Medical Coverage Policy

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Exhaled Nitric Oxide in the Management of Respiratory Disorders

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Related Coverage Resources

Omalizumab

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Overview

This Coverage Policy addresses the proposed uses of exhaled nitric oxide in the management of respiratory disorders including asthma.

Coverage Policy

The measurement of exhaled nitric oxide for the management of asthma and/or other respiratory disorders is considered experimental, investigational or unproven due to insufficient evidence of beneficial health outcomes.

General Background

Fractioned exhaled nitric oxide (FENO) is the amount of nitric oxide (NO) present in the airways that is measureable in the exhaled air using chemiluminescent or electrochemical methods. Analysis of FENO has been proposed as a marker of inflammation that could be useful in diagnosing and monitoring disease activity and directing treatment in patients with asthma and other pulmonary conditions (e.g., bronchiectasis, cystic fibrosis, interstitial lung disease, sarcoidosis, chronic obstructive pulmonary disease, nonasthmatic eosinophilic bronchitis, upper respiratory infections, pulmonary hypertension), lung cancer and inflammatory bowel disease. Nitric oxide affects many organ systems, including the lungs, where it acts as a bronchodilator. Nitric oxide is produced by various lung cells from the amino acid l-arginine by different iso-enzymes of nitric oxide synthase. Exhaled nitric oxide levels have been shown to be elevated in patients with asthma, to be higher during periods of acute exacerbation, and to correlate with other measures of inflammation. However, in addition to asthma and eosinophilic airway inflammation, a number of factors affect FENO levels, including atopy, age, race, gender, sex, height, psychological stress, depressive mood, exercise, genetic phenotypes and smoking status (Cao et al., 2016; Ikonomi, et al., 2016; Liu, et al., 2016; Desai, et al., 2014; Calhoun, 2014).

There is currently no direct measure of inflammation that is widely available clinically. Treatment decisions are typically made based on indirect measures of inflammation, including symptom scores, spirometry measures, rescue medication use, and/or other indicators of disease activity. The test used most frequently to assess the risk of future adverse events is spirometry, especially forced expiratory volume in one second (FEV_1), reported as a percent of the predicted value or as a proportion of the forced vital capacity, or FEV_1/FVC. A number of biomarkers have been studied in an effort to find a simple, easily applied test whose deviations from normal may correlate with risk severity. Biomarkers that have been proposed include airway hyperresponsiveness, blood or sputum eosinophils or eosinophilic cationic protein, serum immunoglobulin E, and fractional exhaled nitric oxide concentration.

Asthma is a chronic inflammatory disorder of the airways that may cause recurrent episodes of wheezing, breathlessness, chest tightness and coughing. These episodes are typically associated with widespread but variable airflow obstruction that resolves spontaneously or with treatment. The inflammation of asthma may cause an increase in existing bronchial hyper-responsiveness to a variety of stimuli. Many cells and cellular elements play a role in asthma, including mast cells, eosinophils, T lymphocytes, macrophages, neutrophils and epithelial cells. Fibrosis may occur in some patients with asthma, resulting in persistent abnormalities in lung function.

FENO has been proposed as a biomarker to aid in the diagnosis and management of patients with asthma. Including predicting a patient’s response to corticoid steroids. For the diagnosis of asthma, studies have reported a sensitivity of 57%–96% and specificity of 62%–85% for exhaled nitric oxide measurements, depending on the selected cutoff values. Two studies reported better sensitivity of FENO for the detection of allergic asthma than for asthma in general (47% versus 32% and 70% versus 64%). In a systematic review and meta-analysis of 25 studies (n=3983) (Guo, et al., 2016), the authors analyzed the accuracy of FeNO. The sensitivity ranged from 32%–92.7% and the specificity ranged from 52%–93%. The pooled sensitivity and specificity were 72% and 78%, respectively. There was significant heterogeneity of the patient population. Although a large number of studies have been conducted that correlate asthma with higher FeNO levels, the sensitivity and specificity is dependent on the cutoff point and today the optimal cutoff point has not been established. Studies comparing FeNO to other testing methods such as circulating eosinophils and immunoglobulin E found no statistically significant differences. Outcomes may vary depending on whether treatment includes an inhaled corticosteroid, leukotriene receptor antagonist, or inhaled long-acting $beta_2$-agonist. Although exhaled nitric oxide may be accurately measured, the clinical utility has not been established. Evidence published to date has not demonstrated that the measurement of exhaled nitric oxide results in meaningful improvement in patient outcomes. Randomized controlled trials evaluating the role of FENO measurements in asthma care have reported conflicting outcomes. Clinical guidelines are also divided on the use of FENO for patients with asthma. (Price, et al., 2018; Petsky, et al., 2016a; Petsky, et al., 2016b; Desai, et al., 2014; Calhoun, 2014).

U.S. Food and Drug Administration (FDA)
The Fenom Pro™ Nitric Oxide Test (Spirosure, Inc., Pleasanton, CA) received U.S. Food and Drug Administration (FDA) approval as a Class II device through the 510(k) process on February 13, 2019. This new device is intended to measure fractional exhaled nitric oxide (FeNO) during the exhalation phase of human respiration. The device is used to detect a decrease in FeNO in diagnosed asthma patients undergoing anti-inflammatory pharmacological treatment. Fenom Pro is intended for children 7-17 years old and adults 18 years and older. Fenom Pro was approved via the predicate device NIOX Mino. The indications for use are identical with alteration in measurable range.

The NIOX Breath Nitric Oxide Test System® (Aerocrine AB, San Diego, CA) received U.S. Food and Drug Administration (FDA) approval as a Class II device through the 510(k) process on April 30, 2003. The device is intended to aid in evaluating an asthma patient's response to anti-inflammatory therapy by measuring changes in fractional exhaled nitric oxide concentration as an adjunct to established clinical and laboratory assessments of asthma. It is suitable for children approximately 7–17 years old and adults 18 years and older.

The NIOX MINO® Airway Inflammation Monitor (Aerocrine AB, Washington D.C), a hand-held device designed to measure fractional exhaled nitric oxide in human breath, received U.S. FDA 510(k) approval on March 3, 2008. The device was determined to be substantially equivalent to the predicate device, the NIOX System. In 2015, The NIOX VERO (Aerocrine, Morrisville, NC) Airway Inflammation Monitor was FDA 510(k) approved and replaced the Niox Mino device. The approval noted that the device cannot be used with infants or by children approximately under age 7 years as measurement requires patient cooperation.

The Apieron INSIGHT™ eNO System received U.S. FDA approval through the 510(k) process on March 14, 2008. The device was considered to be substantially equivalent to the predicate device, Aerocrine NIOX System. The intended use is to quantitatively measure exhaled nitric oxide in expired breath as a maker of inflammation for persons with asthma. The system can be used by trained operators in a physician's office laboratory setting, and should not be used in critical care, emergency care, or in anesthesiology. It is suitable for use in children ages 8 to 17 years of age, and in adults 18 years of age and older.

Literature Review

Exhaled Nitric Oxide - Children: Petsky et al. (2016a) conducted a Cochrane systematic review of the literature to evaluate the efficacy of tailoring asthma interventions for children (mean age 10–14 years) based on FENO compared to clinical management alone (e.g., based on symptoms, spirometry/peak flow and/or asthma guideline). Nine randomized controlled trials (RCTs) (n=1329) met inclusion criteria. Results showed that the number of children having one or more asthma exacerbations during the study was significantly lower in the FENO group (p=0.002) and the number of children in the FENO group required fewer oral corticosteroid courses compared to the control group (p=0.001). However, there were no statistically significant differences between the groups in exacerbation rates (p=0.09), hospitalizations (p=0.37), forced expiratory volume in one second (FEV_1) (p=0.12), symptom scores and inhaled corticosteroid doses at final visit. According to the authors the quality of the evidence for outcomes ranged from moderate (regarding children who had one or more exacerbations over the study period) to very low for exacerbation rate. Additional limitations included: heterogeneity of the inclusion criteria, length of studies (6–12 months), FENO cutoff levels, definitions of exacerbations, lack of blinding and statistical heterogeneity and imprecision. Although there were a significantly decreased number of children who had one or more exacerbations over the study period, there was not a significant impact on day-to-day clinical symptoms or inhaled corticosteroid doses. Therefore, the authors concluded that while the use of FENO to guide asthma therapy in children may be beneficial in a subset of children, it cannot be universally recommended for all children with asthma. Additional RCTs are needed to define the subset of children that may benefit from FENO. Future studies should encompass different asthma severities; different settings (e.g., primary care, less affluent settings); and consider different FENO cut-offs.

Gomersal et al. (2016) conducted a systematic review of the literature to assess the effectiveness of FeNO in the routine management of childhood asthma. Seven randomized controlled trials (n=1979) met inclusion criteria. Studies recruited children (plus adolescents and/or young adults; age ≥5 years) and compared FeNO-guided management to non-FeNO-guided management. The quality of the literature was variable, with no single study being at low risk of bias on every item. Some studies reported that significantly fewer children experienced >1 exacerbation in the FeNO guided group (p=0.017), but the rate of exacerbations was not significantly lower (p=0.102). There was some evidence that FeNO-guided monitoring resulted in improved asthma control during the first year of management, however most results did not attain statistical significance. The impact of FeNO on severe exacerbations and on the use of anti-asthmatic drugs was unclear. Trends toward reduced exacerbation and increased medication use were seen, but typically failed to reach statistical significance. The potential benefit of FeNO monitoring in children with asthma is unclear. The authors noted that there is a clear need for further studies of sufficient size and duration before firm recommendations can be given for routine clinical use.

Petsky et al. (2015) conducted a randomized controlled trial (n=63) to evaluate the use of FENO to improve asthma outcomes for atopy in children. The study assessed whether a treatment strategy based on FeNO levels, adjusted for atopy, reduced asthma exacerbations compared with the symptoms-based management (controls). The planned sample size was not achieved. Children were randomized to receive a treatment hierarchy based on symptoms or FeNO levels. Follow-ups occurred for 12 months. Primary outcome was the number of children with exacerbations over 12-months. Significantly fewer children in the FeNO group (6/27) experienced exacerbation compared to 15/28 in the control (p=0.021). There was no difference between groups for any secondary outcomes (quality of life, symptoms, FEV1). The final daily inhaled corticosteroids (ICS) dose was significantly higher in the FeNO group (p=0.037). According to the authors, taking atopy into account when using FeNO to tailor asthma medications “is likely beneficial” in reducing severe exacerbations but at the expense of increased ICS use but the strategy is unlikely beneficial for improving asthma control. Limitations of the study include: the small patient population; loss to follow-up (n=8); the control treatment strategy did not include placebo as the children were actively managed, planned sample size was not reached as recruitment was halted early; and lack of blinding of authors who conducted FENO and calculated scores. The authors noted that because the secondary outcomes were not significantly improved, use of FENO is likely not beneficial in all children even though some children experienced fewer exacerbations.

Peirsman et al. (2014) conducted a randomized controlled trial to investigate the potential yield of incorporating fractional exhaled nitric oxide (FeNO) in childhood allergic asthma measurement (n=99). Five visits (one visit every three months) were organized by physicians from seven Belgian hospitals for children with mild to severe persistent asthma according to GINA guidelines, of at least six months duration, with allergic sensitization (i.e., a positive skin prick test and/or specific IgE antibodies against inhalant allergens). In the clinical group, asthma control and treatment adjustments during each visit were determined by the reporting of symptoms (i.e., limitation of activities, daytime and nocturnal symptoms), need for rescue treatment during the two preceding weeks, and spirometry based on the GINA Guidelines. In the FeNO group FeNO measurements were primarily used to adjust the treatment, with a goal to keep FeNO below 20 parts per billion (ppb). The primary outcome, symptom-free days, was assessed using the first four questions from the Childhood Asthma Control Test, which were completed each day. An exacerbation was defined as an episode of progressive increased shortness of breath, coughing, wheezing, or chest tightness or a combination of these symptoms. There was no difference between groups in the primary outcome, symptom-free days. In terms of secondary outcomes, there were fewer exacerbations in the FeNO group (p=0.02) and fewer unscheduled contacts (p=0.03), but no significant differences in hospital or emergency room admissions, missed school, or need for caregivers to take time off to care for the child. More months of leukotriene receptor antagonist use (median [interquartile range]) were seen in the FeNO group: 12 (9-12 months) compared with 9 (3-12 months) (p=0.019) in the control group. Measurement of Inhaled corticosteroid use between visits one and five (median change [interquartile range]) showed a significant increase of +100 micrograms (0, +400) in the FeNO group compared with 0 micrograms (-200, +80) in the clinical group (p=0.16). The authors strongly recommended further evaluation of FeNO measurements in double-blind, parallel-group multicenter randomized controlled trials in broad populations in terms of asthma severity, control and level of asthma therapy.

A prospective case series by Woo et al. (2012) evaluated the diagnostic utility of ENO measurements as a test for asthma by investigating the sensitivity, specificity, and predictive values of ENO measurements in consecutive children age 8-16 with a possible diagnosis of asthma (n=245). The authors also explored the combined effect of asthma and atopic status on ENO levels. Children were evaluated using ENO measurement, questionnaires, skin prick tests, spirometry, and methacholine challenge tests. Asthma was diagnosed in 167 children. The sensitivity, specificity, and positive predictive value (PPV), and negative predictive value (NPV) of ENO measurements for the diagnosis of asthma at the best cutoff value of 22 ppb were 56.9%, 87.2%, 90.5%, and 48.6%, respectively. The specificity and PPV were both 100% at a cutoff value of 42 ppb, but at the cost of very low sensitivity (23.4%) and NPV (37.9%). Both atopy (i.e., genetic predisposition to hypersensitivity or allergic reaction) and asthma were identified as independent risk factors for high ENO. The association of asthma with high ENO was found only in atopic children; ENO was low in non-atopic children regardless of asthma status. Although the highest ENO was observed in atopic asthmatic patients, 28% of these patients had ENO values lower than 22 ppb. The authors concluded that atopic asthmatic patients with low ENO values and non-atopic asthmatic patients were responsible for false negative cases that might contribute to low sensitivity of ENO measurements in diagnosing asthma. High ENO may help identify patients with atopic asthma among patients with respiratory symptoms.

Lemanske et al. (2010) assessed the frequency of differential responses to three blinded step-up treatments for children with uncontrolled asthma while receiving low-dose inhaled corticosteroids. Researchers randomly assigned 182 children age 6 to 17 to receive each of three blinded step-up therapies in random order for 16 weeks: 250 micrograms of fluticasone twice daily (ICS step-up); 100 micrograms of fluticasone plus 50 micrograms of a long-acting beta-agonist twice daily (LABA step-up), or 100 micrograms of fluticasone twice daily plus 5 to 10 milligrams of a leukotriene-receptor antagonist daily (LTRA step-up). A triple crossover design and composite of three outcomes (exacerbations, asthma-control days, and forced expiratory volume in one second) were used to determine whether the frequency of a differential response to the step-up regimens was more than 25%. A clinically significant differential response was seen in nearly all the children, and several characteristics of the children predicted the direction of differential responses, including race or ethnic group and two readily available clinical attributes: asthma control, as indicated by the score on the Asthma Control Test, and the presence or absence of eczema. More expensive and labor-intensive measures of physiological factors and biomarkers (e.g., the fraction of exhaled nitric oxide), did not have predictive value.

De Jongste et al. (2008) conducted a randomized parallel group study to assess daily fraction of nitric oxide (FENO) monitoring in the management of childhood asthma (n=151). Children with atopic asthma were assigned to two groups: FENO plus symptom monitoring (n=77) or monitoring of symptoms alone (n=74). Two children in each group were excluded form analysis due to non-compliance, inappropriate inclusion, or unavailability. Patients tracked asthma symptoms in an electronic diary over a 30 week period. Children in the FENO group performed daily measurements with a NIOX MINO portable monitor, transmitting the data to the coordinating center. Patients were phoned every three weeks, and steroid doses were adjusted based on FENO and symptoms, or symptoms alone. All patients were seen at randomization and at 3, 12, 21, and 30 weeks. All patients showed an improvement in symptom-free days, improvement in forced expiratory volume in one second (FEV_1) and quality of life, and a reduction in steroid dose. None of the changes from baseline differed between the groups, although there was a trend toward fewer exacerbations in the FENO group. The difference in symptom-free days over the latest 12 weeks was 0.3% (p=0.95). The authors found no added value of daily FENO monitoring compared with daily symptom monitoring only.

Szefler et al. (2008) conducted a randomized controlled trial to assess whether measurement of exhaled nitric oxide as a biomarker of airway inflammation could increase the effectiveness of asthma treatment for inner-city adolescents and young adults, when used as an adjunct to clinical care based on asthma guidelines. A total of 546 patients aged 12–20 with persistent asthma were randomized to 46 weeks of standard treatment based on guidelines of the National Asthma Education and Prevention Program (n=270) or to treatment modified on the basis of fraction of ENO (n=276). The primary outcome measure, the mean number of days with asthma symptoms, did not differ between the treatment groups (p=0.780). Asthma management that incorporated measurement of fraction of ENO resulted in higher doses of corticosteroids than did management with standard guidelines (p=0.001). This treatment was associated with a small reduction in the need for courses of prednisone, but did not result in an overall improvement in asthma symptoms, lung function or need for health care.

Exhaled Nitric Oxide – Adults: Price et al. (2018) conducted a six-week, double-blind randomized placebo-controlled trial (n=294) to investigate the value of FENO, and other baseline measurements, in predicting a clinical response to four weeks of treatment with inhaled corticosteroids (ICS). The study included a two-week assessment period for screening and measurement of baseline variables followed by a four-week treatment period. At the end of the assessment period participants were randomly assigned to ICS twice a day (n=148) or the control group (n=146) with the same treatment regimen using a placebo. Randomization was stratified by baseline FENO measurement: normal (≤ 25 parts per billion [ppb]), intermediate (> 25 ppb to < 40 ppb), and high (≥ 40 ppb).The primary outcome measure was the change from baseline to follow-up in the Asthma Control Questionnaire (ACQ7) scores. Secondary outcomes included changes from baseline in VAS symptoms and VAS cough, and changes in lung function as seen by forced expiratory volume (FEV1), FEV1 percentage predicted, forced vital capacity (FVC), FVC percentage predicted, and peak expiratory flow. Three visits occurred during the study: initial assessment visit, visit to confirm study eligibility at the end of the assessment period prior to randomization, and at the end of the four-week treatment period. Patients were included if they were age 18–80 years, had non-specific persistent respiratory symptoms (cough, wheeze or chronic dyspnea for ≥ 6 weeks prior to screening) and no previous diagnosis of asthma. Patients were excluded if they had ever been diagnosed with asthma or any other relevant chronic respiratory disease, or had received treatment with oral, inhaled, or systemic corticosteroids, a leukotriene modifier, or long-acting β agonist within four weeks of the first study visit. Data revealed a significant interaction between baseline FENO and treatment in terms of VAS cough (p=0.014) and FEV1 (p=0.01). There were no significant differences in the remaining VAS and spirometry measures. A significant improvement in the ACQ7 score was seen in patients with a high FENO signal (≥ 40 ppb). A significant improvement in outcome was noted as the FENO increased for ICS patients. A decrease in the outcome value of ACQ6 in the ICS group compared with the placebo group was seen after adjustment for smoking and baseline value. The most common adverse events in both groups were nasopharyngitis and respiratory, thoracic, and mediastinal disorders. The number of patients experiencing at least one adverse event during the study did not differ between groups. Limitations of the study include the short term follow-up and loss to follow-up (n=80) which caused the population to fall below the sample size needed to achieve 80% power. The authors noted that this study was one of the first controlled trials investigating the value of FENO for guiding ICS in a difficult-to-manage patient population with unspecific respiratory symptoms. Additional well-designed studies are needed to validate the results of this trial.

Essat et al. (2016) conducted a systematic review to evaluate the clinical effectiveness of fractional exhaled nitric oxide (FeNO) for the clinical management of adults with asthma. Six randomized controlled trials met inclusion criteria. Studies were included that measured FeNO according to the American Thoracic Society 2005 Criteria for the management of asthma, either with or without other indicators of asthma control. Primary outcome measures included incidence of acute exacerbation (any definition of exacerbation severity was acceptable, including use of oral corticosteroids), major or severe exacerbations, inhaled corticosteroid use, unscheduled contact with healthcare officials, hospitalizations, and emergency department visits. Follow-ups ranged from 3–12 months. Two studies reported rates of severe exacerbations (requiring oral corticosteroid use). Two studies reported data on less severe exacerbations (this data was not amenable to meta-analysis due to unreported data). Four studies reported some data on inhaled corticosteroid use. Outcomes were not reported in a standardized manner. Meta-analysis showed a non-statistically significant (p=0.13) overall beneficial effect in favor of FENO-guided management and severe exacerbations (p=0.08). Meta-analysis of three studies showed a statistically significant effect in favor of using FENO-guided management in decreasing exacerbations in adults (p<0.00001). However, due to the high degree of heterogeneity in composite outcomes, the effect is liable to high risk of bias. No statistically significant differences for health-related quality of life or asthma control were found. Meta-analysis showed a fall in exacerbation rates per person per year, but none were statistically significant. Limitations of the studies include: low level of evidence; significant heterogeneity of studies (e.g., patient characteristics, outcome definitions, FENO cut-off points, management protocols, reporting format); young stable, non-smoking patient populations; variation in criteria used for the diagnosis of asthma; and heterogeneous effects on ICS use. The authors concluded that due to the heterogeneity in the studies it was not possible to draw any firm conclusions as to which management protocol or cut-off points offer the best efficacy. The best way to use FENO in the management of asthma, which management protocol and cut-offs to use; which patient groups are likely to benefit from FENO monitoring, (e.g. individuals with atopy, frequent exacerbations or those with poor adherence); and how treatment effect will progress over time are unknown.

Petsky et al. (2016b) conducted a second Cochrane review to assess the efficacy of tailoring asthma interventions for adults (mean age 28–54 years) based on FeNO compared to clinical management alone (e.g. symptoms, spirometry/peak flow, asthma guideline). Seven randomized controlled trials (n=1546) met inclusion criteria. All subjects had a diagnosis of asthma and required asthma medications. The number of people having one or more asthma exacerbations was significantly lower in the FeNO group (p=0.003) and the number of exacerbations per 52 weeks was lower in the FeNO group (p=0.0001). There was no significant difference in exacerbations requiring hospitalization, rescue oral corticosteroids, FEV_1, FeNO levels, symptom scores and inhaled corticosteroid doses at final visit. Limitations of the studies included: heterogeneity of inclusion criteria, the definition of asthma exacerbation, FeNO cut off levels (15–35 ppb), FeNO levels used for decreasing medications (10–25 ppb), duration of the studies (4–12 months); and the variations in the way FeNO was used to adjust therapy. In conclusion, the authors stated that the universal use of FeNO to help guide therapy in adults with asthma cannot be advocated. As the main benefit shown in the studies in this review was a reduction in asthma exacerbations, the intervention may be most useful in adults who have frequent exacerbations. Further RCTs are needed to identify patient selection criteria encompassing different asthma severity, and taking into account different FeNO cutoffs.

Honkoop et al. (2015) conducted a three-armed randomized controlled trial (n=647) to compare the outcomes of three strategies in managing mild to moderately severe asthma in adults. The three strategies were aimed at partly controlled asthma (PCa) (n=232), controlled asthma (CA) (n=210) or fraction of exhaled nitric oxide (FeNO) driven control (FCA group) (n=205). In clinical practice the control of asthma is classified as controlled, partially controlled or uncontrolled. Inclusion criteria were age 18–50 years old, doctor diagnosed asthma, prescription for inhaled corticosteroids (ICS) for at least three months in the previous year, and asthma being managed in primary care setting. The primary outcome was the societal costs per quality-adjusted life year (QALY) gained. Secondary outcomes were asthma control, asthma-related quality of life using the Asthma Quality of Life Questionnaire, number of days with asthma related limitations of activity, medication adherence, severe exacerbation rate, lung function, FENO value, and total medication usage. Treatment decisions were based on an algorithm dedicated to each strategy. Follow-ups occurred for up to twelve months and included medication assessment and asthma control status scores using the 7-item Asthma Control Questionnaire (ACQ) which includes lung function. FENO was tested in the FCa strategy group. Based on the ACQ, asthma control was significantly better in the FCa group compared to the PCa group (p=0.02) but no significant differences were found between the PCA and Ca or the FCa and Ca strategies (p≥0.15, each). The percentage of participants who achieved Ca at 12 months' follow-up was 55% for the PCa strategy, 68% for the Ca strategy, and 61% for the FCa strategy (not significant). There were no significant differences in asthma quality of life scores between the strategies (p≥0.60). FCa strategy decreased the cumulative daily dose of ICS and daily use of long-acting b-agonist (LABAs) and motelukast and had the lowest severe exacerbation rate and use of prednisone but the differences were not statistically significant. Limitations of the study include: the number lost to follow-up (n=71); 14.8% of data was missing overall; since the primary outcome was cost the study was underpowered for some secondary outcomes including severe exacerbations; the practitioners' diagnosis of asthma was not reassessed. According to the authors, another limitation was that the magnitude of the differences in effectiveness between the groups was small and of limited clinical relevance.

Syk at al.(2013) conducted a randomized controlled trial to determine whether an FeNO-guided anti-inflammatory treatment algorithm could improve asthma-related quality of life (QOL) and asthma symptom control, and reduce exacerbations in atopic asthmatics within primary care (n=187). Nonsmoking asthma patients age 18-64 years with perennial allergy and on regular inhaled corticosteroid s (ICS), from 17 primary health care centers, were randomly assigned to the control group (n=88) or active treatment group (n=93). In the control group, FeNO measurement was blinded to both operator and patient, and anti-inflammatory treatment was adjusted according to usual care. In the active group, treatment was adjusted according to FeNO. The Asthma Control Questionnaire score change over one year improved significantly more in the FeNO-guided group (-0.17 [interquartile range, -0.67 to 0.17] vs. 0 (-0.33 to 0.50], p=.045). There was no significant difference between groups in the Mini Asthma QOL Questionnaire. Exacerbations per patient year were reduced by almost 50% in the FeNO-guided group (0.22 [CI, 0.14-0.34] vs. 0.41 [CI, 0.29-0.58], p=0.024). Mean overall corticosteroid use was similar in both groups. Limitations of the study include the fact that treatment of the control group consisted of "usual care" vs. structured, guideline-directed care. In addition, all patients treated with combination inhalers (corticosteroid plus long acting beta agonist [LABA]) were required to switch to the corresponding single corticosteroid inhaler and withdraw the LABA component.

Calhoun et al., for the Asthma Clinical Research Network of the National Heart, Lung, and Blood Institute (2012), conducted a randomized controlled trial to determine if adjustment of inhaled corticosteroid (ICS) therapy based on exhaled nitric oxide or day-to-day symptoms is superior to guideline-informed physician assessment-based adjustment in preventing treatment failure in adults with mild to moderate asthma (n=342; the BASALT Randomized Controlled Trial, 2012). The BASALT trial was a randomized, parallel, three-group placebo-controlled multiply-blinded trial conducted at ten academic medical centers in the US. Adults with mild to moderate asthma controlled by low-dose ICS therapy were assigned to physician assessment-based adjustment (n=114, 101 completed); biomarker-based adjustment (i.e., ENO) (n=115, 92 completed); or to symptom-based adjustment (n=113, 97 completed). For physician assessment-based adjustment and ENO-based adjustment, ICS were taken with each albuterol rescue use. There were no significant differences in time to treatment failure. The nine-month Kaplan-Meier failure rates were 22% (97.5% CI, 14%–33%, 24 events) for physician-assessment-based adjustment; 20% (97.5%, CI 13%–30%; 21 events) for biomarker-based (ENO) adjustment; and 15% (97.5 CI, 9%–25%, 16 events) for symptom-based adjustment. The authors concluded that among participants with mild or moderate persistent asthma, neither symptom-based adjustment nor biomarker (ENO)-

based adjustment was superior to the standard physician-assessment-based adjustment of ICS in time to treatment failure.

Powell et al. (2011) conducted a double-blind randomized controlled trial to test the hypothesis that a management algorithm for asthma in pregnancy based on FeNO and symptoms would reduce asthma exacerbations (n=220). Non-smoking pregnant women with asthma were randomly assigned before 22 weeks' gestation to treatment adjustment at monthly visits by an algorithm using clinical symptoms (n=109, 103 completed) or FeNO concentrations (n=111, 100 completed) to titrate inhaled corticosteroid use. Participants and outcome assessors were blinded to group assignment. The primary outcome was total moderate or severe asthma exacerbations. The exacerbation rate was lower in the FeNO group than in the control group (0.288 vs. 0.615 exacerbations per pregnancy (p=0.001).

Shaw et al. (2007) conducted a randomized, controlled, single-blind trial to test the hypothesis that the use of fraction of exhaled nitric oxide (FENO) for titrating corticosteroid dose results in fewer exacerbations and more efficient use of corticosteroid therapy. Patients, older than age 18 years, with a primary care diagnosis of asthma were randomized to corticosteroid therapy based on either FENO measurement (n=58) or British Thoracic Society guidelines (n=60). Patients were assessed monthly for the first four months, then semimonthly for an additional eight months. The primary outcome was the number of severe asthma exacerbations. The rate of exacerbations in the FENO group was 0.33 per patient per year compared to 0.42 in the control group (p=0.43). The total amount of inhaled corticosteroid used during the study was 11% greater in the FENO group than in the control group (p=0.40), although the final daily dose of inhaled corticosteroid was significantly lower in the FENO group than in the control group (557 vs. 895 micrograms, p=0.028). The authors stated that an asthma treatment strategy based on the measurement of FENO did not result in a large reduction in asthma exacerbations or in the total amount of inhaled corticosteroid therapy used over 12 months when compared to current asthma guidelines.

Exhaled Nitric Oxide Adults and Children: Harnan et al. (2017) conducted a systematic review of the literature to assess the evidence on the diagnostic accuracy of FENO for patients with asthma. A total of 27 prospective and retrospective studies met inclusion criteria. Fifteen studies were conducted in adults, four studies in adults plus adolescents, three studies in all age groups and five studies had no age ranges. Included studies met the following criteria: used a single set of inclusion criteria; measured FENO in accordance with the American Thoracic Society guidelines [flow rate of 50 mL/sec, exhalation time ≥ 10 sec for adults/≥ 6 sec for children/adolescents); and reported/allowed calculation of true-positive, true-negative, false-positive and false-negative patients as classified against any reference standard. Results varied even within subgroups of studies. Cut-off values ranged from 20–40 parts per billion (ppb). Cut-off values for the best sum of sensitivity and specificity varied from 12 to 55 ppb but did not produce high accuracy. Due to the heterogeneity of the studies, meta-analysis could not be performed. Methodological quality was poor or unclear and there was a high to moderate risk of bias. Estimates of diagnostic accuracy and cut-off values for the diagnosis of asthma varied greatly. According to the authors, study designs varied greatly in terms of populations recruited and reference standards used. Diagnostic accuracy, optimal cut-off values and use of FENO within a diagnostic pathway could not be determined.

Lehtimaki et al. (2016) conducted a systematic review of the literature to assess whether FENO could reliably predict clinical outcomes in subjects with asthma being treated with inhaled corticosteroids (ICS) and whether FENO's predictive role was influenced by different inflammatory phenotypes of asthma. Twelve prospective studies met inclusion criteria. Nine studies included adults and three included children. One study assessed the predictive value of FENO separately in different inflammatory phenotypes. Three studies suggested that there was an indication that a low FENO value in an asthmatic subject on regular ICS treatment was predictive of a low risk of exacerbation, while high FENO predicted a high risk of exacerbation. Two adult studies and one children's study showed that in steroid-naive patients with asthma, increased FENO probably predicts favorable response to ICS. Two of the studies had a high risk of bias. There was marked variation in baseline FENO values between the studies, reflecting differences in factors affecting FENO (e.g., age, use of anti-inflammatory medication, possibly differences in phenotypes of asthma). There was insufficient evidence to conclude whether or not a low FENO predicts that the patient could be weaned off ICS without risk of activation of asthma (n=1 study) or to conclude whether or not increased FeNO levels after discontinuing ICS treatment predict asthma relapse (n=2 studies with conflicting results). The studies used different study designs, medication protocols, FENO cut-off values, visit intervals, lengths of follow-up, definitions of asthma exacerbation and inclusion criteria. Due to the poor quality of the evidence, heterogeneity of the studies, small patient populations and high risk of bias, the current evidence on the predictive value of FeNO and its role in the management of asthma for adults and children is unknown.

Petsky et al. (2012) conducted a systematic review and meta-analysis to evaluate the efficacy of tailoring asthma interventions based on inflammatory markers (sputum analysis and FeNO) in comparison with clinical symptoms (with or without spirometry/peak flow). Randomized controlled comparisons of adjustment of asthma treatment based on sputum analysis or FeNO compared with traditional methods (primarily clinical symptoms and spirometry/peak flow) were reviewed. Six studies (2 adult, 4 child/adolescent) utilizing FeNO and three adult studies utilizing sputum eosinophils were included. There was a degree of heterogeneity, including definition of asthma exacerbations, duration of study and variations in cut-off levels for percentage of sputum eosinophils and FeNO used to alter management. Adults who had treatment adjusted according to sputum eosinophils had a reduced number of exacerbations compared with the control group (52 vs. 77 with at least one exacerbation, p<0.0006). There was no significant difference in exacerbations between the FeNO-managed group (26) compared to controls (30) (p=0.763). The daily dose of inhaled corticosteroids (ICS) was decreased at study end in adults whose treatment was based on FeNO compared to the control group (mean difference -450.03 mcg, 95% CI -676.73—223.34, p<0.0001). Children who had treatment adjusted according to FeNO, however, had an increase in their mean daily dose of ICS (mean difference 140.18 mcg, 95% CI -28.94 to 251.42, p<0.014). The authors concluded that tailoring of asthma treatment based on sputum eosinophils is effective in decreasing asthma exacerbations. Tailoring of asthma treatment based on FeNO levels, however, has not been shown to be effective in improving asthma outcomes in children and adults. At present there is insufficient justification to advocate the routine use of either sputum analysis (due to technical expertise required) or FeNO in everyday clinical practice.

Petsky et al. (2008, updated 2009) published a Cochrane systematic review to evaluate the efficacy of tailored interventions based on FENO in comparison to clinical symptoms (with or without spirometry/peak flow meters) for asthma related outcomes in children and adults. The review included two double-blind parallel groups studies (Pijenburg, 2005, Szefler, 2008) and four were single blind, parallel group studies (de Jongste, 2009, Fritsch, 2006, Shaw, 2007, Smith, 2005). The studies differed in a variety of ways, including definition of asthma exacerbations ENO cut-off levels, and the way in which FENO was used to adjust therapy and duration of the studies. In the meta-analysis, there was no significant difference between groups for the primary outcome, asthma exacerbations, or for other outcomes, including clinical symptoms, FENO level and spirometry. Tailoring the dose of inhaled corticosteroids based on FENO (compared to clinical symptoms with or without spirometry/peak flow, was beneficial in reducing the final, but not the overall daily doses of inhaled corticosteroids (ICS) in adults. In children, ICS dose was increased when the ENO guided strategy was used. Therefore, the role of utilizing ENO to tailor the dose of inhaled corticosteroids cannot be routinely recommended for clinical practice at this state and remains uncertain.

Smith et al. (2005) conducted a randomized controlled trial to assess the effectiveness of adjusting inhaled corticosteroid (ICS) dosage based on FENO (n=46) or an algorithm (n=48) based on conventional guidelines. The algorithm was derived from criteria established by the Global Initiative for Asthma 2002 for the control of asthma. The FENO cutoff point was 15 ppb above which an increase in the dose of ICS was prescribed. Primary outcome was the frequency of asthma exacerbations. Included subjects had cohrnic asthma, age 12–75 years and had been on ICS for six months with no change in dosage. Exhaled nitric oxide and spirometry were performed after a two-week run-in period and at every visit thereafter. At the second visit, all patients were started on inhaled fluticasone.During phase 1, the dose of inhaled fluticasone was titrated downward in a stepwise manner until the optimal dose was deemed to have been achieved. Subjects returned after four weeks and were randomly assigned to one of the two study groups. At each visit thereafter, subjects were noted as controlled or uncontrolled and the ICS was adjusted accordingly. During phase 2, which lasted for 12 months, maintenance treatment with inhaled fluticasone was continued at the optimal dose. The final mean daily doses of fluticasone was 370 µg/day for the FENO group and 641 µg for the control group (p=0.003). There was no significant difference in the rates of exacerbation between the groups and no significant differences in other markers of asthma control, use of oral prednisone, pulmonary function, or levels of airway inflammation (sputum eosinophils). Limitations of the study include the small patient populations and short duration. The authors noted that 110 patients were recruited and 13 were lost to the study prior to randomization with an additional three being lost during phase 1 leaving 94 final subjects.

Other Indications: FENO has been investigated for the diagnosis and management of other indications such as sleep apnea, subacute cough, chronic cough, and bronchitis. Studies have primarily been case series and retrospective review with small patient populations. Because of the heterogeneity of FENO cut-off points, patient demographics, selection criteria, and FENO devices used for measurement, data do not support FENO for these other indications (Jiang, et al., 2018; Song, et al., 2017a; Song, et al., 2017b; Zhang, et al., 2017; Kostikas, et al., 2011).

Song et al. (2017a) conducted a systematic review of the literature to assess the diagnostic accuracy of FENO in predicting cough-variant asthma (CVA) and eosinophilic bronchitis (EB) in patients with chronic cough. Fifteen studies (n=2187 adults) which included retrospective reviews and one conference abstract met inclusion criteria. Thirteen studies (n=2019) provided diagnostic information on FENO values for CVA in patients with chronic cough. Ten studies (n=1793) defined chronic cough as cough for ≥ 8 weeks. Optimal cutoff levels ranged from 15.9–55.0 ppb and were between 30–40 ppb in eight studies. Sensitivity and specificity were 72% and 85%, respectively. Four studies (n=529) were analyzed for the diagnostic utility of FENO measurement for either CVA or EB. Optimal cutoff levels ranged from 31.5 to 42.5 ppb. Sensitivity ranged from 61% and in one study 96%. Specificity was 85%. Four studies (n=390) used FENO measurement for EB in nonasthmatic patients with chronic cough. Optimal cutoff levels ranged from 22.5–31.7 ppb. Sensitivity was estimated as 72% and specificity as 83%. The authors noted that overall there was moderate diagnostic accuracy of FENO in the measurement in predicting CVA, EB or both in this subpopulation. However, due to the limited number of studies, heterogeneity of the studies (e.g., demographics, selection criteria, clinical settings, FENO devices, definitions of target conditions) and retrospective study design additional research is needed to support FENO testing in patients with chronic cough.

Song et al. (2017b) conducted a systematic review to assess the usefulness of FENO for predicting inhaled corticosteroid (ICS) responsiveness in adults with chronic cough. Two prospective and three retrospective studies met inclusion criteria. The optimal cutoff values varied from 16.3–38 ppb. The proportion of ICS responders ranged from 44%–59%. Sensitivity and specificity ranged from 53%–90%, and from 63%–97%, respectively. Limitations of the studies included: small patient populations (n=34–81); short-term follow-ups; lack of a comparator; retrospective study designs; heterogeneity of studies; and conflicting outcomes. There is insufficient evidence to support the use of FENO tests for predicting ICS responsiveness in chronic cough.

Kostikas et al. (2011) evaluated ENO and EBC pH in patients with asthma according to the level of control and performance in identifying patients who were not well-controlled. FeNO and EBC were measured in 274 consecutive patients evaluated in two hospital outpatient asthma clinics and evaluated according to GINA guidelines by two respiratory physicians who were blinded to FeNO and pH measurements FeNO was higher and EBC was lower in patients who were not well controlled compared to patients who were well controlled. The authors concluded that FeNO and EBC pH levels may be used in identification of patients with not well-controlled asthma. Their performance, however, was inferior to clinical judgment and may be limited to selected subgroups of asthmatic patients. Further longitudinal studies for the prospective evaluation of these biomarkers to guide the management of asthmatic patients are clearly justified.

Measurement of FeNO from the nasal cavity has also been suggested specifically for diagnosing primary ciliary dyskinesia (PCD). nNO is present in human airways but is observed at lower or absent levels in a patient with PCD. Due to inconsistent measuring protocols, nNO tests are not diagnostic of PCD and further testing and clinical manifestations are necessary. (Bergstrom, 2019) At this time there has been no FDA approved devices to measure nasal Nitric Oxide (nNO).

Technology Assessments

Agency for Healthcare Research and Quality (AHRQ): AHRQ (2017) published a comparative effectiveness systematic review that assessed the role of FENO in the diagnosis, treatment and monitoring of asthma. The report was based on research by the Mayo Clinic Evidence-based Practice Center (EPC) under contract to AHRQ and was sponsored by the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI). The report addressed five questions regarding the accuracy and clinical utility of FENO and focused on the diagnostic accuracy measures, asthma control composite scores, exacerbations, and asthma- specific quality of life as related.

A total of 43 nonrandomized studies, including observational and retrospective, (n=13,747), regarding the diagnostic accuracy of FENO for diagnosing asthma in adults >18 years (n=33 studies) and children ≥ age 5 years (n=10 studies) were reviewed. Results included the following:

- The diagnostic accuracy of FeNO for the diagnosis of asthma varied with the FeNO cutoff level used. Sensitivity and specificity per cutoff were: <20 ppb (79%, 72%), 20-30 ppb (64%, 81%), 30-40 ppb (53%, 84%), ≥40 ppb (41%, 94%) (strength of evidence [SOE]: moderate - observational and retrospective studies with low to high risk of bias). Generally, cutoffs varied and were inconsistent.
- Depending on the FeNO cutoff, the posttest odds of having asthma given a positive FeNO test result increased by 2.80 to 7.00 fold (SOE: moderate; observational and retrospective studies with low to high risk of bias).
- In steroid-naïve asthmatics, FeNO had the highest accuracy at cutoffs of <20 ppb compared to all patients included in the main analysis (sensitivity 79%, specificity 77%)
- Diagnostic accuracy was likely higher in nonsmokers compared to smokers and in children compared to adults.

Regarding the clinical utility of FENO in monitoring disease activity and asthma outcomes in adults and children there was weak evidence associated with asthma control and a weak association with the risk of subsequent and prior exacerbations. FeNO levels did not correlate with exacerbation severity and the levels were poorly reproducible. A total of 58 studies (n=8,999) were included of which seven were randomized controlled trials. The strength of evidence supporting the association between FeNO values and medication adherence (mainly ICS) was low. A low level of evidence showed that the association between FeNO levels and exacerbation risk is likely stronger in individuals with atopy (i.e., asthma associated with either positive skin test or specific IgE to aeroallergens) who are more likely to have eosinophilic inflammation.

The report also assessed the clinical utility of FENO to select medication options for patients ages ≥ 5 years. Twenty-four studies (n=2,820) were included. There was a high level of evidence that the use of asthma management algorithms that included FENO testing reduced the risk of exacerbation and moderate evidence that FENO could possibly predict the risk of exacerbations requiring oral steroids. However, the use of FENO did not affect other outcomes including hospitalization, quality of life, asthma control, or FEV1% predicted. There was a low level of evidence supporting FENO testing to identify patients who were most likely to respond to inhaled corticosteroids.

Forty-one studies (n=1,728) were analyzed to assess clinical utility of FeNO measurements to monitor response to treatment. Although FENO predicted exacerbation after ICS withdrawal or reduction, the response was heterogeneous and prediction could be substantially enhanced by clinical measures such as Asthma Control Test (ACT). The level of evidence supporting the utility of FENO in predicting exacerbations was low due to the observational nature of the studies. According to the authors, there are two situations in which FENO is most beneficial. A patient with compatible asthma symptoms who is clearly atopic (e.g. eczema, positive skin tests, peripheral blood eosinophilia, positive IgE in the blood) with an elevated FENO would imply ICS is indicated. Secondly, in a patient with known asthma with a previously documented elevated FENO who has symptoms that are not well controlled on guideline based therapy FeNO can be a means to monitor adherence to treatment.

Finally, the use of FENO testing in children age ≤ 4 years has not been established. It is unclear whether FENO testing in children suggestive of asthma can predict a future asthma diagnosis nor do the results of FENO correlate well with the Asthma Predictive Index and wheezing.

In the conclusion, the authors stated:

- FeNO has moderate accuracy to diagnose asthma in people ≥ age 5 years.
- Test performance is modestly better in steroid-naïve asthmatics, children, and nonsmokers than the general population with suspected asthma.
- Algorithms that include FeNO measurements can help in monitoring response to anti-inflammatory or long-term control medications, including dose titration, weaning, or treatment adherence.

- There is insufficient evidence supporting the measurement of FeNO in children under the age of 5 as a means for predicting a future diagnosis of asthma.

Overall, limitations of the studies included: heterogeneity in study populations; designs and outcome measures; unclear or high risk of bias (about half of the studies); short-term follow-ups; small patient populations; variation in FENO protocol and how FENO was measured (e.g., online vs. offline); healthy vs. symptomatic controls; and inconsistent and wide range of FENO cutoff levels. The reference tests used to compare with FeNO also varied with some studies using clinical diagnosis, others using a positive bronchial challenge test and some studies used combined testing (clinical diagnosis, positive bronchial challenge, and/or bronchodilator response). The authors noted that they were unable to establish the best cutoff for FENO overall and within specific subgroups. They were also unable to conduct some planned subgroup analyses because of lack of data, including asthma phenotypes, adequate testing procedures, body mass index (BMI) or weight; manufacturer and device model; and exhalation flow rates. It was also noted that clinicians considering FENO as an adjunct to the diagnosis of asthma should expect a “fair number” of false negatives and even more false positives depending on the FENO cutoff level that is used.

HAYES: Hayes conducted a systematic review of the literature to assess FENO as a diagnostic test for asthma (2016a; reviewed 2018). Thirteen nonrandomized trials including case series and retrospective reviews met inclusion criteria. The FENO level used as the cutoff value ranged from 13–60 ppb. FENO sensitivity ranged from 36%–91% and specificity ranged from 62%–96%. Four studies exclusively enrolled children and provided little evidence that FENO is an effective diagnostic tool for asthma. The overall quality of the evidence was rated as low by Hayes. Nine of the studies were considered to be of fair quality evidence and four were considered to be of poor quality. Limitations of the studies included: poor study design; poor reporting of patient characteristics and testing protocols; and the lack of a designated optimal cutoff value for FENO. Hayes concluded that FENO cannot be considered suitable for routine clinical use until a uniform protocol for its use and interpretation has been established and evaluated in clinical trials.

In a second directory report, Hayes (2016b; reviewed 2018) reviewed FENO for the management of asthma. Seventeen randomized controlled trials met inclusion criteria. In 12 studies FENO was used as an adjunct to usual measures of asthma control (e.g., symptoms, medication use, and lung function testing) and five studies evaluated FENO as a replacement for usual measures of control. Outcome measures included: asthma exacerbations, asthma-related urgent or emergent hospital visits, symptom-free days, symptom scores, asthma control, asthma treatment failure, asthma-related quality of life (QOL), asthma medication usage, respiratory complications, and patient satisfaction. Follow-up visits ranged from 6–24 months. Overall, the included studies were highly inconsistent and Hayes rated the quality of evidence as low. Limitations of the studies included: inadequate reporting of any statistically significant baseline differences; poor adherence to medication; loss to follow-up; short-term follow-ups; inconsistency in study protocol; wide variation of protocols used to adjust asthma medication; and conflicting outcomes. Hayes concluded that the highly inconsistent body of evidence suggested that FENO may improve asthma management but the benefit of FENO is unproven and inconsistent.

Professional Societies/Organizations

American Thoracic Society (ATS): An ATS Clinical Practice Guideline, Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications (Dweik et al., 2011) included the following recommendations for the use of FENO and noted that the recommendations may vary based on the target population and unless stated otherwise applied to patients with asthma:

- We recommend the use of FENO in the diagnosis of eosinophilic airway inflammation (strong recommendation, moderate quality of evidence).
- We recommend the use of FENO in determining the likelihood of steroid responsiveness in individuals with chronic respiratory symptoms possibly due to airway inflammation (strong recommendation, low quality of evidence).
- We suggest that FENO may be used to support the diagnosis of asthma in situations in which objective evidence is needed (weak recommendation, moderate quality of evidence).
- We recommend the use of FENO in monitoring airway inflammation in patients with asthma (strong recommendation, low quality of evidence).

For each question, the committee graded the quality of available evidence and made a recommendation for or against. Recommendations were decided by consensus. In discussing the above recommendations, the authors stated that given the long established relationship between eosinophilic inflammation and steroid responsiveness in airways disease, the finding that FENO correlates with eosinophilic inflammation suggested its use as an indirect indicator of eosinophilic inflammation, but more importantly, the potential for steroid responsiveness. Since not all patients respond to corticosteroids, the authors stated that a reason to use FENO is to help decide who might benefit from steroid treatment and who should try other medications, and to determine whether steroid therapy may be safely withdrawn. Regarding the use of FENO in the diagnosis of asthma, the authors stated that increasing FENO provides supportive rather than conclusive evidence for an asthma diagnosis.

American Academy of Allergy, Asthma and Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI): In February 2012 the AAAAI and ACAAI issued a joint statement to formally recognize and support the 2011 ATS Clinical Practice Guideline on the Interpretation of Exhaled Nitric Oxide for Clinical Applications. The statement noted that FENO values, of themselves do not justify a diagnosis or change in treatment and must be interpreted in relation to clinical context.

American Thoracic Society (ATS)/European Respiratory Society (ERS): An ATS/ERS Statement: Asthma Control and Exacerbations, Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice (Reddel et al., 2009) included the following statements regarding the use of fractional nitrous oxide in clinical trials :

- FENO measurements provide easily obtained information on underlying disease activity where it is characterized by eosinophilic airway inflammation, but the positive and negative predictive values for eosinophilia are suboptimal.
- FENO does not provide information about other types of airway inflammation, and this may be a problem in more severe asthma, where neutrophilic inflammation may be more important.
- The clinical utility of FENO -based management strategies has not been explored extensively. Currently available evidence suggested a role in identifying the phenotype in airways disease, particularly in the identification of corticosteroid responsiveness.

The ATS/ERS statement included the following recommendations regarding use of biomarkers in clinical practice:

- Where possible, biomarkers should be employed to provide information about underlying airway inflammation, a domain of the asthma ‘‘syndrome’’ that would not otherwise be available to the clinician
- FENO measurements may be used as a surrogate marker for eosinophilic airway inflammation. They may be used to evaluate the potential for response to corticosteroid treatment.
- Low values of FENO (< 25 ppb in adults, < 20 ppb in children) may be of particular value in aiding decisions about reducing corticosteroid dose, or alternatively for determining that ongoing airway symptoms are

The authors acknowledged that more information is required on the utility of FENO measurement as a tool for monitoring asthma control, and that there is a need for translational research to clarify the relationship between biomarkers and other parameters of asthma control, to establish the optimal frequency of monitoring, and to confirm the clinical and cost effectiveness of biomarker measurements in primary care and other settings.

Global Initiative for Asthma (GINA): GINA was developed as a collaborated effort between the National Heart, Lung and Blood Institute and the World Health Organization which developed the Global Initiative for Asthma Management and Prevention (GINA) report. The report is based on a systematic review of the literature. The updated 2019 GINA report stated that FENO is becoming more widely available in some countries. It is modestly associated with levels of sputum and blood eosinophils. FENO has not been established as useful for ruling in or ruling out a diagnosis of asthma. It is higher in asthma characterized by Type 2 airway inflammation but is also elevated in non-asthma conditions (e.g., eosinophic bronchitis, atopy, allergic rhinitis, eczema) and is not elevated in some asthma phonotypes such as neutrophilic asthma. GINA noted that FENO levels are lower in smokers, decreased during bronchoconstriction and in early phases of allergic response, and may be increased or decreased during viral respiratory infections. One study reported that a FENO > 50 ppb in adult steroid-naïve patients was associated with good short-term response. However, there are no long-term data regarding the risk of exacerbations when withholding ICS in patients with low FENO. As such, in patients with diagnosis or suspected diagnosis of asthma, FENO cannot be recommended for deciding against treatment with ICS. A FENO level > 50 ppb is associated with eosinophilic airway inflammation. In their discussion regarding alternative strategies for adjusting asthma treatment, GINA stated that at the present time FENO is not recommended for guiding treatment for the general asthma population. FENO-guided treatment significantly reduces exacerbation rates compared with guidelines-based treatments at least in children (Evidence A: randomized controlled trials and meta-analyses; rich body of data). However, further studies are needed to identify the population that would likely benefit from FENO-guided treatment and the optimal frequency of FENO monitoring. In mainly non-smoking patients, a FENO > 50 ppb was associated with a good short-term ICS response but no studies have examined the long-term safety with regard to exacerbations of withholding ICS in patients with low initial FENO. Therefore, in patients with a diagnosis or suspected diagnosis of asthma, FENO can support the decision to start ICS but cannot safely be recommended for deciding against treatment with ICS.

The 2019 GINA guide for health professionals for the diagnosis and management of difficult-to-treat and severe asthma in adolescents and adult patients noted that the possibility of refractory Type 2 inflammation should be considered if any of the following are found while the patient is taking high-dose ICS: blood eosinophils ≥◦150/μl and/or FENO ≥ 20 ppb and/or sputum eosinophils ≥ 2% and/or asthma is clinically allergen-driven. These criteria are suggested for initial assessment. Consider repeating blood eosinophils and FENO up to three times (e.g., when asthma worsens, before giving oral corticosteroids [OCS]) before assuming asthma is non-Type 2. OCS rapidly reduces markers of Type 2 inflammation (blood eosinophils, FENO) in most patients so the test should be performed before starting a short course or maintenance OCS, or on the lowest possible dose. GINA noted that one randomized controlled trial reported a greater decrease in exacerbations vs placebo if FENO was ≥ 20 ppb. For oral treatment tapering maybe supported by internet-based monitoring of symptom control and FENO.

International European Respiratory Society (ERS)/American Thoracic Society (ATS): In the guidelines on definition, evaluation and treatment of severe asthma, ERS/ATS (2014) recommended that FENO not be used to guide therapy in adults or children with severe asthma due to “very low” quality evidence and the uncertain benefit from monitoring FENO in this population. The authors noted that FENO has been extensively evaluated in mild-to-moderate asthma. Cross-section studies indicated some potential usefulness of FENO as a measure of symptom frequency in severe asthma and as an index of the most obstructed and frequent users of emergency care. Regarding the use of biomarkers to guide corticosteroid dosage, sputum eosinophils and/or exhaled nitric oxide levels for guiding therapy in severe asthma remains controversial.

National Heart Lung and Blood Institute (NHLBI): The NHLBI Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (2007; updated 2012) stated that minimally invasive markers for monitoring asthma control, including spirometry and airway hyper-responsiveness are currently used appropriately and widely in asthma care. The panel further stated that other markers, such as sputum eosinophils and FeNO, are increasingly used in clinical research and will require further evaluation in adults and children before they can be recommended as a clinical tool for routine asthma management.

Centers for Medicare & Medicaid Services (CMS)
There is no CMS National or Local Coverage Determinations for exhaled nitric oxide.

Use Outside the U.S.
National institute for Health and Clinical Excellence (NICE) (United Kingdom): In a 2017 guidance on the management of chronic asthma, NICE includes FENO levels as an indicator for initial treatment of acute symptoms and as an objective test to use for the diagnosis of asthma in an individual age ≥◦5 years. NICE recommended offering FENO testing to adults if a diagnosis of asthma is being considered and that a FENO level ≥◦40 parts per billion (ppb) is considered a positive test. In children aged 5–16, FENO can be considered if there is diagnostic uncertainty with a normal spirometry or obstructive spirometry with a negative bronchodilator reversibility (BDR) test. NICE stated that a FeNO level ≥ 35 ppb is considered a positive test. The guidance provides FENO levels based on age and FENO levels when considering other testing (e.g., peak flow, direct bronchial challenge test). It was also noted that the results of spirometry and FENO testing may be affected in patients who have been treated empirically with inhaled corticosteroids and in smokers. FeNO measurement may be an option to support asthma management in people who are symptomatic despite using inhaled corticosteroids. However, the routine use of FENO is not recommended by NICE for monitoring asthma control.

NICE Guidance for the use of exhaled nitric oxide measurement was published in April, 2014, and included the following recommendations:

- Fractional exhaled nitric oxide (FeNO) testing is recommended as an option to help with diagnosing asthma in adults and children:
  - who, after initial clinical examination, are considered to have an intermediate probability of having asthma (as defined in the British guideline on the management of asthma, 2012) and
  - when FeNO testing is intended to be done in combination with other diagnostic options according to the British guideline on the management of asthma (2012)

Further investigation was recommended for people with a negative FeNO test because a negative result does not exclude asthma. FENO measurement was recommended as an option to support asthma management (in conjunction with the British guideline on the management of asthma, 2012) in people who are symptomatic despite using inhaled corticosteroids.

British Thoracic Society: The 2019 British Thoracic Society (BTS) guideline on the management of asthma states that a positive FeNO test suggests eosinophilic inflammation and provides supportive, but not conclusive, evidence for an asthma diagnosis. Many factors can affect FeNO level. Levels are increased in patients with allergic rhinitis exposed to allergen, even without any respiratory symptoms; rhinovirus infection in healthy individuals; in men; tall people; and by consumption of dietary nitrates. Levels are lower in children, reduced in cigarette smokers and reduced by inhaled or oral steroids. Based on a low level of evidence, the Society stated that the measurement of FeNO (if available) can be used to find evidence of eosinophilic inflammation. A positive test increases the probability of asthma but a negative test does not exclude asthma. According to the Guideline, a raised FeNO (>◦50 parts per billion [ppb] in adults and >◦35 ppb in children) is predictive of a positive response to corticosteroids. However, the evidence that FeNO can be used to guide corticosteroid treatment is mixed. Low FeNO (<◦25 ppb in adults; <◦20 ppb in the under 12 year old range) may have a role in identifying patients who can step down corticosteroid treatment safely, but additional studies are needed. Protocols for diagnosis and monitoring have not been well defined and more work is needed.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
95012	Nitric oxide expired gas determination

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