White Paper

Summary of Evidence Supporting the Clinical and Economic Value of Monitoring Exhaled Nitric Oxide in the Management of Asthma

Circassia Pharmaceuticals, Inc.

March 31, 2017

Introduction

Asthma management is complex and supported by national guidelines that were initially created to emphasize the importance of treating the inflammatory nature of the disease in order to improve patient outcomes (NHLBI 1991). Control of airway inflammation is central to effective asthma management. Today, FeNO (fractional exhaled nitric oxide) is a well-established and specific biomarker for Th2 driven airway inflammation in asthma following almost 20 years since the Nobel Prize was awarded in 1998 for understanding the importance of nitric oxide in the cardiovascular system. Shortly thereafter, the role of exhaled NO in airway inflammation/ asthma pathophysiology became clear.

Airway inflammation is driven by the activation of antigen-specific T-helper cells (Th) type 2 that produce a variety of inflammatory cytokines. Of these inflammatory cytokines, IL- 4 and IL-13 have been shown to induce gene transcription for the production of the enzyme iNOS (inducible nitric oxide synthase) in the epithelial cells of the airway which then release NO in expired breath.(Ekroos 2002, Chibana 2008)

The first device for measuring FeNO (NIOX®) was CE marked in the EU for medical use (predominately for research) in 2000 and cleared in the US in 2003. A second generation device that was easier and more convenient to use in the clinic (NIOX MINO®) was subsequently developed and launched in 2004 (Europe) and 2008 (US). NIOX MINO® was the first device for measuring FeNO that could be performed at the point-of-care, providing information to the physician 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. The current version 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; providing a FeNO measurement in approximately one minute following a 10 second exhalation. (Maniscalco 2016)

In September 2011, the American Thoracic Society (ATS) published a clinical practice guideline on the *Interpretation of Exhaled Nitric Oxide Levels (FeNO) for Clinical Applications: an official ATS Clinical Practice Guideline* (Dweik 2011).This practice guideline is designed for clinicians and provides evidence-based recommendations for the use and interpretation of exhaled nitric oxide measurements in clinical practice. This guideline was also 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. FeNO has also been included in the most recent guidelines in the United Kingdom. The National Center for Health and Care Excellence (NICE) recommends FeNO to help diagnose and manage asthma in adults and children. (NICE 2014)

The evidence to the support monitoring FeNO in asthma management is considerable. Ever since 2000, FeNO has been included in the majority of clinical trials evaluating potential new anti-inflammatory asthma drugs. Furthermore, a recent literature search of the National Library of Medicine's PubMed for asthma clinical studies involving FeNO, (using nitric oxide and asthma as search terms) produced over 3,000 articles. However, to categorize the majority of literature that supports the clinical and economic value in the management of asthma, we believe the following 5 reasons for monitoring FeNO have the greatest strength of evidence:

1. FeNO Aids in Diagnosis of Asthma and Identifies Patients with Th2 Airway Inflammation
2. FeNO Helps to Determine Steroid Responsiveness and Optimize the Dose of Inhaled Corticosteroids
3. FeNO Uncovers Non-Adherence to Inhaled Corticosteroids
4. FeNO Reduces the Likelihood of Exacerbations in Patients at Risk for Future Events
5. FeNO Helps to Identify Asthmatics Who Are Possible Candidates for Treatment with a Biologic

1. **FeNO Aids in the Diagnosis of Asthma and Identifies Patients with Th2 Airway Inflammation**

Asthma is one of the most common chronic diseases; three hundred million people worldwide and 25.7 million or 8.4% of the US population are affected by asthma, and the prevalence is expected to grow in the next decade (Akinbami 2012). Asthma is a disease of chronic airway inflammation characterized by variable and recurring symptoms and airflow obstruction. Airway inflammation is the central mechanism in the pathogenesis of asthma leading to bronchoconstriction, bronchial hyper-responsiveness and edema, which is manifested as clinical symptoms of cough, wheezing, breathlessness and chest tightness.

Asthma is both over- and under-diagnosed resulting in inappropriate or ineffective treatments for patients. In fact, it has been estimated that approximately one third of patients diagnosed with asthma do not have asthma when objectively assessed and of these misdiagnosed patients more than 70% are receiving asthma treatments (Pakhale 2011). In recent studies, more than half of children and one-third of adults with asthma may be misdiagnosed (Looijmang-van den Akker 2016, Aaron 2017). Misdiagnosis has important health outcome and health economic implications in that lack of proper diagnosis leads to patients taking medications they do not need and costs to the healthcare system that are substantial and inappropriate.

According to 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). While spirometry is considered a very important and objective tool for supporting a diagnosis of asthma, its usefulness is limited to the measurement and interpretation of airflow and lung capacity, particularly for evaluating the degree of airway obstruction. However, none of these tools that are commonly used in clinical practice directly measure the amount of airway inflammation.

Detecting Airway Inflammation

Incorporating biomarkers into the patient's clinical evaluation uncovers untreated airway inflammation and assists practicing physicians to properly classify the patient's asthma phenotype and therefore individualize drug therapy (Fajt 2015, Bush 2016). Though some consider evaluation of induced sputum for the presence of eosinophils a gold standard for detecting airway inflammation, this test is difficult to perform and not often performed in the majority of office based clinical practices. Its use is more common in specialized research centers equipped to perform the test.

FeNO measurement has been directly evaluated in comparison with other diagnostic procedures for asthma including induced sputum for eosinophils, spirometry and bronchial challenge testing. FeNO has high sensitivity and specificity and correlates well with the results of induced sputum and bronchial challenge testing (Sivan 2009, Smith 2004, Hewitt 2008, Schleich 2012, Attanasi 2016). In a recent comparative meta-analysis of a variety of tests for diagnosing asthma (e.g. spirometry, bronchial challenge, and/or bronchial reversibility), FeNO was found to have good performance and the authors even stated that FeNO might render bronchoprovation testing superfluous. (Karrasch 2017) In addition, FeNO has also shown to be equivalent to the use of peripheral blood eosinophils as a surrogate to predict 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 modest degree (Westerhof 2015), FeNO alone provides sufficient accuracy of detecting Th2 airway inflammation and is available for use at the point of care (Wagener 2015).

Asthma is typically variable in most patients and therefore corresponding fluctuations in airway inflammation are to be expected. This underscores the need for periodic assessment of patients and longitudinal monitoring of biomarkers. A recent study assessed the variability of a variety of clinical

tools (patient questionnaires, spirometry, and bronchodilator reversibility) and biomarkers (FeNO, induced sputum for eosinophils and neutrophils) 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 > 35ppb). The authors concluded that higher variability was most likely related to seasonal variations in climate, allergen exposure, medication changes and acute exacerbations and therefore emphasized the importance of longitudinal monitoring of indices that are more specific for Th2 asthma inflammation. (Silkoff 2016).

In 2011, The American Thoracic Society (ATS) published an evidence-based guideline for improving patient care when monitoring FeNO is incorporated into clinical practice (Dweik 2011). Specifically, the ATS Guideline strongly recommends the use of FeNO in the diagnosis of eosinophilic airway inflammation based on a level of moderate evidence. In addition, the ATS Guideline recommends that cut points, rather than reference ranges, be used when interpreting FeNO values. Values of less than 25 ppb in adults (<20 ppb children) are considered low; intermediate values are 25 to 50 ppb in adults (20-35 ppb children), and high values are greater than 50 ppb in adults (>35 ppb children).

2. **FeNO Helps to Determine Steroid Responsiveness and Optimize the Dose of Inhaled Corticosteroids (ICS)**

Evaluating Steroid Responsiveness

Inhaled corticosteroid (ICS) therapy has been and continues to be the mainstay of treatment for asthma ever since the first national guidelines were published (NHLBI EPR-1 1991) that emphasized the importance of treating the inflammatory component of the disease. In more recent years, the need for understanding the phenotypic characteristics of the disease has also become important since it helps clinicians individualize treatment accordingly. Patients with Th2 phenotype have increased airway inflammation associated with eosinophils compared to Th1 phenotype that is associated with more neutrophilic infiltration (Fajt 2015).

Patients respond to various asthma treatments differently depending on their underlying disease characteristics. While the majority of patients with asthma demonstrate a Th2 phenotype and do respond to corticosteroid treatment, a significant portion of patients demonstrate phenotypes not characteristic of Th2 inflammation and thus will respond less. It has been observed that up to 75% of steroid-naïve patients have primarily Th2 driven asthma and respond significantly to ICSs (Bradding 2008). However, up to 45% of asthmatic patients do not benefit from ICS therapy as they exhibit non-eosinophilic Th1 asthma (Spahn 2016). FeNO measurement identifies patients with Th2 driven airway inflammation and helps to predict response to ICS therapy (Price 2013).

An early study done in 1999 by Malmstrom et al, investigated the response to beclomethasone in a large group of asthmatics (n=251) using traditional measures (and prior to the ability to measure FeNO). Using spirometry to identify treatment response, they found only 50% of patients had at least 11% improvement in FEV_1, while 22% had no improvement. Interestingly the majority of their study population had clinical characteristics of having Th2 asthma; over 60% had comorbid allergic disease and the mean peripheral blood eosinophil count was 0.35cells/ul. (Malmstrom 1999) Had FeNO been used in this study the results may have demonstrated a greater percentage of patients responding to inhaled corticosteroids. In addition, this study highlights the need to properly characterize subjects who potentially may have Th2 driven inflammation (e.g. through measurement of FeNO) before commencing a trial of ICS therapy or evaluating other new treatments for asthma.

An example of a study that used FeNO to evaluate ICS response in patients presenting with nonspecific respiratory symptoms was completed by Smith et al (Smith 2005a). They studied 101 patients referred to a respiratory specialist for treatment. Steroid response was evaluated using

spirometry (FEV$_1$, peak flow, bronchodilator response), and bronchial challenge in addition to FeNO. Baseline FeNO provided greater sensitivities and negative predictive values than each of the other predictors. More specifically, a baseline FeNO >47ppb predicted steroid response better than any of the other tests.

Other studies in children and adults have demonstrated that patients who initially present with an increased FeNO value will more likely have a positive response to inhaled corticosteroids. Conversely, patients who have a low FeNO value are more unlikely to respond to ICS therapy. (Price 2013). FeNO measurement predicts the likelihood of steroid responsiveness more consistently than spirometry, bronchodilator response, peak flow variation, or airway hyper responsiveness to methacholine (Knuffman 2009, Szefler 2002).

Optimizing the Dose of ICS

Current national asthma guidelines recommend periodic clinical assessment of patients and adjustment of medications by either stepping-up or -down therapy. Asthma severity and symptoms fluctuate depending on the patient's lifestyle, exposure to environmental triggers and genetic tendencies. Therefore, periodic re-assessment is needed to help individualize drug therapy according to the patient's asthma symptoms, degree of airway inflammation and to minimize adverse effects from medications (NHLBI 2007).

The clinical benefit of periodic assessment of airway inflammation using FeNO in chronic asthma was demonstrated in a study by Smith et al. (Smith 2005b). They followed two groups of patients, one used traditional monitoring (symptoms, spirometry, etc) and the other a FeNO based approach. After 12 months, the ICS dose of fluticasone was 370 µg per day in the FeNO group and 641 µg per day in the control group. More importantly, asthma control was better in the FeNO group with 45.6% less exacerbations compared to the standard care group. Exposure to high doses of ICS was also reduced in this study by using a FeNO based strategy to step patients down; 48% of the standard care group were receiving 1,000ug of fluticasone daily at the end of the study compared to 20% in the FeNO group.

Historically, the dose-response curve for the clinical efficacy of ICS has been considered to be relatively flat, meaning that it plateaus early, with no further therapeutic response (i.e. improvement in symptoms and or lung function) with increasing dose of medication (Szefler 2002). While all studies have demonstrated some clinical benefit of ICS, it has been difficult to demonstrate differences between doses, with most benefit obtained at the lowest doses used (Barnes 2010). The relatively flat dose response curve of ICS (based on changes in symptoms and lung function) combined with a lack of specific measures of airway inflammation to help clinicians guide dosing has led to many patients receiving higher doses than are necessary. Using higher doses of ICS exposes patients to potential adverse effects from steroids. Higher doses and prolonged use of ICSs can have systemic effects on growth, bone density, cataracts, adrenal insufficiency and an increased risk of diabetes (Skoner 2016, Carr 2016, Choi 2017, Nguyen 2003, Suissa 2010).

Recently, Lipworth and colleagues reevaluated the dose response curve for ICSs by adding markers of airway inflammation to the analysis. In their study they confirmed that improvements in symptoms and lung function were only seen with lower doses of ICS. However, addition of measures of inflammation such as FeNO, eosinophilic cationic protein and blood eosinophils was able to detect a clear dose response curve covering low to high doses of ICS (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 supports how monitoring FeNO helps to guide treatment decisions in the management of asthma. LaForce et al demonstrated that without knowledge of the patient's FeNO, the

clinician's assessment did not recognize the amount of airway inflammation in 50% of patients. Measurement of FeNO substantially altered treatment decisions in more than one third of subjects, notably stepping up medication in 20% and stepping down medication in 16% of the patients studied (LaForce 2014). Results from LaForce et al. have been expanded to a summary of experience of using the NIOX® device in over 7,000 patients involved in a real world survey of FeNO use in over 300 asthma clinics in the US (Hanania 2016). Physician's clinical ability to detect the presence of significant airway inflammation using traditional office based tools was able to recognize the likelihood of the FeNO being > 50 ppb in approximately 1/3 of patients. However, once the physician knew that the patient had an elevated FeNO (> 50 ppb), anti-inflammatory treatment was then stepped up in 96% of patients.

Lastly, ATS Guideline recommendations for the use of FeNO monitoring states that a FeNO > 50 ppb (> 35 ppb in children) be used to indicate eosinophilic inflammation is likely and, in symptomatic patients, responsiveness to corticosteroids are also likely (strong recommendation, moderate quality of evidence) (Dweik 2011).

3. FeNO Uncovers Non-Adherence to Inhaled Corticosteroid Therapy

ICS treatment is widely considered to be the cornerstone therapy for the control of asthma symptoms (NHLBI 2007), 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). A number of factors are associated with non-adherence to asthma therapy. Medication-related factors include difficulties with inhaler devices, complex regimens, side effects, cost of medication, dislike of medication, and distant pharmacies.

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-quarters 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 unanimously stress the importance of identifying and addressing non-adherence in this population (Bousquet 2010, Bel 2011).

INOS (inducible nitric oxide synthase enzyme) expressed by airway epithelial cells is very sensitive to the effect of corticosteroids (Kharitonov 1996). Therefore, as discussed in the previous section on the role of FeNO in ICS dosing, it would make sense that FeNO would also be a useful tool to determine if patients have been using their inhaled or oral medications that contain a corticosteroid. Indeed good adherence to prescribed asthma therapy has been associated with better disease control and lower FeNO concentrations (Klok 2014).

An early study in 2002 investigated the effect of budesonide on changes in FeNO and spirometry. Fifty-four pediatric and adolescent patients were followed for 8 weeks during treatment with budesonide or placebo following a 4 week washout period. They found a significant relationship of budesonide dosing and changes in FeNO while no effect was observed on 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 to asthma control and medication adherence in 30 pediatric and adolescent patients that were followed periodically for 2.5yrs using NHLBI Guidelines. 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 clearly demonstrates that the dynamic effect of ICSs on FeNO may be used as an accurate discriminator of non-adherence to inhaled corticosteroids in adults (McNicholl 2012).

Patients in this study received 7 days of direct observed administration of their ICS medication (DOICS). Those patients who had a history of poor adherence as measured by ICS refills of less than 50% experienced a greater reduction in FeNO following 7days of DOICS compared to the group of adherent patients who had > 80% history of ICS refills (47 +/- 21% versus 79 +/- 26%) of baseline measurement (P < 0.003).

In another novel study that investigated using FeNO as a surrogate marker of medication adherence, Kaminsky et al evaluated 27 children who attended a summer camp for asthma. Throughout the one week duration of the summer 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 the patient's FeNO that was attributed to improved adherence (via direct observed administration) (Kaminsky 2008).

There are other situations in which FeNO monitoring is useful in the management of patients with difficult-to-treat asthma, for example, when invasive therapeutic interventions or expensive biologicals are being considered (Fajt 2015). In this case, FeNO monitoring is used to help verify that ICS based medications have been optimized and non-adherence ruled out before progressing to additional more expensive therapies or diagnostic tests. Many managed care organizations and pharmacy benefit managers require prescribers to provide evidence that the patient has a steroid resistant inflammatory process that is not adequately treated by ICS/LABA medications (Pavord 2012). Use of FeNO in these situations helps to provide objective evidence of steroid responsiveness and medication adherence.

4. FeNO Reduces the Likelihood of Exacerbations in Patients at Risk for Future Events

The frequency and severity of exacerbations of asthma in patients is often variable. Some patients have periods of increased symptoms and more severe exacerbations depending on exposure to environmental allergens and other triggers; others have a more mild form of the disease and less exacerbations (NHLBI 2007). It is estimated that only 20% of asthmatics have had exacerbations requiring treatment in the emergency department or hospitalization, yet these patients account for more than 80% of total direct costs (Rodrigo 2004). For example, 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 in patients that are more prone to exacerbations 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). Other factors associated with more difficult to control asthma include comorbid allergic disease, obesity, smoking, and markers of airway inflammation such as elevated FeNO and blood or sputum eosinophils (Chen 2008, Kupczyk 2014, Zeiger 2011). Specifically, elevated FeNO (> 50ppb) has been shown to be a significant independent risk factor for uncontrolled asthma (Malinovischi 2016). 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).

Asthma exacerbations significantly impact patient lives and lead to an increase in direct and indirect costs. In 2008, at least one half (52.6%) of persons with asthma in the US reported having an asthma attack in the preceding 12 months. Those who had attacks had a higher proportion of emergency department and urgent care visits, and reported fair to poor health (CDC, MMWR 2011). In 2007, there were 1.75 million asthma-related emergency department visits and 456,000 asthma hospitalizations (Akinbami 2011). Asthma is the most common reason for an emergency department "treat and release" visit for children. Asthma is the second most common reason for hospitalization for children and the fourth most common reason for adults. Despite effective treatments, asthma morbidity remains high with up to 15% of well controlled patients and up to 49% of poorly controlled patients requiring a hospitalization, emergency room visit or other unscheduled visit for their asthma each year (AIM Survey

2009). The cost of inpatient hospitalizations and emergency department visits in 2007 are estimated at over $16 billion (2009 dollars). There has been no significant reduction in the hospitalization rate for asthma while costs have continued to increase (Barnett 2011).

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. For example, Bai et al (2007) conducted a study to investigate the effect of severe exacerbations on the progression of airway obstruction in 93 nonsmoking asthmatics with moderate-to-severe disease prior to treatment with inhaled corticosteroids. Subjects were followed for >5 yrs. (median follow up was 11 yrs.). The exacerbation rate significantly predicted an excess decline in FEV_1, such that one severe exacerbation per year was associated with a 30.2 mL greater annual decline in FEV_1

How can clinicians better identify patients at risk for future uncontrolled asthma and exacerbations? Studies have demonstrated that the addition of monitoring FeNO, a biomarker of airway inflammation, to usual clinical assessments during routine asthma visits such as asthma control patient questionnaires and spirometry helps to identify patients at risk for future exacerbations (Zeiger 2011). 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 sooner. Using a FeNO based strategy compared to usual care was associated with a significant reduction in asthma exacerbations and improved quality of life. (Powell 2011). Interestingly, there were benefits seen in the offspring as neonatal hospitalizations were reduced too. The offspring from this study were also followed up later in life. In the year following birth there was a 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, ED visits and doctor diagnosed asthma were all significantly lower in children from the FeNO group. (Morten 2016).

The most compelling evidence to support the use of monitoring FeNO in asthma management has been summarized in two recent Cochrane meta-analyses that concluded exacerbations were reduced 40-50%.

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 2016) By monitoring FeNO, the number of exacerbations were reduced by 40% and the exacerbation rates by at least 41%. The number of people having one or more asthma exacerbations 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 on FeNO on reducing asthma exacerbations was determined to be moderate even though exacerbations were not defined the same across all of the studies included in the analysis.

Additional secondary endpoints were examined in the meta-analysis (symptoms, ICS dosing and measures of asthma control such as spirometry). None were found to be significant, however consistency of reporting data across the 7 studies on secondary outcome measures affected the ability to accurately compare groups using meta-analysis methodology. No mention of the grade of evidence to support the conclusions was provided (except for ICS dosing where the authors found low evidence). Despite this, the authors still went on to conclude that FeNO did not impact day-to-day clinical symptoms, end-of-study FeNO levels, or inhaled corticosteroid dose.

In a second 2016 Cochrane Systematic Review focusing on pediatrics, 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. 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; 8 studies; p< 0.0002) (Petsky 2016).

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 (Petsky 2016). Furthermore, the incorporation of FeNO monitoring into asthma management is a cost-effective strategy that improves outcomes and medication use (Bukstein 2011, Honkoop 2015). Our pharmacoeconomic cost model of justifying the use of FeNO monitoring based on data in reducing the likelihood of exacerbations demonstrates an overall cost savings in a typical managed care payer organization (Massanari 2017).

5. FeNO Helps to Identify Asthmatics Who Are Possible Candidates for Treatment with a Biologic

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 according to current guidelines (NHLBI 2007). 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, Kupcyzk 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 such as a biologic (e.g., omalizumab, mepolizumab or reslizumab).

To characterize difficult to control asthma vs severe refractory asthma, Hekking et al (2015) conducted an epidemiological investigation of asthma control in the Netherlands where there is documentation of healthcare utilization among its inhabitants receiving care through their nationalized system. They found 74.1% of asthma patients receiving moderate to high dose 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 prescription and only 41.6% of those patients had correct inhalation technique. Thus only 20.5% of the patients with difficult-to-control asthma qualified for the definition of truly severe refractory asthma which corresponded to 3.6% (95% CI, 3.0% to 4.1%) of the overall Dutch adult asthmatic population.

Treatment decisions in patients with difficult to control asthma are complicated. Before treatment with a biologic is considered, patients need to be reevaluated and comorbidities, medication nonadherence and poor inhaler technique ruled out. Using FeNO monitoring in asthma management helps to confirm ICS non-adherence/compliance and identifies patients with more severe disease that have persistent airway inflammation despite treatment with an ICS/LABA with or without additional drugs such as LTRAs (McNicholl 2012) (see previous section on Optimizing ICS Dosing and Treatment Adherence).

<u>Use of FeNO with Biologics</u>

Omalizumab

The EXTRA study enrolled 850 patients (aged 12-75 years) with uncontrolled severe persistent allergic asthma despite treatment with ICS/LABA with or without other controllers 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 28.5ppb in the omalizumab patients and 29.2ppb in the placebo patients. Use of omalizumab was associated with a modest 25% relative reduction in asthma exacerbations (larger rate reductions in exacerbations were seen in the phase II studies which studied patients on ICS alone since LABAs were not available when the studies were started) (Hanania 2011).

A subsequent pre-specified analysis was performed to evaluate the reduction in exacerbation rate of omalizumab in relation to baseline biomarkers of airway inflammation (FeNO and blood eosinophils), and serum periostin (done post hoc). (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 (>19.5 ppb); mean 53% reduction compared to 16% when baseline FeNO was < 19.5ppb. For high blood eosinophils the mean reduction in asthma exacerbations was 32% (eosinophils > 260ul) vs 9% for low eosinophils (< 260ul). In summary, use of biomarkers of persistent airway inflammation helps to identify patients who may benefit most from treatment with omalizumab.

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 (Massanari 2017). 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.

Anti-IL 5 Monoclonal Antibodies

FeNO has been utilized as one of the study entry criteria during phase III clinical trials with mepolizumab in patients with severe asthma with a Th-2 eosinophilic phenotype.

The DREAM mepolizumab study evaluated 621 patients with eosinophilic asthma who had a history of severe recurrent exacerbations. Baseline entry criteria included one or more of the following criteria: a sputum eosinophil count of ≥ 3%, a FeNO of ≥ 50 ppb, an asthma-related peripheral blood eosinophil count of ≥ 0·3×10^9 per L, or prompt deterioration of asthma control after a ≤ 25% reduction in regular maintenance inhaled or oral corticosteroids. Patients were randomized to receive one of 4 treatment regimens: placebo, 75mg, 250mg and 750mg of mepolizumab IV every 4 weeks for one year. The mean baseline FeNO ranged from 29.2 to 33.7 ppb. The rate of clinically significant exacerbations was 2.40 per patient per year in the placebo group, 1.24 in the 75 mg mepolizumab group (48% reduction, 95% CI 31–61%; P<0·0001), 1.46 in the 250 mg mepolizumab group (39% reduction, CI 19–54%; P=0·0005), and 1.15 in the 750 mg mepolizumab group (52% reduction, CI 36–64%; P<0·0001). Post treatment FeNO was not significantly different across the groups of mepolizumab doses. (Pavord 2012)

However, in the patients who had elevated FeNO at baseline ≥ 50 ppb there appears to be an effect on the rate of exacerbations (but not statistically significant) (see table 1 below) (FDA 2015).

Other anti-IL5 monoclonal antibodies for severe asthma such as reslizumab and benralizumab have not reported use of FeNO as a baseline enrollment criteria nor an outcome measure during their phase III registration trials.

Therefore, the role of FeNO in helping to identifying candidates for treatment with anti-IL5 monoclonal antibodies appears to be similar to other drugs, i.e. it helps to identify patients who have persistent airway inflammation despite treatment with ICS/LABA combinations. However, unlike omalizumab no data is currently available to suggest that FeNO can be used as an outcome measure associated with treatment with anti-IL5 monoclonal antibodies nor a predictor of a patient to respond better to treatment.

Table 1: Exploratory analysis of the primary endpoint: rate of exacerbations by inclusion criterion from Dream study

		Mepolizumab		
	Placebo N=155	**75mg IV N=153**	**250mg IV N=152**	**750mg IV N=156**
Blood eosinophils ≥ 300 cells/uL				
N	96	85	93	91
Exacerbation rate per year	2.22	1.08	1.16	1.22
Sputum eosinophilia ≥ 3%				
N	16	18	16	14
Exacerbation rate per year	2.03	1.13	0.96	1.40
Exhaled nitric oxide ≥ 50 ppb				
N	70	61	57	74
Exacerbation rate per year	2.83	1.25	1.5	0.92
Deterioration of asthma control following at least a 25% reduction in corticosteroid use				
N	48	46	41	47
Exacerbation rate per year	2.57	1.04	1.48	0.88

Source: Study 97 CSR Table 11
FDA Joint Clinical and Statistical Briefing Document BLA 125526
Tests for treatment by subgroup interaction each are not statistically significant

References

Aaron SD, Vandemheen KL, Fitzgerald M et al. Reevaluation of Diagnosis in Adults with Physician-Diagnosed Asthma. JAMA 2017; 317(3):269-279.

AIM- Asthma Insight & Management Survey 2009 – largest US survey in decade; 60,283 households surveyed, 2500 asthma patients; conducted by Abt SRBI, Inc.

Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use and mortality: United States. 2005-2009. National Health Statistics Reports: 2011. January 12, 2011:32.

Akinbami LJ, Moorman JE, Bailey C, et al. Trends in asthma prevalence, health care use, and mortality in the United States. 2001-2010. National Center for Health Statistics Data Brief No. 94: May 2012.

Anderson, WJ, Short, PM, Jabbal, S, Lipworth, BJ. Inhaled corticosteroid dose response in asthma. Should we measure inflammation? Ann Allergy Asthma Immunol 2017, 118, 179e185

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

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.

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. Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome (U-BIOPRED) Consortium, Consensus Generation. 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 Immunology. 2008; 4: 84-90.

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

Bush A, Fleming L. Is asthma over diagnosed? Arch Dis Child August 2016 Vol 101 No 8

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

Centers for Disease Control and Prevention. Vital signs: asthma prevalence, disease characteristics, and self-management education-United States, 2001-2009. Morbidity and Mortality Weekly Report. May 3, 2011:60.

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. Clinical and Experimental 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.

Clearie KL, Jackson CM, Fardon TC, et al. Supervised step-down of inhaled corticosteroids in the community-an observational study. Respir Med. 2011; 105:558-565.

Delgado-Corcoran 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.

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 Vol.96, 895-900

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 125526. 2015 Downloaded from:
https://www.fda.gov/downloads/drugs/developmentapprovalprocess/developmentresources/ucm479963.pdf

GINA-Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA). Full text available online at: www.ginasthma.org (Accessed on January 19, 2017).

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

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, Peddicord T, et al, Impact of feno on treatment decisions: results from the ASTH2MA (assessment of TH2 inflammation) survey. Annals of Allergy, Asthma & Immunology, 2016, Vol. 117, Issue 5, S116.

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

Hewitt RS, Modrich CM, Medlicott T, et al. Supporting the diagnosis of non-specific respiratory symptoms in primary care: the role of exhaled Nitric Oxide measurement and spirometry. Prim Care Respir J. 2008; 17 (2):97-103.

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. Journal of Allergy and Clinical Immunology. 2015; 135(3): 682–688.e11.

Kaminsky, DA., Rice AA, Bissonette, M, et al. Exhaled Nitric Oxide Decreases in Association with Attendance at an Asthma Summer Camp',Journal of 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, S. A., Yates, D. H., Barnes, P. J. Inhaled glucocorticoids decrease nitric oxide in exhaled air of asthmatic patients. Am J Respir Crit Care Med. 1996 Jan; 153(1):454-7.

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; for the Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute. 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.

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

Looijmang-van den Akker I, Luijn K, Verheij T. Overdiagnosis of asthma in children in primary care: a retrospective analysis. Br J Gen Pract 2016; 66 (644): e152-e157.

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

Malmstrom K. Rodriguez-Gomez G, Guerra J. Oral Montelukast, Inhaled Beclomethasone, and Placebo for Chronic Asthma. Ann Intern Med. 1999; 130:487-495.

Maniscalco M, Vitale C, Vatrella A. et al. Fractional exhaled nitric oxide-measuring devices: technology update. Medical Devices: Evidence and Research. 2016:9 151–160

Massanari M, Brooks EA, Rickard KA, et al. Cost-effectiveness of using FeNO in the management of asthma. ISPOR Annual Meeting 2017.

Massanari M, Brooks EA, Rickard KA, Roman AA. Investigation of the cost effectiveness of FeNO measurement as a screening tool to detect omalizumab responsiveness in difficult to treat asthma patients. ISPOR Annual Meeting, 2017

Matsunaga K, Hirano T, Oka A et al. Persistently high exhaled nitric oxide and loss of lung function in controlled asthma. Allergology International 2016; 65: 266e271

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

McNicholl DM, Stevenson M, McGarvey LP, et al. The Utility of Fractional Exhaled Nitric Oxide Suppression in the Identification of Non-adherence in Difficult Asthma. Am J Respir Crit Care Med. 2012; 186(11):1102-1108.

Morten M, Collison A, Meredith J, et al. FeNO-guided management of asthma during pregnancy reduces respiratory symptoms and asthma diagnosis in childhood. European Respiratory Journal 2016 48: PA330

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. National Asthma Education and Prevention Program Expert Report: Guidelines for the Diagnosis and Management of Asthma 1991.

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

National Center for Health and Care Excellence (NICE). Measuring fractional exhaled nitric oxide concentration in asthma: NIOX MINO, NIOX VERO and NObreath. NICE diagnostics guidance 12, Issued: April 2014.

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):656-64.

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.

Pakhale S, Sumner A, Coyle D, et al. (Correcting) misdiagnoses of asthma: a cost effectiveness analysis. BMC Pulmonary Medicine. 2011; 11:27.

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.

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

Pijnenburg MW, Bakker EM, Hop WC, et al. Titrating steroids on exhaled nitric oxide in children with asthma: a randomized controlled trial. Am J Respir Crit Care Med. 2005; 172:831-836

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: 983–90.

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. Clinical and Translational Allergy 2013, 3:37.

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

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.

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

Smith AD, Cowan JO, Brassett KP, et al. Use of Exhaled Nitric Oxide Measurements to Guide Treatment in Chronic Asthma. N Engl J Med 2005b; 352:2163-73

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.

Szefler SJ, Martin RJ, King TS, et al; for the Asthma Clinical Research Network of the National Heart, Lung, and Blood Institute. Significant variability in response to inhaled corticosteroids for persistent asthma. J Allergy Clin Immunol. 2002; 109:410-418.

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

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.

Zacharasiewicz AN, Wilson C, Lex EM, et al. Clinical use of noninvasive measurements of airway inflammation in steroid reduction in children. Am J Respir Crit Care Med. 2005; 171(10):1077-1082.

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.