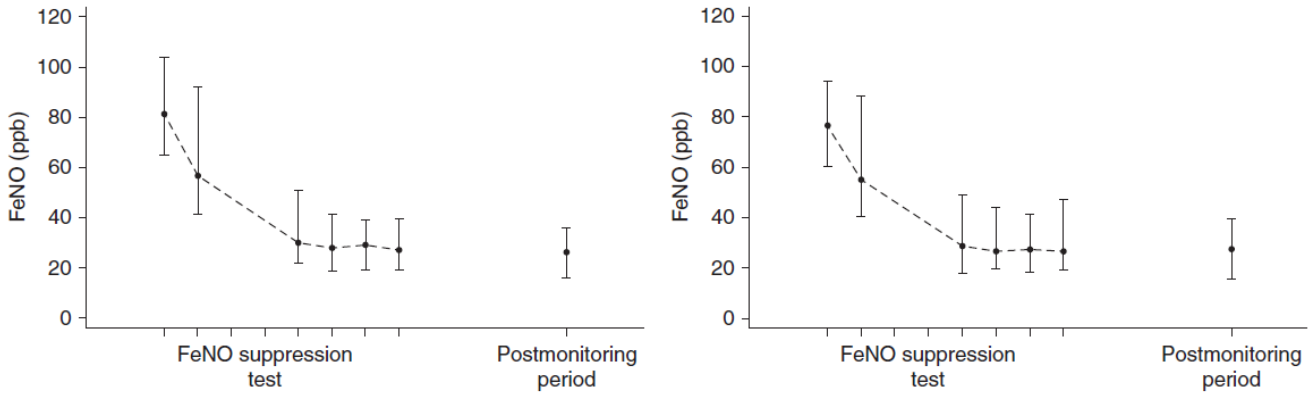


Figure 4: Left panel, positive "FeNO suppression test" in 54 patients with good adherence to ICS/LABA; Right panel, positive "FeNO suppression test" in 28 patients with good adherence to prednisolone (adapted from Heaney 2019)

Other situations in which FeNO monitoring is useful include when invasive therapeutic interventions or expensive biologicals are being considered in patients with difficult-to-treat asthma (Fajt 2015). Recent studies have shown that patients with moderate-severe asthma taking high dose ICS or ICS/LABA therapies are poorly adherent in over 50-70% of cases (Lee 2018, Jeffery 2018). FeNO monitoring can be used to help verify that ICS medications have been optimized and non-adherence ruled out before progressing to additional more expensive therapies or diagnostic tests (McNicholl 2012). In an editorial accompanying the Jeffery publication, the authors propose that asthma patients being considered for a biologic therapy be assessed measuring FeNO to ensure therapy with an ICS or ICS/LABA regimen has been optimized (Corren 2018). Many managed care organizations and pharmacy benefit managers require prescribers to provide evidence of a true steroid-resistant inflammatory process that is not adequately treated by ICS or ICS/LABA medications before authorization is granted (Pavord 2012). Use of FeNO in these situations may help provide objective evidence of steroid responsiveness and medication adherence.

Implications for clinicians: Measuring FeNO can aid in the management of asthma by helping to identify patients who are non-compliant with steroid therapy. Good compliance with ICS (in steroid-responsive patients) will typically result in reduced FeNO levels.

FeNO Helps Reduce the Likelihood of Exacerbations in Patients at Risk For Future Events (Compared to Traditional Monitoring)

The frequency and severity of exacerbations of asthma in patients is often variable (NHLBI 1991, GINA 2019a). Some patients may have periods of increased symptoms and more severe exacerbations, depending on exposure to environmental allergens and other triggers. Others may have a milder form of the disease and fewer exacerbations (NHLBI 2007). It is estimated that only 20% of asthmatics experience exacerbations requiring treatment in the emergency department or hospitalization, yet these patients account for more than 80% of total direct costs (Rodrigo 2004). In one study of 3,151 patients presenting to 83 US emergency departments with acute asthma, 73% reported at least one visit for asthma in the prior year, with 21% reporting six or more visits (Griswold 2005).

Risk factors for exacerbations and difficult-to-control asthma have been well described. The most common risk factor for a severe asthma exacerbation is a history of a prior attack in the previous year that required treatment with systemic corticosteroids (Dougherty 2009). Factors associated with more difficult to control asthma include comorbid allergic disease, obesity, smoking, and elevated markers of airway inflammation such as FeNO and blood or sputum eosinophils (Chen 2008, Kupczyk 2014, Zeiger 2011). Specifically, FeNO >50 ppb has been shown to be a significant independent risk factor for uncontrolled asthma (Malinovischi 2016).

Asthma exacerbations significantly impact patient lives and increase direct and indirect costs. Asthma is the second most common reason for hospitalization for children and the fourth most common reason for adults (Meltzer 2012). In 2017, nearly one-half (45.6%) of all persons with asthma in the US and over one-half of children with asthma (51.6%) reported having one or more asthma attack. In 2016, there were 1.77 million asthma-related emergency department visits and 189,000 asthma hospitalizations (CDC 2019). Despite effective treatments, up to 15% of well controlled patients and up to 49% of poorly controlled patients require a hospitalization, emergency room visit, or other unscheduled visit for their asthma each year (Meltzer 2012). The cost of inpatient hospitalizations and emergency department visits in 2007 was estimated at over $16 billion (2009 dollars) (Barnett 2011). The total economic burden of asthma in 2013, including absenteeism and mortality, was estimated to be a staggering $81.9 billion (2015 dollars) (Nurmagambetov 2018).

Besides the impact of exacerbations on healthcare utilization and economic consequences, asthma patients with frequent severe attacks have a significantly larger annual decline in lung function. Bai et al. investigated the effect of severe exacerbations on the progression of airway obstruction in 93 nonsmoking asthmatics with moderate-to-severe disease prior to treatment with ICS (Bai 2007). Subjects were followed for >5 years (median follow up was 11 years). The exacerbation rate significantly predicted an excess decline in FEV_1, such that one severe exacerbation per year was associated with a 30.2 milliliters (mL) greater annual decline in FEV_1 (Bai 2007). Furthermore, in a 3-year longitudinal study examining loss of lung function, a persistently high FeNO level of >40 ppb was independently associated with an accelerated decline in FEV_1 (Matsunaga 2016). These findings were recently corroborated in a study of 141 newly diagnosed adult asthmatics. An accelerated decline in FEV_1 (>54.2 mL per year) was associated with nasal polyps, number of blood and sputum eosinophils, body mass index, and level of exhaled nitric oxide. Only the latter two identified patients at highest risk using body mass index (BMI) $\leq$23 kg/m^2 and cut-off values of FeNO $\geq$57 ppb (Coumou 2018).

How can clinicians better identify patients at risk for future uncontrolled asthma and exacerbations? Studies have demonstrated that the addition of monitoring FeNO to usual clinical assessments such as asthma control patient questionnaires and spirometry, helps to identify patients at risk for future exacerbations (Zeiger 2011). The Seasonal Asthma Exacerbation Predictive Index (saEPI), which was developed based on data from 2 National Institute of Allergy and Infectious Diseases trials, identified 8 variables (including elevated FeNO) as risk factors for asthma exacerbations. Exacerbations in children were associated with a higher saEPI along with higher markers of allergic inflammation, ICS treatment and a history of a recent exacerbation (Hoch 2017).

The benefit of using a FeNO based monitoring strategy was also demonstrated in a study of asthma in pregnancy (Powell 2011). Women were enrolled in the study at 22 weeks gestation or earlier. A FeNO-based strategy was associated with a significant reduction in asthma exacerbations and improved quality of life, compared to usual care (Powell 2011). The offspring from this study were also followed, and benefits seen. Neonatal hospitalizations were reduced. In the year following birth there was also reduced incidence of recurrent bronchiolitis in the infants born from mothers in the FeNO group (Mattes 2014). When the children were followed up as toddlers (mean age 5 years), the prevalence of wheezing, emergency department visits and doctor diagnosed asthma were all significantly lower in children from the FeNO group (Morten 2018).

The most comprehensive summaries of evidence to support monitoring FeNO in asthma management were published in 2 Cochrane meta-analyses that concluded exacerbations were reduced 40-50% (Petsky 2016a, Petsky 2016b). The 2016 Cochrane Systematic Review on “Exhaled Nitric Oxide Levels to Guide Treatment for Adults with Asthma” included 7 randomized controlled trials and 1,700 adult participants (Petsky 2016a). By monitoring FeNO, exacerbations were reduced by 40% and exacerbation rates were reduced by at least 41%. The number of people having one or more asthma exacerbation was significantly lower in the FeNO group compared to the control group (odds ratio (OR) 0.60, 95% confidence interval (CI) 0.43-0.84). Those in the FeNO group were also significantly more

likely to have a lower exacerbation rate than the controls (rate ratio 0.59, 95% CI 0.45- 0.77). The quality of the evidence to support the effect of FeNO on reducing exacerbations was determined to be moderate, even though exacerbations were not defined the same across all studies included in the analysis (Petsky 2016a).

Secondary endpoints were examined in the meta-analysis (symptoms, ICS dosing, and measures of asthma control such as spirometry) and none were found to be significant; however, the inconsistency of data reporting across the 7 studies affected the ability to accurately compare groups using meta-analysis methodology. While, the grade of evidence was not reported (except for ICS dosing, noted to be low), the authors concluded that FeNO did not impact day-to-day clinical symptoms, end-of-study FeNO levels, or ICS dose (Petsky 2016a).

In a second 2016 Cochrane Systematic Review focused on pediatric patients, Petsky and colleagues evaluated the efficacy of tailoring asthma interventions based on monitoring FeNO, in comparison to management based on clinical symptoms (with or without spirometry/peak flow) or asthma guidelines (or both), for asthma-related outcomes (Petsky 2016b). This meta-analysis included 9 randomized controlled trials and 1,426 children. Using traditional monitoring, 40 out of 100 children experienced at least one exacerbation over 48.5 weeks, compared to 28 out of 100 children where treatment was guided by FeNO (OR 0.58, 95% CI 0.45 to 0.75; 1279 participants in 8 studies; p<0.0002) (Petsky 2016b). Of note, the number needed to treat to benefit (NNTB) over 52 weeks was clinically relevant and very low; 12 in the adult and 9 in the pediatric meta-analyses, respectively (Petsky 2016a, Petsky 2016b).

A third review was published and summarized the clinical impact of FeNO-based monitoring on reducing exacerbations (Petsky 2018). In total 13 studies (5 adult, 8 pediatric) and combined data from over 2,000 patients were included. Again, the FeNO-based strategy was significantly better than traditional clinical monitoring in terms of reducing exacerbations (Figure 5) (Petsky 2018).

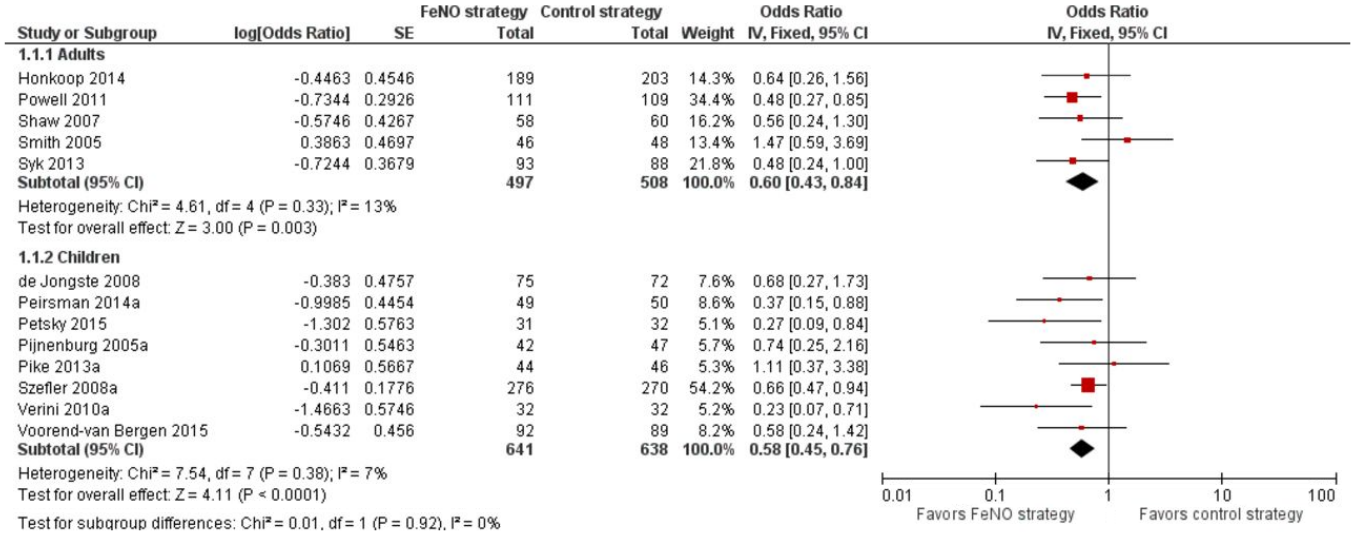


Figure 5: Number of subjects who had ≥1 exacerbation over the study period (adapted from Petsky 2018)

Following the two Cochrane meta-analyses, an evidence-based review of measuring FeNO in adults (ages of >18 years) and children (age 5-18 years) was prepared for the HHS Agency for Healthcare Research and Quality (AHRQ). This analysis also concluded that using asthma management algorithms that incorporate FeNO testing reduced the risk of exacerbations (strength of evidence: High), and possibly the risk of exacerbations requiring oral steroids (strength of evidence: Moderate) (Wang 2017).

Cost-Effectiveness of FeNO

The incorporation of FeNO monitoring into asthma management is a cost-effective strategy based on improvements in outcomes and medication use (Bukstein 2011, Honkoop 2015). We have developed a pharmacoeconomic cost model of FeNO monitoring based on the above data from the Cochrane Review and other studies. This model demonstrates an overall cost savings in a typical managed care payer organization (Brooks 2018). Our decision analytic model investigated the cost-effectiveness of the addition of FeNO monitoring to standard of care management compared to standard of care alone (i.e., no FeNO monitoring). A comparison of the 12-month average medical costs and quality-adjusted life years (QALYs) between the addition of FeNO monitoring and standard of care management found decreased expected 12-month costs per patient ($2,228 vs. $2,637, respectively) and increased effectiveness (0.844 vs. 0.767 QALYs, respectively) in the FeNO group. The improved outcomes and decreased cost indicate that FeNO in addition to standard of care is the dominant strategy (Brooks 2018).

The cost model was also used to examine the impact of FeNO monitoring on the cost of asthma management among patients with infrequent and frequent exacerbations. The savings associated with FeNO monitoring was proportional to the frequency of exacerbations. In the simulated population of patients with infrequent exacerbations who received FeNO monitoring, the projected annual per patient cost savings compared to those patients without FeNO monitoring ranged from $72 to $217 (Table 2). In the population of patients with frequent exacerbations, FeNO monitoring demonstrated even greater annual per patient cost savings between $316 and $1,331, depending on the assumed frequencies of exacerbations and number of annual FeNO measurements (Table 2) (Brooks 2018).

Impact of FeNO on cost of asthma management in patients with infrequent exacerbations						
Annual number of exacerbations	0.25	0.25	0.50	0.50	1	1
Annual number of FeNO measurements	1	2	1	2	2	4
Per patient annual cost of SOC asthma management	$1,904	$2,036	$1,990	$2,122	$2,294	$2,557
Per patient annual cost of FeNO in addition to SOC asthma management	$1,809	$1,964	$1,847	$2,002	$2,077	$2,387
Annual cost savings due to FeNO	$95	**$72**	$143	$120	**$217**	$170

Impact of FeNO on cost of asthma management in patients with frequent exacerbations						
Annual number of exacerbations	2	2	4	4	6	8
Annual number of FeNO measurements	4	6	8	10	10	12
Per patient annual cost of SOC asthma management	$2,901	$3,165	$4,115	$4,379	$5,066	$6,016
Per patient annual cost of FeNO in addition to SOC asthma management	$2,538	$2,849	$3,461	$3,771	$4,073	$4,685
Annual cost savings due to FeNO	$363	**$316**	$654	$608	$993	**$1,331**
SOC=standard of care. Red type indicates high and low ends of the range of savings from FeNO monitoring						

Table 2: Impact of FeNO monitoring on the cost of asthma management in patient with infrequent and frequent exacerbations. (adapted from Brooks 2018).

The cost of asthma-related events before and during FeNO monitoring in a Medicare database of patients with a history of exacerbations has been investigated (Arnold 2018). Asthma-related emergency department (ED) or inpatient hospitalization (IP) claims (per patient per day) decreased from 0.004 pre-FeNO use to 0.002 during the FeNO monitoring period ($p<0.04$). Likewise, daily asthma-related ED/IP charges decreased from $16.21 to $6.46 ($p<0.01$). Kaplan-Meier analysis demonstrated a strong trend of an increased time to exacerbation with FeNO monitoring (Figure 6). The median days to an ED/IP pre-FeNO was 413 days vs. 606 days during FeNO monitoring ($p=0.0974$) (Arnold 2018).

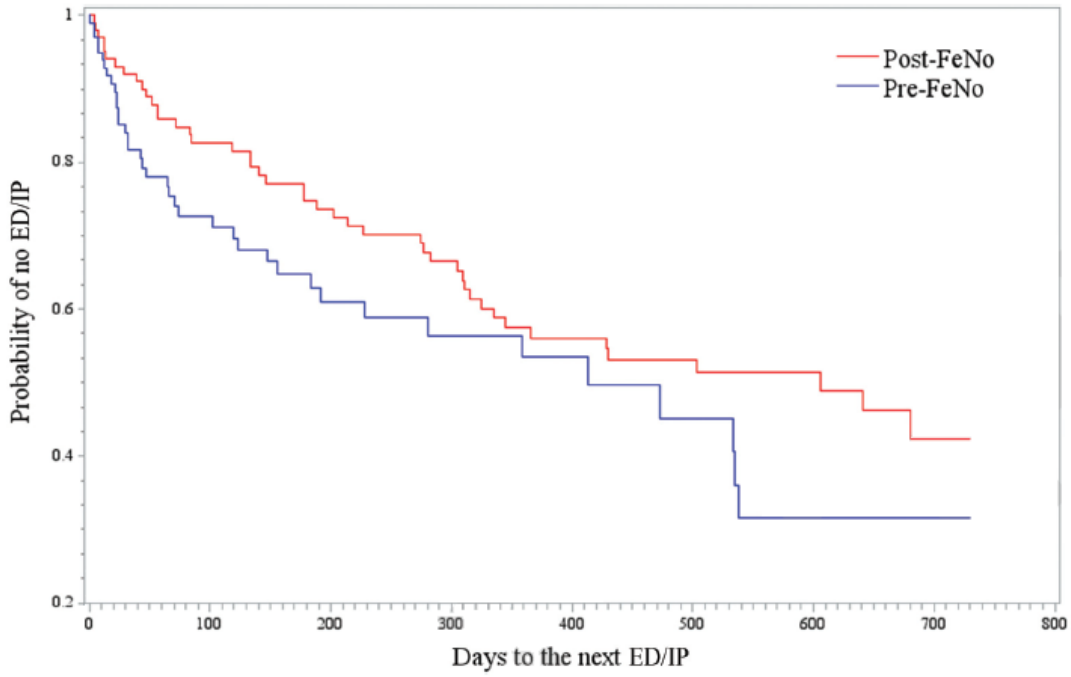


Figure 6: Kaplan-Meier curve of pre-FeNO and post-FeNO periods (adapted from Arnold 2018)

Implications for clinicians: Measuring FeNO can aid in the management of asthma by helping to reduce the likelihood of asthma exacerbations in patients at risk for future events. FeNO monitoring is cost-effective based on improved outcomes.

FeNO Helps Identify Asthmatics Who Will Benefit Most from Treatment with Certain Biologic Agents

A small minority of asthma patients cannot achieve control of their disease with traditional therapies (i.e., ICS/LABA combinations with or without LTRAs and OCS) and are considered for additional treatment with a biologic agent (NHLBI 2007, GINA 2019b). However, before a patient is considered to have truly severe refractory asthma, other factors related to achieving disease control should be considered. Difficult to control or treat asthma differs from severe refractory asthma and includes confounding factors such as allergic comorbidities, smoking, medication nonadherence and poor inhaler technique (Hekking 2015, Bel 2011). This is an important distinction since methods to improve asthma control in difficult patients relate to addressing the confounding factors compared to the refractory patient where additional anti-inflammatory treatment is needed. Anti-inflammatory biologic agents include monoclonal antibodies to IgE (omalizumab), IL-5 (mepolizumab, reslizumab or benralizumab), and IL-4 receptors (dupilumab).

To characterize difficult to control asthma vs, severe refractory asthma, Hekking et al., conducted an epidemiological investigation of asthma control in the Netherlands, where healthcare utilization is documented through a nationalized system (Hekking 2018). It was found that 74.1% of asthma patients receiving moderate to high dose of ICS with or without a LABA were difficult to control; 21.7% had experienced 3 or more exacerbations, and 21.7% had been hospitalized. In addition, less than half of patients (49.3%) with difficult-to-control asthma were adherent to their medium to high-dose ICS and only 41.6% of those patients used correct inhalation technique. Thus, only 20.5% of patients with difficult-to-control asthma truly met the definition of severe refractory asthma, representing just 3.6% (95% CI, 3.0% to 4.1%) of the overall Dutch adult asthma population (Hekking 2018).

While the newer biologic therapies offer patients the possibility of improved asthma control compared to traditional ICS-based regimens, they are substantially more expensive. Due to their increased cost, there is concern about how to choose the appropriate biologic agent and which patients will benefit most (Pavord 2017). The Institute for Clinical and Economic Review (ICER) recently published a review of the cost-effectiveness of these therapies and concluded that none of the currently available agents meet the established thresholds for cost-effectiveness due to their expense (ICER 2018). The report found that all 5 of the assessed biologics modestly reduce asthma exacerbations and improve daily quality of life, but their high costs appear to be far out of alignment with the incremental clinical benefits. The entire therapy class would need price discounts of at least 50% to reach commonly cited thresholds for cost-effectiveness. Higher value care is more likely to be achieved through careful patient selection and continuing biologic therapy for only those patients who respond to treatment (ICER 2018).

Biomarkers can be used to help improve patient selection as well as predict and/or assess treatment response (Godar 2018). For biologics targeted for patients with T2-driven asthma, FeNO has been shown to help identify patients for treatment and assess their response. The most recent GINA Guideline for Difficult-to-Treat and Severe Asthma consistently recommends the use of an algorithm based on spirometry and FeNO for identifying patients with T2 airway inflammation, predicting which patients will respond, and assessing response to treatment (GINA 2019b).

Use of FeNO with Omalizumab

Omalizumab is an anti-IgE biologic that was approved for treating moderate-severe persistent asthma in the US in 2003 and in Europe in 2005. The omalizumab EXTRA study enrolled 850 patients (age 12-75 years) with uncontrolled severe persistent allergic asthma despite treatment with ICS/LABA with or without other controllers (Hanania 2011). The study was designed to evaluate the additional benefit of omalizumab in reducing future exacerbations. Patients were enrolled in the study regardless of their FeNO level. Baseline FeNO levels were 28.5 ppb in the omalizumab treatment group and 29.2 ppb in the placebo treatment group. Use of omalizumab was associated with a modest 25% relative reduction in asthma exacerbations (Hanania 2011). Larger rate reductions in exacerbations were seen in earlier studies of omalizumab which studied patients on ICS alone since LABAs were not available when the studies were started. The authors also noted that patient were more severe in the EXTRA study (Hanania 2011).

A subsequent post-hoc analysis was performed to evaluate the reduction in exacerbation rate with omalizumab in relation to baseline biomarkers of airway inflammation (FeNO and blood eosinophils), and serum periostin (Hanania 2013). Patients were divided into low- and high-biomarker groups. After 48 weeks of omalizumab treatment, reductions in exacerbations were greater in the high biomarker sub-groups than in the low biomarker subgroups. The greatest reduction in asthma exacerbations was seen in the high FeNO-group (defined as >19.5 ppb), with a mean reduction of 53% compared to 16% when baseline FeNO was <19.5 ppb (Figure 7). For patients with high blood eosinophils (defined as >260 cells/μL) the mean reduction in asthma exacerbations was 32% compared to just 9% for patients with low eosinophils (<260 cells/μL). In summary, the use of biomarkers of persistent airway inflammation helps to identify patients who may benefit most from treatment with omalizumab. Similarly, in children with elevated biomarkers of T2 asthma that were enrolled in the omalizumab PROSE study also experienced a greater reduction in exacerbations if their baseline FeNO was >20 ppb or blood eosinophils >300 cells/μL (Szefler 2018).

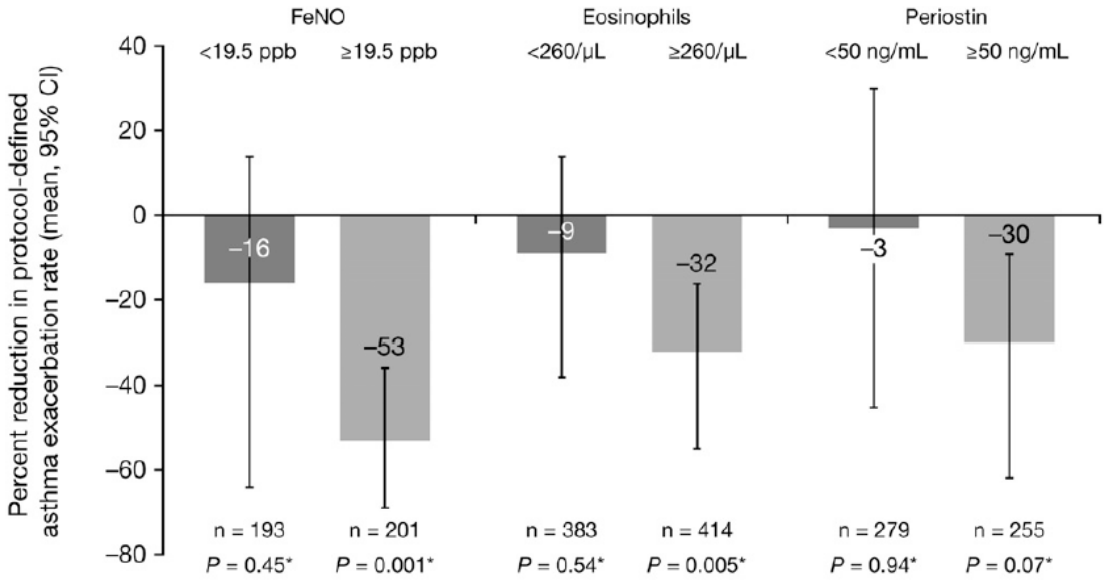


Figure 7: Reduction of asthma exacerbation rate in the low- and high-biomarker groups (adapted from Hanania 2013)

Monitoring FeNO has the advantage of being available at the point of care, enabling physicians to make treatment decisions during the patient's visit. Furthermore, the use of FeNO to predict omalizumab responders has been shown to have significant cost savings (Brooks 2019). Without the use of FeNO, evaluating the response to a trial course of omalizumab (typically 16-28 weeks) can be difficult. The addition of FeNO helps to identify responders to omalizumab and significantly reduces overall costs of both FeNO and omalizumab.

FeNO can also be helpful to monitor for asthma relapse following withdrawal of omalizumab. The question of how long to treat asthma patients with omalizumab is difficult to answer, however recently a study described the outcomes in patients who had been treated for at least 5 years. Rising FeNO concentrations following discontinuation of omalizumab were significantly associated with an increased risk for exacerbations and asthma relapse (Ledford 2017). Conversely, FeNO has also been shown to help identify which patients will have a persistent response to long-term treatment. Following treatment for 1-4 years with omalizumab, an elevated FeNO pretreatment was significantly associated with patients who experienced the greatest benefit from omalizumab in terms of improvements in lung function (Solidoro 2019).

Use of FeNO with Anti-IL-5 Monoclonal Antibodies

Mepolizumab is an anti-IL-5 monoclonal antibody for the treatment of severe asthma. It was approved in the US and Europe in 2015. Reslizumab and benralizumab, are two other anti-IL-5 monoclonal antibodies approved for treating severe asthma. Reslizumab was approved in both Europe and the US in 2016, while benralizumab was approved in the US in 2017 and in Europe in 2018. Neither utilized FeNO as a baseline enrollment criterion or an outcome measure during phase III registration trials. In phase III clinical trials of mepolizumab in patients with severe asthma with T2 airway inflammation, FeNO was utilized as one of the study entry criteria.

The mepolizumab DREAM study evaluated 621 patients with eosinophilic asthma and a history of severe recurrent exacerbations. Baseline entry criteria included FeNO of ≥50 ppb and patients were randomized to receive placebo or various doses of mepolizumab every 4 weeks for one year. Post-treatment FeNO was not significantly different across the groups of mepolizumab doses (Pavord 2012). However, the patients who had elevated FeNO at baseline (≥50 ppb) appeared to show an effect on the rate of exacerbations (FDA 2015). These data were recently confirmed in a study presented at the

2019 ATS International Conference. Patients with elevated FeNO and peripheral blood eosinophils at baseline had a better response to mepolizumab vs. placebo in exacerbation reduction (relative risk reduction 0.39 [0.3-0.5]) as compared to low concentrations of the biomarkers (relative risk reduction 0.76 [0.38-1.53]) (Shrimanker 2019).

The role of FeNO in helping to identify candidates for treatment with anti-IL5 monoclonal antibodies appears to be similar to its role in identifying patients who have persistent airway inflammation despite treatment with ICS or ICS/LABA combinations. Unlike omalizumab, little data is currently available to suggest that FeNO can be used as an outcome measure or a predictor of response to treatment. However as mentioned previously, there is emerging data suggesting that a combination of FeNO and peripheral blood eosinophils may have value in predicting the response to mepolizumab in severe asthmatics (Shrimanker 2019).

Use of FeNO with Dupilumab

Dupilumab is an anti-IL-4 receptor α monoclonal antibody approved for moderate-to-severe asthma in the US in 2017 and in Europe in 2019. It inhibits the action of both IL-4 and IL-13, the key drivers of T2 inflammation. Phase IIb and phase III clinical trials with dupilumab have demonstrated significant reduction in asthma exacerbations and improvements in lung function in moderate to severe patients who were receiving moderate-high doses of ICS/LABA (Wenzel 2016, Castro 2018). Significant improvements in outcomes occurred in treated patients compared to placebo, regardless of baseline markers of T2 airway inflammation (eosinophils or FeNO). However, larger improvements in outcomes were associated with higher levels of T2 biomarkers (Figure 8). In the phase III Liberty Asthma QUEST Study, dupilumab decreased asthma exacerbations 46-48% across all patients. However, in patients with baseline FeNO 25-50 ppb exacerbations were reduced 61-65% and an even greater reduction in exacerbations was seen in patients with baseline FeNO of >50 ppb (mean 70%) (Castro 2018). This is remarkable since a FeNO concentration >50 ppb in patients who were receiving moderate-high doses of ICS indicates these patients have persistent airway inflammation despite intensive anti-inflammatory treatment.

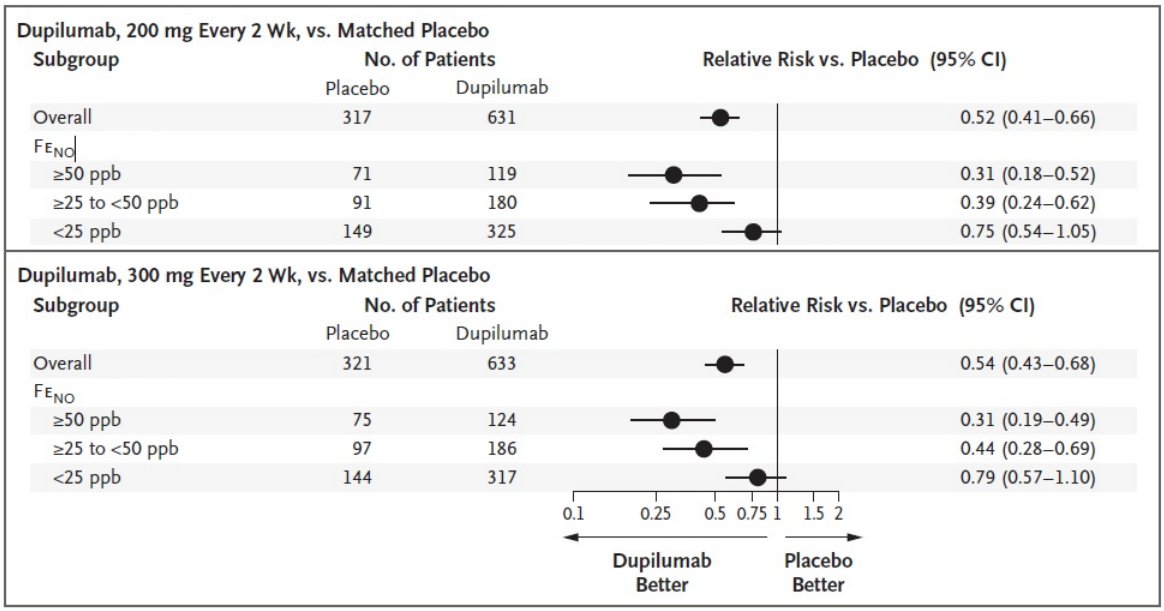


Figure 8: Relative risk of severe asthma exacerbations in FeNO subgroups treated with dupilumab vs. placebo (adapted from Castro 2018)

Of note, the approved therapeutic indication for dupilumab in Europe (for asthma) makes specific mention of FeNO: “Dupixent is indicated in adults and adolescents 12 years and older as add-on

maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment" (Dupixent 2019). Thus, FeNO can be considered a screening tool for severe asthma patients being considered for treatment with dupilumab.

Implications for clinicians: Measuring FeNO can aid in the management of asthma by helping to identify severe asthma patients who will benefit most from treatment with certain biologic agents (omalizumab and dupilumab, specifically) when such agents are appropriate. The role of FeNO with biologics continues to evolve with emerging data.

Conclusions

In this review we have summarized the current clinical evidence that supports measuring FeNO in asthma. Adding FeNO to the armamentarium of diagnostic tools provides a unique measure of airway inflammation that compliments pulmonary function and other clinical assessments. Incorporating FeNO monitoring into asthma management helps to identify patients that may respond favorably to steroids and helps optimize therapy and can help identify those who are non-compliant with steroids. Compared to traditional monitoring, FeNO can help reduce the likelihood of future exacerbations in patients at risk for future events. FeNO can also help identify severe asthma patients who will benefit most from omalizumab and dupilumab. As more biologic therapies are developed for treating asthma, there will be an increasing need for clinically relevant biomarkers, such as FeNO, that can assist clinicians in identifying appropriate patient candidates and monitoring treatment response in a cost-effective manner.

References

Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use and mortality: United States, 2005-2009. National Health Stat Report. 2011; January 12 (32): 1-14.

Anderson WJ, Short PM, Jabbal, S, et al. Inhaled corticosteroid dose response in asthma. Should we measure inflammation? Ann Allergy Asthma Immunol. 2017; 118: 179-185.

Apter AJ. Enhancing patient adherence to asthma therapy. Up To Date. August 2015.

Arnold RJG, Layton A, Massanari M. Cost impact of monitoring exhaled nitric oxide in asthma management. Allergy Asthma Proc. 2018; Sep 13, 39(5): 338-344.

Attanasi M, Consilvio NP, Rapino D, et al. Bronchial hyper responsiveness to mannitol, airway Inflammation and Asthma Control Test in atopic asthmatic children. Arch Med Sci. 2016; 12(1): 137-144.

Bai TR, Vonk JM, Postma DS, et al. Severe exacerbations predict excess lung function decline in asthma. Eur Respir J. 2007; 30: 452-456.

Barnes PJ. Inhaled corticosteroids. Pharmaceuticals (Basel). 2010; Mar 3(3): 514-540.

Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002-2007. J Allergy Clin Immunol. 2011; 127(1): 145-152.

Beasley R, Harper J, Bird G, et al. Inhaled corticosteroid therapy in adult asthma. Time for a new therapeutic dose terminology. Am J Respir Crit Care Med. 2019; 199(12): 1471-1477.

Beck-Ripp J, Griese M, Arenz S, et al. Changes of exhaled nitric oxide during steroid treatment of childhood asthma. Eur Respir J. 2002; 19: 1015-1019.

Bel EH, Sousa A, Fleming L, et al. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). Thorax. 2011; 66: 910-917.

Bender BG, Rand C. Medication non-adherence and asthma treatment costs. Curr Opin Allergy Clin Immunol. 2004; 4: 191-195.

Bousquet J, Mantzouranis E, Cruz AA, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on severe asthma. J Allergy Clin Immunol. 2010; 126: 926-938.

Bradding P. Asthma: eosinophil disease, mast cell disease or both? Allergy Asthma Clinical Immunol. 2008; 4: 84-90.

Brooks E, Massanari M. Cost-effectiveness analysis of monitoring fractional exhaled nitric oxide (FeNO) in the management of asthma. Manag Care. 2018; Jul 27(7): 42-48.

Brooks E, Massanari M, Hanania N, et al. Cost-effectiveness of fractional exhaled nitric oxide (FeNO) measurement in predicting response to omalizumab in asthma. Clinicoecon Outcome Res. 2019; 11: 301-307.

Buhl R, Bals R, Baur X, et al. [Guideline for the Diagnosis and Treatment of Asthma - Guideline of the German Respiratory Society and the German Atemwegsliga in Cooperation with the Paediatric Respiratory Society and the Austrian Society of Pneumology]. Pneumologie. 2017; 71(12): 849-919.

Bukstein D, Luskin AT, Brooks EA. Exhaled nitric oxide as a tool in managing and monitoring difficult-to-treat asthma. Allergy Asthma Proc. 2011; 32(3): 185-192.

Bush A, Fleming L. Is asthma overdiagnosed? Arch Dis Child. 2016; 191(8): 688-689.

Carr WW, Szefler SJ. Inhaled corticosteroids ocular safety and the hypothalamic-pituitary-adrenal axis. Ann Allergy Asthma Immunol. 2016; 117: 589-594.

Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med. 2018; 378(26): 2486-2496.

CDC. Centers for Disease Control and Prevention. Vital signs: asthma prevalence, disease characteristics, and self-management education-United States, 2001-2009. MMWR Morbid Mortal Weekly Rep. 2011 May 6; 60(17): 547-552.

CDC. Most recent national asthma data. May 2019. Available online at: https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm (Accessed: July 31, 2019).

Chang D, Teper A, Balinotti J, et al. Exhaled nitric oxide predicts loss of asthma control in children after inhaled corticosteroids withdrawal. Pediatr Pulmonol. 2019; 54(5): 537-543.

Chen H, Blanc PD, Hayden ML, et al. Assessing productivity loss and activity impairment in sever or difficult-to-treat asthma. Value Health. 2008; 11(2): 231-239.

Chibana K, Trudeau JB, Mustovitch AT, et al. IL-13 induced increases in nitrite levels are primarily driven by increases in inducible nitric oxide synthase as compared with effects on arginases in human primary bronchial epithelial cells. Clin Exp Allergy. 2008; 38: 936-946.

Choi IS, Dim D, Kim S, et al. Adrenal insufficiency associated with long-term use of inhaled steroid in asthma. Ann Allergy Asthma Immunol. 2017; 118: 66-72.

Corren J, Panettieri RA. How important is adherence to inhaled medications before starting a biologic therapy for asthma? J Allergy Clin Immunol Pract. 2018; 6: 1578-1579.

Coumou H, Westerhof GA, de Nijs SB, et al. Predictors of accelerated decline in lung function in adult-onset asthma. Eur Respir J. 2018; 51: 1701785.

Delgado-Corcoran C, Kissoon N, Murphy SP, et al. Exhaled nitric oxide reflects asthma severity and asthma control. Pediatr Crit Care Med. 2004; 5(1): 48-52.

Dougherty RH, Fahy JV. Acute exacerbations of asthma: epidemiology, biology, and the exacerbation-prone phenotype. Clin Exp Allergy. 2009; 39(2): 193-202.

Dupixent (dupilumab) product information (Europe), updated June 28, 2019. Available online at: https://www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf (Accessed: July 30, 2019).

Dweik RA, Boggs PB, Erzurum SC, et al. Interpretation of exhaled nitric oxide levels (FeNO) for clinical applications: an official ATS clinical practice guideline. Am J Respir Crit Care Med. 2011; 184: 602-615.

Ekroos H, Karjalainen L, Sarna S. Short-term variability of exhaled nitric oxide in young male patients with mild asthma and in healthy subjects. Resp Med. 2002; 96: 895-900.

Fahy JV. Type-2 inflammation in asthma; present in most, absent in many. Nat Rev Immunol. 2015; 15(1): 57-65.

Fajt ML, Wenzel, SE. Asthma phenotypes and the use of biologic medications in asthma and allergic disease: the next steps toward personalized care. J Allergy Clin Immunol. 2015; 135: 299-310.

FDA Briefing Document, BLA 125-526. 2015. Downloaded from: https://www.fda.gov/downloads/drugs/developmentapprovalprocess/developmentresources/ucm479963.pdf (Accessed: July 30, 2019).

Fletcher M, Jha A, Dunlop W, et al. Patient reported burden of asthma on resource use and productivity across 11 countries in Europe. Adv Ther. 2015; 32: 370-380.

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, 2019a. Available online at: https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf (Accessed: July 30, 2019).

Global Initiative for Asthma (GINA). Difficult-to-Treat & Severe Asthma in Adolescent and Adult Patients: Diagnosis and Management. A Pocket Guide for Healthcare Professionals, 2019b. Available online at: https://ginasthma.org/wp-content/uploads/2019/04/GINA-Severe-asthma-Pocket-Guide-v2.0-wms-1.pdf (Accessed: July 30, 2019).

Godar M, Blanchetot C, de Haard H, et al. Personalized medicine with biologics for severe type 2 asthma: current status and future prospects. MABS. 2018; 10(1): 34-45.

Griswold SK, Nordstrom CR, Clark S, et al. Asthma exacerbations in North American adults. Chest. 2005; 127: 1579-1586.

Gustafsson LE, Leone AM, Persson MG, et al. Endogenous nitric oxide is present in the exhaled air of rabbits, guinea pigs and humans. Biochem Biophys Res Comm. 1991; 181(2): 852-857.

Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy. Ann Intern Med. 2011; 154: 573-582.

Hanania NA, Wenzel S, Rosen K, et al. Exploring the effects of omalizumab in allergic asthma. Am J Respir Crit Care Med. 2013; 187(8): 804-811.

Hanania N, Massanari M, Jain N. Measurement of fractional exhaled nitric oxide in real-world clinical practice alters asthma treatment decisions. Ann Allergy Asthma Immunol. 2018; 120: 414-418.

Heaney LG, Busby J, Bradding P, et al. Remotely monitored therapy and nitric oxide suppression identifies non-adherence in severe asthma. Am J Respir Crit Care Med. 2019; 199(4): 454-464.

Hekking PW, Wener RR, Amelink M, et al. The prevalence of severe refractory asthma. J Allergy Clin Immunol. 2015; 135: 896-902.

Hekking PP, Amelink M, Wener RR, et al. Comorbidities in difficult-to-control asthma. J Allergy Clini Immunol Pract. 2018; 6(1): 108-113.

Hoch HE, Calatroni A, West JB, et al. Can we predict fall asthma exacerbations? Validation of the seasonal asthma exacerbation index. J Allergy Clin Immunol. 2017; 140(4): 1130-1137.e1135.

Hong J, Bao Y, Chen A, et al. Chinese guidelines for childhood asthma 2016: Major updates, recommendations and key regional data. J Asthma. 2018; 55(10): 1138-1146.

Honkoop PJ, Loijmans RJ, Termeer EH, et al. Symptom- and fraction of exhaled nitric oxide-driven strategies for asthma control: a cluster-randomized trial in primary care. J Allergy Clin Immunol. 2015; 135(3): 682-688.e11.

ICER. Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks: Final Evidence Report. Boston, MA: Institute for Clinical and Economic Review. December 20, 2018.

Jeffery MM, Shah ND, Karaca-Mandic P, et al. Trends in omalizumab utilization for asthma: evidence of suboptimal patient selection. J Allergy Clin Immunol Pract. 2018; 6: 1568-15677.

Jones SL, Kittelson J, Cowan JO, et al. The predictive value of exhaled nitric oxide measurements in assessing changes in asthma control. Am J Respir Crit Care Med. 2001; 164: 738-743.

Kaminsky, DA, Rice AA, Bissonette, M, et al. Exhaled nitric oxide decreases in association with attendance at an asthma summer camp. J Asthma. 2008; 45(5): 415-419.

Karrasch S, Linde K, Rücker G, et al. Accuracy of FENO for diagnosing asthma: a systematic review. Thorax. 2017; 72: 109-116.

Kharitonov SA, Yates DH, Barnes PJ. Inhaled glucocorticoids decrease nitric oxide in exhaled air of asthmatic patients. Am J Respir Crit Care Med. 1996; 153(1): 454-457.

Kharitonov S, Alving K, Barnes PJ. Exhaled and nasal nitric oxide measurements: recommendations. Eur Resp J. 1997; 10: 1683-1693.

Klok T. Adherence to inhaled corticosteroids strongly predicts long-term asthma control in young children. Eur Resp J. 2014; 43: 783-791.

Knuffman JE, Sorkness CA, Lemanske RF Jr., et al. Phenotypic predictors of long-term response to inhaled corticosteroid and leukotriene modifier therapies in pediatric asthma. J Allergy Clin Immunol. 2009; 123: 411-416.

Kupczyk M, ten Brinke A, Sterk PJ, et al. Frequent exacerbators-a distinct phenotype of severe asthma. Clin Exp Allergy. 2014; 44: 212-221.

LaForce C, Brooks E, Herje N, et al. Impact of exhaled nitric oxide measurements on treatment decisions in an asthma specialty clinic. Ann Allergy Asthma Immunol. 2014; 113: 619-623.

Lazarus SC, Krishnan J, King TS, et al. Mometasone or tiotropium in mild asthma with a low sputum eosinophil level. N Engl J Med. 2019; 380: 2009-2019.

Ledford D, Busse W, Trzaskoma B, et al. A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. J Allergy Clin Immunol. 2017; 140: 162-169.

Lee J, Tay TR, Radhakrishna N, et al. Nonadherence in the era of severe asthma biologics and thermoplasty. Eur Respir J. 2018; 51(4): 1701836.

Lindsay JT, Heaney LG. Nonadherence in difficult asthma-facts, myths, and a time to act. Patient Prefer Adherence. 2013; 7: 329-336.

Lundberg JO, Nordvall SL, Weitzberg E, et al. Exhaled nitric oxide in pediatric asthma and cystic fibrosis. Arch Dis Child 1996; 75: 323-326.

Malinovschi, A, Janson, C, Borres M. Simultaneously increased fraction of exhaled nitric oxide levels and blood eosinophil counts relate to increased asthma morbidity. J Allergy Clin Immunol 2016; 138(5): 1301-1308.

Maniscalco M, Vitale C, Vatrella A, et al. Fractional exhaled nitric oxide-measuring devices: technology update. Med Devices (Auckl). 2016 Jun 23; 9: 151-160.

Matsunaga K, Hirano T, Oka A, et al. Persistently high exhaled nitric oxide and loss of lung function in controlled asthma. Allergol Int. 2016; 65: 266-271.

Mattes J, Murphy VE, Powell H, et al. Prenatal origins of bronchiolitis: protective effect of optimized asthma management during pregnancy. Thorax. 2014; 69(4): 383-384.

Mazurek JM, Syamlal G. Prevalence of asthma, asthma attacks, and emergency department visits for asthma among working adults-national health interview survey, 2011-2016. MMWR Morb Mortal Wkly Rep. 2018 Apr 6; 67(13): 377-386.

McNicholl DM, Stevenson M, McGarvey LP, et al. The utility of fractional exhaled nitric oxide suppression in the identification ofnNon-adherence in difficult asthma. Am J Respir Crit Care Med. 2012; 186(11): 1102-1108.

Meltzer EO, Blaiss MS, Nathan RA, et al. Asthma burden in the United States: results of the 2009 Asthma Insight and Management survey. Allergy Asthma Proc. 2012; 33(1): 36-46.

Michils A, Baldassarre S, Van Muylem A. Exhaled nitric oxide and asthma control: a longitudinal study in unselected patients. Eur Respir J. 2008; 31: 539-546.

Morten M, Collison A, Murphy VE, et al. Managing asthma in pregnancy (MAP) trial: FeNO levels and childhood asthma. J Allergy Clin Immunol. 2018; 142(6): 1765-1772.

Murphy AC, Proeschal A, Brightling CE, at al. The relationship between clinical outcomes and medication adherence in difficult-to-control asthma. Thorax. 2012; 67: 751-753.

National Heart, Lung, and Blood Institute (NHLBI). National Asthma Education and Prevention Program Expert Report: Guidelines for the Diagnosis and Management of Asthma. 1991.

National Heart, Lung, and Blood Institute (NHLBI). National Asthma Education and Prevention Program Expert Report 3: Guidelines for the Diagnosis and Management of Asthma. 2007.

NICE. National Institute for Health and Clinical Excellence. Asthma: diagnosis, monitoring and chronic asthma management NICE guideline [NG80]. November 2017. Available online at: https://www.nice.org.uk/guidance/ng80 (Accessed: August 30, 2019).

Nolte H, Pavord I, Backer V, et al. Dose-dependent anti-inflammatory effect of inhaled mometasone furoate/formoterol in subjects with asthma. Respir Med. 2013; 107(5): 656-664.

Nguyen K, Lauver D, Kim I, et al. The effect of a steroid “burst” and long-term, inhaled fluticasone propionate on adrenal reserve. Ann Allergy Asthma Immunol. 2003; 91: 38-43.

Nurmagambetov T, Kuwahara R, Garbe P. The economic burden of asthma in the United States: 2008-2013. Ann Am Thorac Soc. 2018 15(3): 348-356.

Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicenter, double-blind, placebo-controlled trial. Lancet. 2012; 380: 651-659.

Pavord ID, Beasley R, Agusti A, et al. The Lancet Commissions. After asthma: refining airways diseases. Lancet 2017. Published Online September 11, 2017. http://dx.doi.org/10.1016/S0140-6736(17)30879-6.

Petsky HL, Kew KM, Turner C, et al. Exhaled nitric oxide levels to guide treatment for adults with asthma. Cochrane Database of Systematic Reviews. 2016a, Issue 9. Art. No.: CD011440.

Petsky HL, Kew KM, Chang AB. Exhaled nitric oxide levels to guide treatment for children with asthma. Cochrane Database of Systematic Reviews. 2016b, Issue 11. Art. No.: CD011439.

Petsky HL, Cates CJ, Kew KM, et al. Tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils): a systematic review and meta-analysis. Thorax. 2018; 73: 1110-1119.

Pijnenburg MW, Hofhuis W, Hop WC, et al. Exhaled nitric oxide predicts asthma relapse in children with clinical asthma remission. Thorax. 2005; 60: 215-218.

Plaza Moral V, Alonso Mostaza S, Alvarez Rodriguez C, et al. Spanish guideline on the management of asthma. J Invest Allergol Clin Immunol. 2016; 26(Suppl 1): 1-92.

Powell H, Murphy VE, Taylor DR, et al. Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomized controlled trial. Lancet. 2011; 378: 983-990.

Price D, Berg J, Lindgren P. An economic evaluation of NIOX MINO airway inflammation monitor in the United Kingdom. Allergy. 2009; 64: 431-438.

Price D, Ryan D, Burden A. et al. Using fractional exhaled nitric oxide (FeNO) to diagnose steroid-responsive disease and guide asthma management in routine care. Clin Transl Allergy. 2013, 3: 37.

Price D, Buhl R, Chan A, et al. Fractional exhaled nitric oxide as a predictor of response to inhaled corticosteroids in patients with non-specific respiratory symptoms and insignificant bronchodilator reversibility: a randomised controlled trial. Lancet Resp Med. 2018; 6(1): 29-39.

Rodrigo GJ, Rodrigo C, Hall JB. Acute asthma in adults a review. Chest. 2004; 125: 1081-1102.

Samitas K, Zervas E, Gana M. T2-low asthma: current approach to diagnosis and therapy. Curr Opin Pulm Med. 2017; 23(1): 48-55.

Schleich FN, Asandei R, Manise M, et al. Is FE(NO50) useful diagnostic tool in suspected asthma? Int J Clin Pract. 2012; 66(2): 158-165.

SIGN158. British guideline on the management of asthma. Revised July 2019. Available online at: https://www.sign.ac.uk/assets/sign158.pdf (Accessed: July 30, 2019).

Shrimanker R, Keene O, Hynes G, et al. Prognostic and predictive value of blood eosinophil count, fractional exhaled nitric oxide and their combination in severe asthma: a post-hoc analysis. Am J Respir Crit Care Med. (In Press). Published online on July 12, 2019 as doi:10.1164/rccm.201903-0599LE.

Silkoff PE, Laviolette M, Singh D, et al. Longitudinal stability of asthma characteristics and biomarkers from the airways disease endotyping for personalized therapeutics (ADEPT) study. Resp Res. 2016; 17: 43.

Sivan Y, Gadish T, Fireman E, et al. The use of exhaled nitric oxide in the diagnosis of asthma in school children. J Pediatr. 2009; 155: 211-216.

Skoner DP. Inhaled corticosteroids effects on growth and bone health. Ann Allergy Asthma Immunol. 2016; 117: 595-600.

Smith AD, Cowan JO, Filsell S, et al. Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests. Am J Respir Crit Care Med. 2004; 169: 473-478.

Smith AD, Cowan JO, Brassett KP, et al. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. N Engl J Med. 2005a; 352: 2163-2173.

Smith AD, Cowen JO, Brassett KP, et al. Exhaled nitric oxide: a predictor of steroid response. Am J Respir Crit Care Med. 2005b; 172: 453-459.

Solidoro P, Patrucco F, de Blasio F, et al. Predictors of reversible airway obstruction with omalizumab in severe asthma: a real-life study. Ther Adv Respir Dis. 2019; 13: 1-12.

Spahn JD, Malka J, Szefler SJ. Current application of exhaled nitric oxide in clinical practice. J Allergy Clin Immunol. 2016; 138: 1296-1298.

Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and the risks of diabetes onset and progression. Am J Med. 2010; 123: 1001-1006.

Sutherland L, Shaw K, Parrish C, et al. A low exhaled nitric oxide level excludes a short-term benefit from inhaled corticosteroids in suspected asthma. Am J Respir Crit Care Med. 2019; 199: A7083.

Szefler SJ, Martin RJ, King TS, et al. Significant variability in response to inhaled corticosteroids for persistent asthma. J Allergy Clin Immunol. 2002; 109: 410-418.

Szefler SJ, Kattan M, Ortiz B, et al. Greater treatment benefit with omalizumab in children with increased asthma severity: exploratory analyses from the preventative omalizumab or step-up therapy for fall exacerbations (PROSE) study. Am J Respir Crit Care Med. 2018; 197: A1157.

Wagener AH, de Nijs SB, Lutter R, et al. External validation of blood eosinophils, FENO and serum periostin as surrogates for sputum eosinophils in asthma. Thorax. 2015; 70: 115-120.

Wang Z, Pianosi P, Keogh K, et al. The Clinical Utility of Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management. Comparative Effectiveness Review No. 197 (Prepared by the Mayo Clinic Evidence-based Practice Center under Contract No. 290-2015-00013-I). AHRQ Publication No.17(18)-EHC030-EF. Rockville, MD: Agency for Healthcare Research and Quality. December 2017. Available online at: https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/cer-197-fractional-exhaled-nitric-oxide_0.pdf (Accessed: August 30, 2019).

Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet. 2016; 388(10039): 31-44.

Westerhof GA, Korevaar DA, Amelink M. Biomarkers to identify sputum eosinophilia in different adult asthma phenotypes. Eur Respir J. 2015; 46: 688-696.

Williams LK, Pladevall M, Xi H, et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. J Allergy Clin Immunol. 2004; 114: 1288-1293.

Zeiger RS, Schatz M, Zhang F, et al. Elevated exhaled nitric oxide is a clinical indicator of future uncontrolled asthma in asthmatic patients on inhaled corticosteroids. J Allergy Clin Immunol. 2011; 128(2): 412-414.

Zitt M, Oppenheimer J, Bernstein D, et al, on behalf of the ACAAI/AAAAI Joint Work Group. AAAAI/ACAAI joint statement of support of the ATS clinical practice guideline: interpretation of exhaled nitric oxide for clinical applications. Available online at: https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/My%20Membership/FeNOJointStatement3-6-12.pdf (Accessed: July 29, 2019).

Indications for Use (US):

NIOX VERO® measures Nitric Oxide (NO) in human breath. Nitric Oxide is frequently increased in some airway inflammatory processes such as asthma. The fractional NO concentration in expired breath (FeNO), can be measured by NIOX VERO according to guidelines for NO measurement established by the American Thoracic Society.

Measurement of FeNO by NIOX VERO is a quantitative, non-invasive, simple and safe method to measure the decrease in FeNO concentration in asthma patients that often occurs after treatment with anti-inflammatory pharmacological therapy, as an indication of the therapeutic effect in patients with elevated FeNO levels. NIOX VERO is suitable for children, 7-17 years, and adults 18 years and older.

NIOX VERO 10 second test mode is for age 7 and up

NIOX VERO 6 second test mode is for ages 7-10 only, who cannot successfully complete a 10 second test.

FeNO measurements provide the physician with means of evaluating an asthma patient's response to anti-inflammatory therapy, as an adjunct to the established clinical and laboratory assessments in asthma. The NIOX VERO is intended for prescription use and should only be used as directed in the NIOX VERO User Manual by trained healthcare professionals. NIOX VERO cannot be used with infants or by children under the age of 7, as measurement requires patient cooperation.

NIOX VERO should not be used in critical care, emergency care or in anesthesiology.