

REVIEW ARTICLE

A Review of the Utility and Cost Effectiveness of Monitoring Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management

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Abstract

Asthma is a common chronic respiratory disease affecting nearly 8% of the U.S. population. It results in substantially higher direct and indirect costs as well as an increased mortality risk and poorer quality of life, particularly among patients with difficult-to-control asthma. While several physiologic tests, including spirometry, are typically used to diagnose and characterize asthma, they do not provide the sensitivity and specificity required to accurately reflect the underlying heterogeneous inflammatory pathways. Fractional exhaled nitric oxide (FeNO) is a validated, noninvasive biomarker for T2-driven (i.e., allergic) airway inflammation that correlates with sputum eosinophils at or greater than 3% across various asthma phenotypes. Its use as a biomarker in asthma is well supported by numerous peer-reviewed articles and guidelines. There is also evidence that its use in clinical settings for patients with uncontrolled asthma is cost effective, given its ability to improve the accurate diagnosis of asthma, monitor treatment response, optimize inhaled corticosteroid dosing, and identify patient nonadherence. It may also have a role in identifying patients who are possible candidates for treatment with biologics.

Introduction

Asthma is a common chronic respiratory disease characterized by inflammation, bronchial hyper-responsiveness, and intermittent bronchoconstriction. It affects approximately 8% of the population and is associated with impaired quality of life, decreased work productivity, greater mortality risk, and higher health care utilization and costs (Chastek 2016, CDC 2018). Overall, asthma costs the U.S. health care system an estimated \$18 billion a year in adult health expenditures. When lost school and work days and early deaths are included for children and adults, the total costs rise to about \$56 billion (Sullivan 2014, CDC 2011).

The costs are disproportionately and substantially higher in patients with uncontrolled, severe, or difficult-to-control asthma (Sullivan 2014). These patients account for a substantial proportion (one third to one half) of all people with asthma (NAEPP 2007). Annual per-member spend for asthma medications ranks in the top 10 of all chronic diseases.

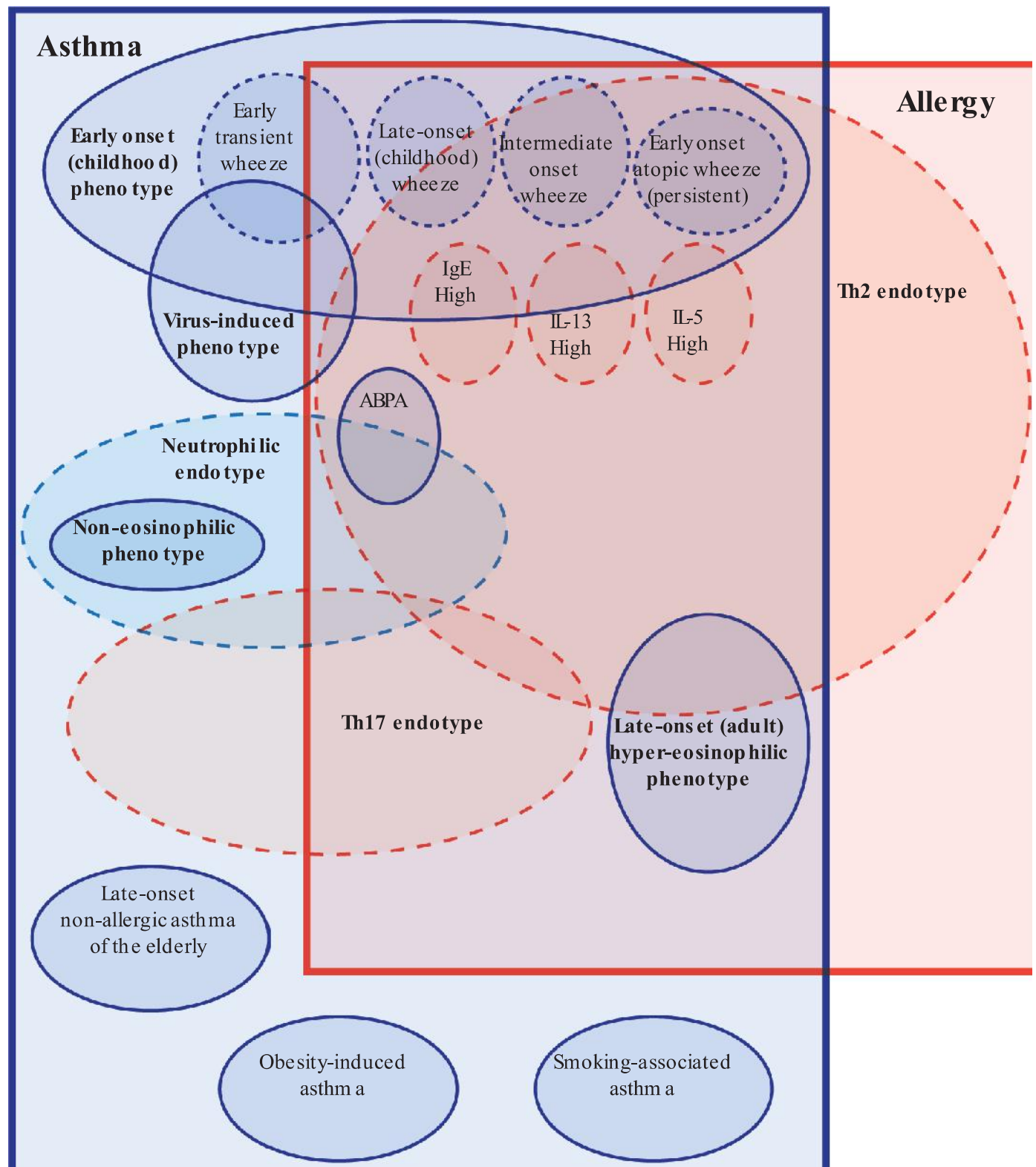
With respect to spending on prescription drugs, asthma is the eighth most expensive chronic disease on an annual per member basis for commercial payers, tenth most for Medicare, and fourth for Medicaid (Express Scripts 2017). Medicaid enrollees have a high prevalence of asthma, and Medicaid is the largest payer for asthma-related hospitalizations among children and adults (Barrett 2014).

It has long been known that asthma is a heterogeneous disease; however, in recent years different phenotypes have been defined that better describe the underlying pathophysiology and help to improve therapy by targeting drug treatment. With the introduction of expensive biologic therapies for severe asthma, the need to identify appropriate patients using biomarkers has become even more clinically important (Wenzel 2013).

Asthma is divided broadly into two inflammatory subtypes, Th2/T2 and non-Th2/T2 (Table and Figure). T2 has more recently evolved from the older designation of Th2 asthma. Th2 asthma was defined as a disease that is caused by inflammatory cytokines released by Th2 CD4 T cells. However, it is now recognized that other inflammatory cells (basophils, mast cells, and eosinophils) can also produce these cytokines. Thus, the terminology was broadened to T2 asthma in recognition of this more diverse origin of inflammation (Gauthier 2015).

Table Common characteristics of asthma types	
Asthma type	Common characteristics
Th2/T2 asthma	• More common • Early age of onset • Associated with atopy/allergy, elevated serum IgE • Eosinophilia • Elevated FeNO • Corticosteroid responsive
Non-Th2/T2 asthma	• Later age of onset • Poor response to corticosteroids • Neutrophilic • Higher likelihood of history of smoking • Associated with infections

FIGURE Overview of asthma phenotypes



ABPA=allergic bronchopulmonary aspergillosis, IgE=immunoglobulin E, IL=interleukin.

Adapted from Wenzel S. *Nature Medicine*. 2012;18:716–725

Asthmatic patients with the T2 phenotype are more common, tend to have an allergic-mediated component to their disease, and tend to have higher levels of blood/sputum eosinophils and fractional exhaled nitric oxide (FeNO). Therefore, asthma that is associated with T2-driven airway inflammation is generally referred to as allergic or eosinophilic asthma. These patients are more likely to respond to

corticosteroid therapy than those with the non-T2 phenotype, which is driven more by neutrophils (Fajt 2015).

Clinical use of biomarkers in asthma for detecting airway inflammation

Common pulmonary function measures used to assess asthma, including spirometry and bronchoprovocation, measure airway obstruction and smooth muscle dysfunction but are not sufficiently accurate to detect the presence of airway inflammation (Bukstein 2011). For many years the measurement of sputum eosinophils has been considered the gold standard for detecting eosinophilic airway inflammation. However, this measurement is technically difficult and is not typically performed in the outpatient setting (Arron 2013). Coinciding with the introduction of biologic therapies for asthma, the use of blood eosinophils in place of sputum eosinophils has become more accepted, presumably due to the ease of collection.

FeNO is a validated and specific biomarker for T2-driven airway inflammation in asthma. Shortly after the 1998 Nobel Prize in Physiology or Medicine was awarded to Robert Furchgott, Louis Ignarro, and Ferid Murad for their discovery that nitric oxide (NO) acts as a signaling molecule in the cardiovascular system, the role of exhaled NO in airway inflammation and asthma pathophysiology became clear and clinical guidelines for its use were developed (ATS 1999). While induced sputum for the presence of eosinophils is considered to be the gold standard for detecting airway inflammation, this test is difficult to perform and not done in most office-based clinical practices. FeNO correlates with sputum eosinophils at or greater than 3% across various asthma phenotypes. (Westerhof 2015). 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 minor degree (Westerhof 2015), FeNO alone provides sufficient accuracy of detecting T2 airway inflammation and is available for use at the point of care (Wagener 2015). Its use as a biomarker in asthma is well supported by numerous peer-reviewed articles and evidence-based reviews. Guidelines from the American Thoracic Society (ATS) recommend its use in the clinical assessment of asthma (Bukstein 2011, Wang 2017, Dweik 2011).

The first FeNO monitoring device was approved by the FDA in 2003. The device was expensive, technically difficult to use, and required complicated maintenance. Thus, the majority of its use was in major asthma research centers. After a less expensive, portable device was cleared by the FDA in 2008, the use of FeNO monitoring in clinics and office practices became more common. The first CPT code (95012, nitric oxide expired gas determination) was approved for use in reimbursement shortly after a FeNO device for clinical use became available (Spahn 2016). In 2017, the national reimbursement rate for FeNO in Medicare averaged \$19.38, while reimbursement was generally lower in the fee-for-service Medicaid system. While the majority of national and regional payers and state Medicaid organizations pay for FeNO monitoring (typically about \$20 per test), there are a few notable exceptions that have negative FeNO policies that conflict with the more recent government-sponsored evidence reports and guidelines from professional societies (Wang 2017, NICE 2017, Dweik 2011).

The majority of clinical evidence to support the use of FeNO monitoring can be categorized into the following areas: 1) diagnosis of asthma, 2) steroid responsiveness and dosing of inhaled corticosteroids (ICS), 3) monitoring asthma control, 4) medication adherence, and 5) asthma biologics (NICE 2017, Wagener 2015, Petsky 2016a, Petsky 2016b, Smith 2005a, Hanania 2013).

The purpose of this review is to summarize the cost-effectiveness data that support the use of FeNO monitoring within the areas related to the diagnosis and management of asthma.

Diagnosis of asthma

Current national clinical guidelines recommend the use of family and medical history, physical examination, clinical signs and symptoms, and spirometry to establish the diagnosis of asthma (NAEPP 2007). However, there is no gold standard, and a substantial number of patients are incorrectly diagnosed with a large portion of overdiagnoses. The problem of overdiagnosis was confirmed in a study showing that nearly a third of individuals in the community with an asthma diagnosis did not have asthma (Aaron 2017). The study demonstrated that the most common reason for misdiagnosis of asthma was a failure to consistently use objective testing at the time of initial diagnosis. The individuals who are overdiagnosed have unnecessary expenditures for the treatment of asthma.

The value of FeNO as a diagnostic tool is related to its unique ability to detect the presence of T2 airway inflammation in a rapid, noninvasive manner (Wagener 2015, Smith 2004, Dinakar 2017). The accuracy of using FeNO in the diagnosis of asthma is related to the baseline exhaled NO concentration (higher concentrations are associated with greatest accuracy) (Karrasch 2017). Indeed, a recent evidence-based analysis that included 43 studies with a total of 13,747 patients concluded that (depending on the FeNO level) the likelihood of people ages five years and older having asthma increases by 2.8 to 7.0 times given a positive FeNO test result (based on evidence rated as moderate) (Wang 2017). Because the FeNO test is relatively inexpensive compared to other procedures (e.g., reimbursement for spirometry ranges from approximately \$40 to \$100), it is not surprising that it was found to be cost effective (Price 2009). However, using FeNO alone in the diagnosis of asthma has been criticized since it is not a measure of airway obstruction. Only recently has FeNO been evaluated as part of a diagnostic algorithm that incorporates the contribution of both airway inflammation and obstruction. In this scenario, 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).

Steroid responsiveness and dosing of ICS

ICS therapy has been the mainstay of treatment for asthma ever since the first national guidelines emphasized the importance of treating the inflammatory component of the disease (NAEPP 1991). In addition, current asthma guidelines recommend periodic clinical assessment of patients and adjustment of medications by either stepping up or stepping down therapy because asthma symptoms fluctuate depending on the patient's lifestyle, exposure to environmental triggers, and genetic tendencies (NAEPP 2007). Periodic reassessment is needed to help individualize drug therapy according to the patient's asthma symptoms, degree of airway inflammation/obstruction, and adverse effects to medications.

The ATS guidelines recommend using FeNO concentrations of less than 25 parts per billion (ppb) (for children, the standard is <20 ppb) to indicate that eosinophilic inflammation and responsiveness to corticosteroids is less likely (strong recommendation, moderate quality of evidence). Concentrations greater than 50 ppb (>35 ppb in children) are used to indicate eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids is likely (strong recommendation, moderate quality of evidence) (Dweik 2011).

The cost impact of using FeNO to adjust asthma medication (predominately ICS) has not been formally evaluated in a cost-effectiveness analysis. In an observational study of 50 adults with asthma, the impact of FeNO monitoring on treatment decisions was investigated. Prior to measuring FeNO, clinicians determined asthma treatment based on their clinical experience coupled with spirometry and symptom scores. However, after gaining knowledge of the patient's FeNO level, they changed treatment in 36% of patients, adding medication or increasing the dose in 10 patients and discontinuing or decreasing the medication

dose in eight. The use of FeNO plus standard of care in managing asthma was estimated to provide annual savings of \$629 per patient (2013 dollars) (LaForce 2014).

A landmark study in the *New England Journal of Medicine* demonstrated the impact of using FeNO in the management of patients receiving ICS therapy (Smith 2005b). The clinical benefit of periodic assessment of airway inflammation using FeNO was compared with traditional monitoring (symptoms, spirometry, etc.). While no cost analysis was performed, a clinically significant difference was found favoring the FeNO-based approach. After 12 months, the ICS dose of fluticasone was 370 µg per day in the FeNO group versus 641 µg per day in the control group. More importantly, asthma control was better in the FeNO group, with 45.6% fewer exacerbations compared with 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 was receiving 1,000 µg of fluticasone daily at the end of the study compared with 20% in the FeNO group.

The potential for FeNO to be cost effective in this scenario can be related to improving asthma control, reducing the cost of high- versus medium-dose ICS in addition to costs associated with avoiding adverse effects from long-term exposure to higher doses of inhaled steroids (Choi 2017, Suissa 2010, Carr 2016).

Monitoring asthma control

Elevated FeNO concentrations are associated with a greater likelihood for future uncontrolled asthma and exacerbations (Zeiger 2011, Kupczyk 2014). FeNO levels >45 ppb in children and 20–35 ppb in adults correlate with uncontrolled inflammation and exacerbation risk, even in patients without clinical symptoms (Agache 2012, Dweik 2010, van Veen 2008). Establishing a baseline FeNO measurement and monitoring it over time with serial assessments is strongly recommended by the ATS Clinical Practice Guideline for FeNO use (Dweik 2011).

Honkoop et al. (2015) investigated the cost effectiveness of FeNO monitoring among 611 primary care patients with mild-to-moderate asthma in comparing a partial-control strategy (Asthma Control Questionnaire [ACQ] score <1.50), full-control strategy (ACQ score <0.75); or FeNO-assisted control strategy (ACQ score <0.75 and FeNO <25 ppb) over 12 months, with medication adjusted every three months using a decision-support tool.

Overall, the FeNO-guided strategy had the highest probability of being cost effective over a wide range of willingness-to-pay values (\$0–\$125,000/QALY). At the commonly used willingness-to-pay threshold of \$50,000 per quality-adjusted life year (QALY), the probability that the FeNO-guided control strategy was cost effective was 86% (partial control, 2%; complete control, 12%).

A decision-analytic model investigated the cost effectiveness of the addition of FeNO monitoring to standard of care versus standard of care alone (Brooks 2018). A comparison of the 12-month average medical costs and QALYs between the addition of FeNO monitoring and standard-of-care asthma management alone found decreased expected 12-month costs per patient (\$2,228 vs. \$2,637) and increased effectiveness (0.844 versus 0.767 QALYs) in the FeNO group versus the control group, respectively, indicating that FeNO in addition to standard of care is the dominant strategy (i.e., results in both improved outcomes and decreased costs versus standard of care alone).

The role of FeNO monitoring in reducing asthma exacerbations

Asthma exacerbations are a major contributor to emergency department (ED) visits and inpatient hospitalizations as well as higher medical expenditures and loss of productivity. Costs for individuals who

had at least one exacerbation in a year were \$1,399 higher than for those without asthma and \$771 higher for those with asthma but without exacerbations (Sullivan 2014).

There is strong evidence that patients who receive FeNO-guided therapy are less likely to experience exacerbations. The results are similar across populations, including children, adults, and pregnant women, with exacerbation rates as much as 50% lower in more than 16 studies that included more than 3,000 patients (Petsky 2016a, Petsky 2016b, Peirsman 2014, Syk 2013). Cochrane meta-analyses of the use of FeNO in guiding asthma management in children and adults concluded that tailoring medications based on FeNO levels was more effective in reducing exacerbations than basing treatment on symptom and lung function alone (Petsky 2016a, Petsky 2016b). Adults had a 40% reduction in exacerbation frequency compared with patients assessed on clinical symptom evaluation alone (OR 0.60, 95% CI 0.43–0.84; $P=.003$), although there were no differences in hospitalizations, ED visits, daily symptoms, or ICS dose between groups due to insufficient power in the meta-analysis resulting from either too few events or overall heterogeneity of data from the included studies (Petsky 2016b).

Similar to data from adults, FeNO-based asthma monitoring in children was associated with a 42% reduction in exacerbations (OR 0.58, 95% CI 0.45–0.75; $P<.001$) (Petsky 2016a). Based on the data from the Cochrane meta-analyses, the number of patients needed to treat to benefit was estimated to be 12 in adults and nine in children (Petsky 2016a, Petsky 2016b).

The use of FeNO in asthma monitoring may also predict exacerbations. In one study, a FeNO level of less than 30 ppb predicted that an exacerbation was unlikely to occur within the next three months (Michils 2008). Another study demonstrated that among patients with a combined FEV1 $\leq 76\%$ of predicted and a FeNO of 28 ppb or more 85% experienced an exacerbation over the following 18 months, while among those with an FEV1 $>76\%$ and FeNO less than 28 ppb there were no exacerbations over that same time period (Gelb 2006).

The Seasonal Asthma Exacerbation Predictive Index (saEPI), which was developed based on data from two National Institute of Allergy and Infectious Diseases trials, identified eight variables (including 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 decision-analytic cost-effectiveness model previously described was used to examine the impact of FeNO monitoring on the cost of asthma management among patients with infrequent and frequent exacerbations. The cost savings associated with FeNO monitoring was proportionate to the frequency of exacerbations; patients with infrequent exacerbations who received FeNO monitoring compared with those who did not had projected annual per-patient cost savings ranging between \$72 and \$217. In the simulated population of patients with frequent exacerbations, FeNO monitoring demonstrated annual per patient cost savings between \$316 and \$1,331, depending on the assumed annual frequency of exacerbations as well as the assumed frequency of FeNO measurement (Brooks 2018).

Recently, a study investigated the cost of asthma-related events before and during FeNO monitoring in a Medicare database of patients with a history of exacerbations. Asthma-related ED or inpatient (IP) claims (per patient per day) decreased from 0.004 pre-FeNO use to 0.002 during the FeNO monitoring period ($P<.04$). Likewise, daily asthma-related ED/IP charges decreased from \$16.21 to \$6.46 ($P<.01$). Kaplan-Meier analysis demonstrated an increased time to exacerbation. The median days to an ED/IP before FeNO monitoring was 413 days versus 606 days during FeNO monitoring ($P=.10$) (Massanari 2018).

Medication adherence

ICS treatment is widely considered to be the cornerstone therapy for the control of asthma symptoms (NAEPP 2007), but adherence to ICS-based medication regimens tends to be very poor, with reported rates of nonadherence ranging from 30% to 70% (Lindsay 2013). Medication-related reasons for nonadherence include difficulties with inhaler devices, complex regimens, side effects, cost of medication, dislike of medication, and distant pharmacies (Hekking 2015). Nonadherence is a major reason for poor asthma control, asthma-related ED visits, hospitalizations, and increased oral steroid use (Murphy 2012, Williams 2004). Up to three quarters of the total costs associated with asthma may be a result of poor asthma control (Apter 2015). Guidelines and consensus statements on the diagnosis and assessment of patients with difficult-to-control asthma unanimously stress the importance of identifying and addressing non-adherence in this population (Bousquet 2010, Bel 2011).

Identifying patients who are nonadherent offers opportunities for clinicians to intervene and improve outcomes. However, tracking adherence is difficult in clinical practice. While prescription refills are often used as a surrogate for adherence, they do not provide information on whether medications are used as directed. FeNO monitoring provides a unique biomeasure of adherence with ICS-based regimens because its expression is linked with the direct effect of corticosteroids on nitric oxide synthase, the enzyme responsible for regulating production of exhaled NO (Kharitonov 1996).

Clinical research investigating the role of FeNO in identifying nonadherence with ICS has been favorable, but studies were observational and, thus, evidence for this use has been rated low quality in guidelines (Kaminsky 2008, McNicholl 2012). In a recent Agency for Healthcare Research and Quality review of FeNO evidence, the impact of FeNO monitoring on medication adherence was summarized from three studies involving more than 1,000 patients. In the summary of the review, the use of FeNO as a measure of adherence to asthma medications (primarily ICS) was listed as one of five recommended key areas for using FeNO in asthma management (Wang 2017).

Asthma biologics

Four biologics—omalizumab, mepolizumab, reslizumab, and benralizumab—have been approved in the United States, and all are indicated for patients with severe asthma who have a history of exacerbations despite treatment with medium- to high-dose ICS combination therapies. In addition, phase 3 trials have been completed for dupilumab, which is expected to enter the U.S. market soon. The need for measuring biomarkers and phenotyping patients to help identify candidates for treatment with a biologic has been the focus of many recent reviews (Blaiss 2017).

However, before a patient is considered to have severe refractory asthma, other factors related to achieving disease control should be considered. Asthma that is difficult to control or treat differs from severe refractory asthma and includes confounding factors that can interfere with the ability to achieve disease control, such as allergic comorbidities, smoking, medication nonadherence, and poor inhaler technique (Hekking 2015, Bel 2011). This is an important distinction because methods to improve asthma control in patients whose asthma is difficult to control are focused on addressing the confounding factors; it is the severe refractory asthma patient for whom additional anti-inflammatory treatment (e.g., a biologic) is needed.

Treatment decisions in patients with difficult-to-control asthma are complicated. Before treatment with a biologic is considered, patients need to be re-evaluated, and comorbidities, medication nonadherence, and poor inhaler technique should be ruled out. Using FeNO monitoring in asthma management helps to identify nonadherence with ICS therapy and helps to identify patients with more severe disease who have persistent airway inflammation despite treatment with an ICS/long-acting beta agonist (LABA) with or without additional drugs such as leukotriene receptor antagonists (LTRAs) (McNicholl 2012).

Besides using FeNO as a tool to help determine if patients have been adherent with their ICS-based medications, FeNO also is an important biomarker related to the use of some biologics, such as omalizumab and dupilumab, that are targeted for patients with allergic or T2-mediated airway inflammation. In these patients, FeNO can be used to help identify candidates for treatment and may also be used as a marker for determining treatment response. However, concerning anti-interleukin-5 biologics and use in patients with severe persistent eosinophilic asthma, the role of FeNO is less clear because FeNO was not collected routinely as a baseline biomarker in the pivotal trials of mepolizumab, reslizumab, or benralizumab (except for the DREAM study) (Pavord 2012, Castro 2015, FitzGerald 2018). During the DREAM study, mean FeNO levels were not statistically significantly decreased compared to baseline values. However, in those patients with a baseline FeNO >50 ppb, response to mepolizumab was associated with an approximately 50% reduction in asthma exacerbations (Chaudhry 2015).

The concept of using biomarkers to characterize a patient's response to omalizumab was explored in the EXTRA study (Hanania 2011). In this postapproval study, FeNO, serum periostin, and blood eosinophils were measured at baseline in 850 patients with uncontrolled severe persistent allergic asthma despite combination therapy with ICS/LABAs to identify omalizumab responders. After 48 weeks of treatment, the mean relative reduction in asthma exacerbations was 25%. However, when patients were stratified according to baseline biomarkers, the greatest reduction in asthma exacerbations was seen in the high-FeNO group (>19.5 ppb), with a mean 53% reduction compared with only a mean 16% reduction when baseline FeNO was <19.5 ppb. For high blood eosinophils, the mean reduction in asthma exacerbations was 32% (eosinophils >260 μ l) versus 9% for low eosinophils (<260 μ l) (Hanania 2013).

The potential cost impact of these data was modeled in a decision analysis comparing use of omalizumab with FeNO to omalizumab without FeNO. The FeNO-based strategy was associated with an almost 50% reduction in patient costs (FeNO+omalizumab) compared with usual care (omalizumab alone). The budget impact of using FeNO as a prior authorization criterion on a typical managed care organization's omalizumab annual expenditure has the potential to translate into considerable cost savings (Massanari 2017).

Conclusion

While most patients with asthma can achieve control and avoid significant exacerbations, rates of uncontrolled asthma remain significant and patients are often misdiagnosed. In the past decade, numerous studies have demonstrated the value and importance of incorporating objective measures and biomarkers into improving the diagnosis and management of asthma. In addition, clinical evidence that describes how to incorporate the use of FeNO into asthma management has been produced in recent years that better describes which patients will benefit most from FeNO monitoring. FeNO monitoring has the potential to be cost effective; the device used for monitoring is relatively inexpensive and adds clinical value when combined with other clinical tools for managing patients with asthma. In this review, we have summarized the current evidence on the cost effectiveness of FeNO monitoring in asthma. Adding FeNO to the diagnostic armamentarium provides a unique measure of airway inflammation that complements pulmonary function assessments in a cost-effective manner. Likewise, incorporating FeNO into asthma management helps to identify patients at risk for future exacerbations and is associated with substantial cost savings in those patients. Potential areas of FeNO use that could be cost effective are related to medication management (i.e., optimizing ICS dosing and use of biologics). As more biologic therapies are developed for treating asthma, there will be an increasing need for clinically relevant biomarkers to help practitioners identify appropriate patient candidates and monitor treatment response in a cost-effective manner.

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which has received support from Circassia for development of cost-effectiveness assessments of FeNO use in asthma management.

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