Medical Policy

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Title: Measurement of Exhaled Nitric Oxide and Exhaled Breath Condensate in the Diagnosis and Management of Asthma and Other Respiratory Disorders

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DESCRIPTION

Current techniques for diagnosing and monitoring asthma and predicting exacerbations are suboptimal. Two new strategies, evaluation of exhaled nitric oxide (NO) and exhaled breath condensate are proposed. These techniques are also potentially useful in the management of other conditions such as chronic obstructive pulmonary disease (COPD) and chronic cough. There are commercially available devices for measuring NO in expired breath and various laboratory techniques for evaluating components of exhaled breath condensate.

Background

Guidelines for the management of persistent asthma stress the importance of long-term suppression of inflammation using steroids, leukotriene inhibitors, or other anti-inflammatory drugs. Existing techniques for monitoring the status of underlying inflammation have focused on bronchoscopy, with lavage and biopsy, or analysis by induced sputum. Given the cumbersome nature of these techniques, the ongoing assessment of asthma focuses not on the status of the underlying chronic inflammation, but rather on regular assessments of respiratory parameters such as forced expiratory volume in one second (FEV1) and peak flow. Therefore, there has been interest in noninvasive techniques to assess the underlying pathogenic chronic inflammation as reflected by measurements of inflammatory mediators.

Two proposed strategies are the measurement of exhaled nitric oxide (NO) and the evaluation of exhaled breath condensate. Nitric oxide is an important endogenous messenger and inflammatory mediator that is widespread in the human body, functioning, for example, to regulate peripheral blood flow, platelet function, immune reactions, and neurotransmission and to mediate inflammation. In biologic tissues, NO is unstable, limiting measurement. However, in the gas phase, NO is fairly stable, permitting its measurement in exhaled air. Exhaled NO is typically measured during single breath exhalations. First, the subject inspires nitric oxide-free air via a mouthpiece until total lung capacity is achieved, followed immediately by exhalation through the mouthpiece into the measuring device. Several devices measuring exhaled NO are commercially available in the United States. According to a 2009 joint statement by the American Thoracic Society (ATS) and European Respiratory Society (ERS), there is a consensus that the fractional concentration of exhaled nitric oxide (FeNO) is best measured at an exhaled rate of 50 mL per second (FeN 50 mL/s) maintained within 10% for more than 6 seconds at an oral pressure between 5 and 20 cm H2O. (1) Results are expressed as the NO concentration in parts per billion (ppb) based on the mean of 2 or 3 values.

Exhaled breath condensate (EBC) consists of exhaled air passed through a condensing or cooling apparatus, resulting in an accumulation of fluid. Although EBC is primarily derived from water vapor, it also contains aerosol particles or respiratory fluid droplets, which in turn contain various nonvolatile inflammatory mediators, such as cytokines, leukotrienes, oxidants, antioxidants, and various other markers of oxidative stress. There are a variety of laboratory techniques to measure the components of EBC, including such simple techniques as pH measurement, to the more sophisticated gas chromatography/mass spectrometry or high performance liquid chromatography, depending on the component of interest.

Measurement of NO and EBC has been investigated in the diagnosis and management of asthma. Potential uses in management of asthma include assessing response to anti-inflammatory treatment, monitoring compliance with treatment and predicting exacerbations. Aside from asthma, they have also been proposed in the management of

patients with chronic obstructive pulmonary disease (COPD), cystic fibrosis, allergic rhinitis, and primary ciliary dyskinesia.

Regulatory Status

In 2003, the U.S. Food and Drug Administration (FDA) cleared for marketing the Nitric Oxide Monitoring System (NIOX) (Aerocrine; Sweden) with the following indication: "[Measurements of the fractional nitric oxide (NO) concentration in expired breath (FE-NO)] provide the physician with means of evaluating an asthma patient's response to anti-inflammatory therapy, as an adjunct to established clinical and laboratory assessments in asthma. NIOX should only be used by trained physicians, nurses and laboratory technicians. NIOX cannot be used with infants or by children approximately under the age of 4, as measurement requires patient cooperation. NIOX should not be used in critical care, emergency care or in anesthesiology." In March 2008, the NIOX MINO was cleared for marketing. The main differences between this new device and the NIOX are that the NIOX MINO is hand-held and portable and that it is not suitable for children under age 7 years.

The Breathmeter (Ekipstech) is another device used to measure exhaled nitric oxide using laser spectroscopy. As of November 2010, the Breathmeter is available for research only; it has not yet received FDA approval or clearance.

The RTube Exhaled Breath Condensate collection system (Respiratory Research, Inc) is registered with the FDA as a Class I device that collects expired gas. Respiratory Research has a proprietary gas-standardized pH assay, which, when performed by the company, is considered a laboratory-developed test.

POLICY

A. Measurement of exhaled or nasal nitric oxide is considered **experimental / investigational** in the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough.

B. Measurement of exhaled breath condensate is considered **experimental / investigational** in the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough.

RATIONALE

An initial literature search was performed in 2003. The policy was updated regularly with a literature review using MEDLINE; the most recent search dates were October 2011 through November 2012. Evaluation of the tests for diagnosis requires that the test findings are reproducible on test-retest and that the test is reasonably accurate compared to a validated

reference standard. Assessment of the clinical role of exhaled nitric oxide (NO) and exhaled breath condensate (EBC) tests requires controlled studies of those managed conventionally compared to those whose management was additionally directed by test measurements. Following is a summary of literature to date.

Exhaled Nitric Oxide

Asthma

Reproducibility of fractional concentration of exhaled nitric oxide (FeNO) measurements
In 2010, Selby and colleagues published a study from the UK that evaluated the reproducibility of exhaled NO measurements in young people. (2) The study included 494 teenagers, aged 16-18 years, from an unselected birth cohort and 65 asthma patients between the ages of 6 and 17 years. Paired readings were obtained from each participant. The mean within-participant difference in FeNO (second reading minus the first reading) was 1.37 parts per billion (ppb) (95% confidence interval [CI]: -7.61 to 10.34 ppb); this difference was statistically significant; p less than 0.001. When participants with high FeNO values (above 75 ppb) were excluded, there was a lower mean within-participant difference, 0.90 ppb (95% CI:-4.89 to 6.70 ppb). Among the 71 participants with asthma, the mean within-participant difference in FeNO in the 2 measurements was 2.37 ppb (95% CI: -11.38 to 16.12 ppb). When FeNO values were categorized as low, normal, intermediate, or high (using different values for participants younger than age 12 years and 12 years or older), the findings were reproducible. That is, there were no statistically significant differences in the categorization using the first and second measurement.

Does FeNO aid in the diagnosis of asthma in individuals with signs or symptoms of asthma?
The sensitivity and specificity of FeNO for the diagnosis of asthma is dependent upon the cutoff point that is used. To date, the optimal cutoff point remains undefined, and this has been the focus of some of the published studies on using FeNO in the diagnosis of asthma.

Most recently, in 2012, Malinovschi and colleagues in Denmark evaluated 282 individuals with symptoms suggestive of asthma. (3) Study participants were part of a sample of 10,400 individuals aged 14-44 years randomly selected from the civil registration list in Denmark. Individuals were eligible for the study if they had at least 2 symptoms suggestive of asthma. FeNO was measured with the NIOX MINO device, and patients were examined by a respiratory specialist to determine the clinical diagnosis of asthma. Among the 282 participants, 112 were current smokers, 108 never smoked and 62 were ex-smokers. According to clinical evaluation, 96 of 282 (34%) had asthma, 32 smokers, 45 never smokers, and 19 ex-smokers. The authors examined different cut-offs of FeNO to determine the value with the optimal sensitivity and specificity for diagnosing asthma. They proposed a cutoff of 17 ppb in current smokers (56.3% sensitivity and 82.5% specificity), 15 ppb in never smokers (77.8% sensitivity and 63.5% specificity), and 22 ppb in ex-smokers 63.2% sensitivity and 86.1% specificity.

Another 2012 study, by Schleich and colleagues in Belgium, prospectively evaluated 174 individuals with suspected asthma who were referred for a methacholine challenge and who were not currently receiving inhaled corticosteroids (ICS). (4) FeNO was measured with a NIOX device set at a flow rate of 50 mL/s. According to the methacholine challenge test findings, 82 of 174 (47%) of participants were diagnosed with asthma (i.e., provocative concentration of methacholine [PC20M] was 16 mg/mL or lower). FeNO was significantly higher in patients with a positive methacholine

challenge (19 ppb) than a negative challenge test (15 ppb), p<0.05. Receiver operating characteristic (ROC) analysis found that a FeNO cutoff of 34 ppb best predicted the outcome of the methacholine challenge test (sensitivity 35.4%, specificity 95.4%).

Woo and colleagues in Korea also published a study in 2012 using prospectively collected data on 245 consecutive steroid-naïve children with respiratory symptoms suggestive of asthma. (5) FeNO was measured using the NIOX MINO, and lung function tests were performed with spirometry. Asthma was diagnosed in 167 (68%) of participants. Using ROC analysis, the investigators found that the optimal cutoff for FeNO in diagnosing asthma was 22 ppb, which provided 56.9% sensitivity and 87.2% specificity. At a cutoff of 42 parts per trillion (ppt), the specificity was 100%, but the sensitivity was very low, 23.4%.

Other representative studies include one using the NIOX MINO device that was published in 2010 by Pedrosa and colleagues in Spain. (6) The study included 114 individuals at least 14 years-old who had symptoms consistent with asthma, with or without rhinitis symptoms, and had normal parameters on spirometry and a negative bronchodilator test. Definitive diagnosis was based on symptom assessment and a positive methacholine bronchial challenge test. Individuals underwent FeNO assessment (flow rate of 50 mL/s) just before the methacholine inhalation challenge test. According to challenge test findings, 35 patients (31%) were diagnosed with asthma. FeNO levels were significantly higher in individuals diagnosed with asthma (mean 58 ppb) than in non-asthmatics (mean ppb 30 ppb); p<0.001. Using ROC analysis, the cut-off point with maximum sensitivity (74.3%) and specificity (72.5%) for diagnosing asthma was a FeNO value of 40 ppb. A 2010 study conducted in Italy included 280 children with asthma, allergic rhinitis or both. (7) The authors used ROC analysis and found that the optimal cut-off for discriminating between patients with bronchial hyperactivity from those with absent or borderline bronchial hyperactivity was 32 ppb of NO.

In addition, in 2009 Schneider and colleagues in Germany published data on 160 patients with symptoms suspicious of asthma. (8) All patients underwent measurement of exhaled NO. The reference standard was a stepwise series of tests, beginning with spirometry. Those with forced expiratory volume in one second (FEV1) less than 80% of predicted or FEV1/vital capacity (VC) ratio of 0.70 or less were referred to bronchodilator reversibility testing. Otherwise, patients received bronchial provocation with methacholine. Patients were classified as having asthma when: 1) bronchodilation testing found a change in FEV1 was at least 12% compared to baseline, and at least 200 mL, and lung volumes returned to predicted normal range; 2) bronchial provocation found a 20% decrease in FEV1 from the baseline value after inhaling methacholine stepwise until the maximum concentration. Exhaled NO test findings were compared to the final diagnosis status. According to standard testing, 75 (46.9%) of the patients had asthma. ROC analysis found the highest sum of sensitivity and specificity of exhaled NO at a cut-off of 46 ppb. Among patients with unsuspicious spirometry findings (n=101), 49 had asthma. The optimal cut-off of exhaled NO in this subgroup was also 46 ppb; the sensitivity of exhaled NO was 35%, and the specificity was 90%.

A 2011 clinical practice guideline from the American Thoracic Society (ATS) (described in more detail and critically appraised in the section on Practice Guidelines and Position Statements) recommended FeNO cutoff values for predicting the presence of eosinophilic inflammation. (9) Many, but not all, patients with asthma will have eosinophilic inflammation. The guidelines recommended that FeNO less than 25 ppb (<20 ppb in children) be used to indicate that

eosinophilic inflammation is less likely and that FeNO greater than 50 ppb (>35 ppb in children) be used to indicate that eosinophilic inflammation is more likely. The sensitivity and specificity of these recommended cutoffs have not been evaluated in published studies for the diagnosis of asthma.

Conclusions:
Numerous studies have evaluated measurement of FeNO as a tool to aid in the diagnosis of asthma. The optimal cutoff of FeNO for diagnosing asthma has varied among studies; studies determining the optimal cutoff of FeNO are still being published as of 2012. There is still no validated standardized cutoff of FeNO to use for diagnosing asthma. As a result, it is not possible to determine the true sensitivity and specificity of the test for diagnosing asthma. Available studies tend to report low to moderate sensitivity and moderate to high specificity, but with wide variability among studies that may be related to different cutoff levels used. Due to these limitations, it is not possible to determine whether exhaled NO has incremental utility for diagnosing asthma compared to the usual clinical evaluation.

Does FeNO level predict response to medication therapy in patients with asthma?
The 2011 clinical practice guideline from the ATS recommended the use of FeNO to determine the likelihood of response to steroids in individuals with chronic respiratory symptoms that are possibly due to airway inflammation. (9) Three studies were cited in the guideline in support of this recommendation; all used data from randomized controlled trials (RCTs). In a 2002 open-label trial, Szefler and colleagues randomized 30 asthma patients to 1 of 2 types of inhaled corticosteroids (ICS). (10) There was a higher rate of response to ICS (defined as an increase in forced expiratory volume in one second [FEV1] of at least 15%) in individuals with higher baseline FeNO (median 17.6 ppb) compared to lower baseline FeNO (median 11.1 ppb). Other factors associated with a response to ICS in this study included high bronchodilator reversibility and a low FEV1/forced vital capacity ratio before treatment. In 2005, Smith and colleagues conducted a single-blind placebo-controlled trial of inhaled fluticasone in 60 patients presenting with undiagnosed respiratory symptoms. (11) Steroid response was defined as an increase in FEV1 of at least 12% or an increase in peak morning flow (over the previous 7 days) of 15% or greater. In the 52 (87%) patients who completed the study, steroid response was significantly higher in patients with the highest FeNO quartile at baseline (over 47 ppb) for both of the study endpoints. In addition, a baseline FeNO of over 47 ppb had a 67% sensitivity and 78% specificity for predicting response to steroids, when defined as an increase in FEV1. When response to steroids was defined as an increase in peak morning flow, there was an 82% sensitivity and 81% specificity for predicting response. The third study cited in the ATS guideline in support of FeNO for predicting response to corticosteroids was published by Knuffman and colleagues in 2009. (12) The study was a planned *post hoc* analysis of data from an RCT comparing different treatment regimens in children with asthma. The authors evaluated predictors of long-term response to treatment in 191 children who received either fluticasone or montelukast. In a multivariate analysis, statistically significant predictors of a better asthma control days (ACD) response to fluticasone over montelukast were a baseline FeNO of at least 25 ppb ($p=0.01$) and a parental history of asthma ($p=0.02$).

All of these 3 studies found significant associations between baseline FeNO and response to inhaled corticosteroids. It is worth noting, however, that the authors of 2 of the above studies (Smith et al. and Szefler et al.) have also published RCTs evaluating FeNO measurement for guiding treatment decisions for patients with asthma. Neither of those RCTs found better health

outcomes e.g., exacerbation rates when FeNO was used to manage patients. (The RCTs are described in more detail in a later section of the policy).

No additional recent trials were identified in the 2012 literature update that specifically addressed the association between baseline FeNo and subsequent response to ICS.

Conclusions:
Several studies have found a statistically significant association between baseline FeNO and response to inhaled corticosteroids. The number of studies addressing this topic is small and they have used different cutoff points for FeNO and different definitions of the outcome, i.e., response to steroids. As a result, there is uncertainty as to the degree of association between FeNO and response to steroids, as well as uncertainty in the optimal cutoff point that should be used for this purpose. It is also not clear that the ability to predict responsiveness to steroids will result in management changes. Inhaled steroids are a mainstay of treatment of asthma and have been associated with a variety of health outcome benefits. Therefore, it may not be defensible to withhold inhaled steroids for symptomatic asthmatics even if there is evidence for reduced responsiveness.

Does measurement FeNO to guide treatment decisions in patients with asthma improve health outcomes?
In 2005, a TEC Assessment was published on exhaled NO monitoring for guiding treatment decisions in patients with chronic asthma. (13) The assessment identified 2 randomized controlled trials; both were published in 2005. Smith and colleagues reported that equivalent outcomes (e.g. exacerbations, pulmonary function) were achieved in the group managed using exhaled NO measurements compared to the group managed using conventional guidelines (14) The FeNO group, however, used lower doses of ICS at the end of the study. Pijnenburg and colleagues found similar changes in steroid dose and FEV1 in groups managed with and without FeNO measurements. (15) Bronchial hyperreactivity, an intermediate outcome, improved more in the FeNO group. The TEC Assessment concluded that the available evidence did not permit the conclusion that use of NO monitoring to guide treatment decisions in asthma leads to improved outcomes.

In 2012, Petsky and colleagues published a meta-analysis of RCTs evaluating the use of tailoring asthma treatment based on levels of eosinophilic markers (exhaled NO or sputum eosinophils) compared to clinical symptoms (with or without spirometry/peak flow). (16) The study combined 2 Cochrane reviews including a 2009 review on exhaled NO. (17) Updated literature searches were not performed. As in the 2009 Cochrane review, the 2012 review identified a total 6 RCTs on FeNO. In addition to the 2 RCTs described above in the section on the TEC Assessment, the studies were Shaw et al. 2007, (18) Fritsch et al. 2006, (19) Szefler et al. 2008, (20) and de Jongste et al. 2009. (21) Four of the studies included children or adolescents, 1 included only adults and the sixth included both adolescents and adults. Two studies were double-blind and the other 4 were single-blind. Five studies used hospital-based FeNO measurements, and one used a portable at-home NO analyzer. Four studies measured FeNO at a flow rate of 50 mL/s.

The primary outcome of the meta-analysis was the difference in the number of patients in each group who had asthma exacerbations during follow-up. When findings for the 2 FeNO studies that included adults and/or adolescents were pooled (Shaw et al. 2007 and Smith et al. 2005), there was not a significant difference in the number of patients experiencing an exacerbation (odds ratio

[OR]: 0.85, 95% CI: 0.30 to 2.43). There was also no significant difference in symptom scores (mean difference of -0.10 [95% CI: -0.33 to 0.12]). Findings from 3 of the 4 pediatric trials were pooled, Pijnenburg et al. 2005, (15) Szefler et al. 2008, (20) and de Jongste et al. 2009 (21). As with the adult studies, there was not a significant difference in the number of patients experiencing an exacerbation (OR: 0.75, 95% CI: 0.55 to 1.01). A pooled analysis of 2 of the pediatric studies (Pijnenburg et al. 2005 and Szefler et al. 2008) did not find a significant difference in symptom scores between patients managed with and without FeNO measurement (mean difference: 0.13: 95% CI: -0.32-0.57).

There were, however, statistically significant differences between groups in the final dose of ICS, although the direction of this relationship was different in adults and children. In adults, patients who had their medication doses adjusted based on exhaled NO levels had a significantly lower final dose of ICS than those in the control group (pooled analysis of 2 studies: mean difference: -450 ug budesonide equivalent, 95% CI: -677 to -223). In contrast, children in the FeNO group had a significantly higher dose of ICS compared to the control group (pooled analysis of 3 studies, mean difference: 140 ug, 95% CI: 29 to 251).

Three additional, more recent RCTs were identified in literature searches for policy updates. Two of these had findings similar to the Petsky systematic review. In 2012, an RCT by Pike and colleagues in the U.K. included 90 children with severe asthma. (22) Medication management decisions were based on clinical symptoms (i.e., standard management) (n=46) or clinical symptoms and FeNO levels (n=44). In the standard management group, therapy was increased if symptoms were poorly controlled or decreased if symptoms were well-controlled for 3 months. Medications were given according to a stepped care algorithm consistent with British clinical guidelines. In the exhaled NO group, when symptoms were poorly controlled and FeNO was less than 25 ppb, long-acting beta-agonist therapy (LABA) was maximized before ICS was increased. If FeNO was at least 25 ppb or doubled from baseline, ICS was increased. ICS was decreased if symptoms were well-controlled for 3 months (as in the standard care group) or if FeNo was 15 ppb or lower and symptoms were controlled. Seventy-seven of 90 (86%) of participants completed the 12-month study; analysis was intention to treat. During the follow-up period, 37 (84.1%) of patients in the FeNO group and 38 (82.6%) of patients in the standard care group experienced at least one asthma exacerbation. The proportion of children with exacerbations did not differ significantly between groups, p=0.85. Five (11.4%) children in the FeNO group and 3 (6.5%) in the standard care group experienced a severe exacerbation; the difference between groups was not statistically significant, p=0.42. In addition, there was not a significant difference between groups in the initial ICS dose, the final ICS dose, and the change in ICS during the study. Median final dose of ICS was 800 mcg in the FeNO group and 500 mcg in the standard management group.

Also in 2012, Calhoun and colleagues published a multicenter trial funded by the National Institutes of Health (NIH) known as the Best Adjustment Strategy for Asthma in the Long Term (BASALT) trial. (23) The study included 342 adults with mild to moderate persistent asthma that was well or partially controlled by low-dose ICS. Participants were randomized to one of 2 strategies for medication adjustment: 1) adjusted by physicians at clinic visits (every 6 weeks) according to NIH clinical guidelines; 2) adjusted according to levels of exhaled NO at clinic visits (every 6 weeks); or 3) adjusted by patients on a day-to-day basis based on their symptoms. The third strategy involved patients using an inhaler that contained corticosteroids whenever they used an inhaler containing a short-term beta-agonist for symptom relief. No details were provided in the

article or supplemental material regarding how steroid dose was adjusted according to FeNO level. A total of 290 of 342 randomized patients completed the 9-month study; analysis was intention to treat. The primary study outcome was time to first treatment failure according to pre-defined criteria. The 9-month Kaplan-Meier first treatment failure rate did not differ significantly among the 3 groups. The rates were 22% (97.5% CI: 14% to 33%) in the physician-directed medication adjustment group, 20% (97.5% CI: 13% to 30%) in the exhaled NO medication adjustment group, and 15% (97.5% CI: 9% to 25%) in the symptom-based medication adjustment group. The failure rate in the physician-based and exhaled NO-based medication adjustment groups were not significantly different (hazard ratio: 1.2, 95.5% CI: 0.6 to 2.3). Secondary outcomes, including measures of lung function and asthma symptoms, also did not differ significantly among groups. The mean monthly dose of ICS was significantly higher in both the physician-directed medication adjustment group (1610 ug) and the exhaled NO-based medication adjustment group (1617 ug) compared to the patient-based symptom medication adjustment groups (832 ug, p=0.01 for both comparisons). An editorial accompanying the publication of the BASALT trial noted that, given the trials findings, it is difficult to recommend routine monitoring of exhaled NO in adults with mild to moderate asthma. (24)

The third RCT, conducted by Powell and colleagues, found improved outcomes in pregnant women with asthma managed with an algorithm including FeNO. (25) Eligibility included being between 12 and 20 weeks' gestation a non-smoker and using inhaled therapy for asthma within the past year. Women were randomized to a FeNO algorithm to adjust therapy (n=111) or a clinical guideline algorithm that did not include FeNO measurement (n=109). The FeNO algorithm appeared to be devised by the study investigators. According to the algorithm, the cut-off for reducing the dose of ICS was less than 16 ppb, and the cut-off for dose increase was at least 30 ppb. Both treatment groups also had their symptoms assessed by the Asthma Control Questionnaire (ACQ), and ACQ scores were utilized in both medication adjustment algorithms. A total of 203 of 220 women (92%) completed the study; analysis was intention to treat. The primary study outcome was the total number of asthma exacerbations during pregnancy (and after study enrollment) for which the patient sought medical attention. The mean total exacerbation rate was significantly lower in the FeNO group (0.29 per pregnancy) compared to the control group (0.62 per pregnancy), p=0.01. Overall, 28 (25%) of women in the FeNO group and 45 (41%) in the control group had at least one exacerbation; the difference between groups was statistically significant, p=0.01. Among the secondary outcomes, there were significantly fewer unplanned doctors visits in the FeNO group (mean of 0.26 per patient) than the control group (mean of 0.56 per patient), p=0.002.

The Powell study demonstrates a potential benefit to using a treatment algorithm that incorporates FeNO levels. However, this trial is prone to many of the same limitations as previous trials of FeNO management algorithms. Most importantly, patients in each group end up on differing regimens of medications according to the algorithm followed. It is then difficult to isolate the effect of the algorithm from the efficacy of the medications themselves. For example, if a FeNO algorithm uses a lenient cut-off point for increasing ICS, then the FeNO group will likely end up on higher doses of ICS. Improved outcomes are then more likely to be due to the efficacious effect of ICS, rather than the inclusion of FeNO in the algorithm. In the Powell study, (25) the cut-off point for increasing ICS was lowered compared to previous algorithms, thus resulting in more patients being started this medication. Additionally, the control group was treated by an algorithm that differed from current treatment guidelines in at least 2 important ways, both which resulted in less intensive treatment compared to treatment guidelines. The net effect of these algorithms was that more patients in the FeNO group received both long-acting beta-agonists and ICS, although patients

treated with inhaled steroids in the control group were treated at higher doses. Therefore, the differences in outcomes may be due to differences in treatment regimens that could have been achieved with or without the use of FeNO in the guidelines.

Conclusions:
Numerous RCTs comparing management of asthma with and without FeNO have been published. These studies are heterogenous in terms of the patient populations, the FeNO cutoff levels, and the protocol for management of patients in the control group. A meta-analysis of the 6 RCTs did not find significantly improved outcomes (e.g., a lower rate of asthma exacerbations, lower symptom scores) when medication dose was tailored to FeNO level. Two subsequent RCTs, including a large multicenter NIH-funded trial, had similar findings of no benefit. One recent RCT in pregnant women did find a lower rate of asthma exacerbations in women managed with an algorithm that included FeNo measurement compared to an algorithm without FeNo. However, in that RCT, it was difficult to determine that improved outcomes were due to FeNO measurement and not to other factors such as dose of medication. Efficacy of this treatment algorithm has not been confirmed in other studies.

Respiratory conditions other than asthma

Does FeNO aid in the diagnosis of respiratory disorders other than asthma?
Rouhos and colleagues in Finland published a study in 2011 on repeatability of FeNO measurements in 20 patients with stable chronic obstructive pulmonary disease (COPD) and 20 healthy controls. (26) FeNO was measured 3 times in each individual; a baseline measurement and measurements 10 minutes and 24 hours after baseline. In COPD patients, median FeNO values were 15.2 ppb at baseline, 17.4 ppb 10 minutes later, and 14.5 ppb 24 hours later. In healthy controls, corresponding median FeNO values were 15.6 ppb, 19.6 ppb, and 15.7 ppb. Differences between the baseline and 24-hour measurements in both groups were not statistically significant. FeNO values 10 minutes after baseline were significantly higher than the 24-hour measurement in both groups; the authors attributed this difference to the fact that patients did not rinse their mouths with sodium bicarbonate between the baseline and 10-minute measurements.

Does FeNO level predict response to medication therapy in patients with respiratory conditions other than asthma?
A double-blind cross-over trial by Dummer and colleagues evaluated the ability of exhaled NO test results to predict corticosteroid response in chronic obstructive pulmonary disease (COPD). (27) The study included 65 patients with COPD who were 45 years or older, were previous smokers with at least a 10-pack a year history, had persistent symptoms of chronic airflow obstruction, had a post-bronchodilator forced expiratory volume in one second/forced vital capacity ratio (FEV1/FVC) of less than 70% and a FEV1 of 30–80% predicted. Patients with asthma or other co-morbidities and those taking regular corticosteroids or had used oral corticosteroids for exacerbations more than twice during the past 6 months were excluded. Treatments, given in random order, were 30 mg/d of prednisone or placebo for 3 weeks; there was a 4-week washout period before each treatment. Patients who withdrew during the first treatment period were excluded from the analysis. Those who withdrew between treatments or during the second treatment were assigned a net change of zero for the second treatment period. Fifty-five patients completed the study. Two of the 3 primary outcomes, 6-minute walk distance (6MWD and FEV1) increased significantly from baseline with prednisone compared to placebo. There was a non-significant decrease in the third primary outcome, score on the St. George's Respiratory

Questionnaire (SGRQ). The correlation between baseline fraction of exhaled NO was not significantly correlated with change in 6MWD (r=0.10, p=0.45) or SGRQ (r=0.12, p=0.36) but was significantly related to change in FEV1 (r=0.32, p=0.01). At the optimal fraction of exhaled NO cut-off of 50 ppb, as determined by ROC analysis, there was a 29% sensitivity and 96% specificity for predicting a 0.2-liter increase in FEV1. (A 0.2-liter change was considered to be the minimal clinically important difference.) The authors concluded that exhaled NO is a weak predictor of short-term response to oral corticosteroid treatment in patients with stable, moderately severe COPD and that a normal test result could help clinicians decide to avoid prescriptions that may be unnecessary; only about 20% of patients respond to corticosteroid treatments. Limitations of the study include that the response to treatment measured was short term, and this was not a trial of management decisions based on exhaled NO test results.

A prospective uncontrolled study by Prieto and colleagues assessed the utility of exhaled nitric oxide measurement for predicting response to ICS in patients with chronic cough. (28) The study included 43 patients with cough of at least 8 weeks' duration who were non-smokers and did not have a history of other lung disease. Patients were evaluated at baseline and after 4 weeks of treatment with inhaled fluticasone propionate 100 µg twice daily. Nineteen patients (44%) had a positive response to the treatment, defined as at least a 50% reduction in mean daily cough symptom scores. ROC analysis showed that, using 20 ppb as the FeNO cut-off, the sensitivity was 53% and the specificity was 63%. The authors concluded that exhaled NO is not an adequate predictor of treatment response.

Does measurement of FeNO improve health outcomes when used to guide treatment decisions in patients with respiratory disorders other than asthma?
No controlled studies were identified that compared health outcomes in patients with COPD or other respiratory diseases whose treatment was managed with and without FeNO measurement.

Exhaled Breath Condensate
In general, it appears from the published literature that exhaled breath condensate (EBC) is at an earlier stage of development compared to exhaled NO. A 2012 review by Davis and colleagues noted that this is due, in part, to the fact that FeNO is a single biomarker and EBC is a matrix that contains so many potential biomarkers that research efforts have thus far been spread among numerous of these markers. (29) In addition, several review articles note that before routine clinical use in the diagnosis and management of respiratory disorders can be considered, the following issues must be resolved (29-33):

Standardization of collection and storage techniques
- Effect of dilution of respiratory droplets by water vapor
- Effect of contamination from oral and retropharyngeal mucosa
- Variability in EBC assays for certain substances, including assay kits for the same biomarker and kit lot numbers from the same manufacturer.
- Lack of gold standard for determining absolute concentrations of airway lining fluid non-volatile constituents to compare with EBC.
- Lack of normative values specific to each potential EBC biomarker.

Are components of EBC useful as markers of asthma severity?
Several studies have been published on components of exhaled breath condensate (EBC) and their relationship with asthma severity. A 2011 study by Liu and colleagues, the Severe Asthma

Research Program, was a multicenter study funded by the National Institutes of Health. This study had the largest sample size with 572 patients. (34) Study participants consisted of 250 patients with severe asthma, 291 patients with non-severe asthma, and 51 healthy controls. Samples of EBC were collected at baseline and were analyzed for pH levels. Overall, the median pH of asthma patients (2 groups combined), 7.94, did not differ significantly from the median pH of controls, 7.90, p=0.80. However, the median pH of patients with non-severe asthma, 7.90, was significantly lower than patients with severe asthma, 8.02 (p value not reported).

A 2012 cross-sectional study by Karakoc and colleagues in Turkey evaluated 42 children; 20 with persistent asthma (group 1); 10 with intermittent asthma (group 2), and 12 healthy controls (group 3). (35) EBC was collected from all participants and levels of matrix metalloprotease (MMP-9) and tissue inhibitors of metalloproteinases (TIMP-1) levels were analyzed. Mean MMP-9 of EBC levels was 57.7 ng/mL, 35.4 ng/mL, and 30.6 ng/mL in groups 1, 2 and 3, respectively. Levels were significantly higher in children with persistent asthma and intermittent asthma compared to controls. There were no significant differences among groups in levels of TIMP-1 of EBC.

In 2011, Piotrowski and colleagues in Poland prospectively studied adult patients with asthma. (36) The study included 27 patients with severe asthma who were receiving treatment (group 1), 16 newly diagnosed and never-treated asthma patients (group 2), and 11 health controls (group 3). At baseline and at weeks 4 and 8, EBC was collected and patients underwent spirometry and other tests of asthma severity. Patients were able to take all medications needed to control symptoms throughout the study. Levels of 8-isoprostane (8-IP) in breath condensate were analyzed. At baseline, the median level of 8-IP was 4.67 pg/mL, 6.93 pg/mL, and 3.80 pg/mL in groups 1, 2 and 3, respectively. There were no statistically significant differences among groups in 8-IP levels. In addition, 8-IP levels did not significantly correlate with asthma severity measures, including the number of symptom-free days, FEV1 reversibility, and scores on the asthma control test (ACT). In this study, 8-IP in EBC was not found to be a useful marker of asthma severity.

Conclusions:
There is limited evidence on the use of EBC for determining asthma severity. The available evidence is insufficient to form conclusions on the utility of EBC for this purpose.

Are components of EBC useful as markers of respiratory disorders other than asthma?
There is little published literature on EBC levels in patients with respiratory disorders other than asthma. A 2010 study by Antus and colleagues evaluated EBC in 58 hospitalized patients (20 with asthma and 38 with COPD) and 36 healthy controls (18 smokers and 18 non-smokers). (37) The EBC pH was significantly lower in patients with asthma exacerbations (all non-smokers) at hospital admission compared to non-smoking controls (6.2 vs. 6.4, respectively, p<0.001). The pH of EBC in asthma patients increased during the hospital stay and was similar to that of non-smoking controls at discharge. Contrary to investigators' expectations, EBC pH values in ex-smoking COPD patients (n=17) did not differ significantly from non-smoking controls, either at hospital admission or discharge. Similarly, pH values in EBC samples from smoking COPD patients (n=21) at admission and discharge did not differ significantly from smoking controls.

Are components of EBC useful in guiding treatment decisions for patients with asthma or other respiratory disorders?
No controlled studies were identified that evaluated the role of EBC tests in the management of asthma or other respiratory disorders. Uncontrolled studies include a 2009 case series investigating

whether components of EBC could predict response to steroid treatment in patients with asthma. (38) Eighteen steroid-naive asthma patients were included; EBC collection, spirometry, and methacholine challenge were performed before and 12 weeks after inhaled steroid therapy (equivalent dose of 400 µg fluticasone propionate/d). Among the molecules in EBC examined, higher IL-4 and RANTES levels and lower IP-10 levels at baseline were correlated with an improvement in FEV1. The study had a small sample size, was uncontrolled, and did not address whether EBC measurement could improve patient management or health outcomes.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received through 3 physician specialty societies (1 specialty society submitted 2 reviews) and 5 academic medical centers when this policy was under review in 2012. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. Input was mixed on whether measurement of exhaled NO is considered investigational in the diagnosis and management of asthma and other respiratory disorders. There was consensus that measurement of exhaled breath condensate is considered investigational in the diagnosis and management of asthma and other respiratory disorders. Input was mixed on additional questions posed to reviewers including whether there is a well-accepted cutoff for FeNO, whether FeNO levels would affect their decision regarding prescribing inhaled corticosteroids, whether there is published evidence that using FeNO measurements to guide treatment improves health outcomes and whether recommendations in ATS guidelines are supported by evidence.

Summary

Evaluation of exhaled nitric oxide and exhaled breath condensate are proposed as techniques to diagnose and monitor asthma and/or other respiratory conditions. While several prospective studies have addressed FeNO measurement for the diagnosis of asthma, there is still no standardized and validated cut-off to use in clinical care.

Multiple randomized controlled studies have evaluated the use of FeNO tests for the management of patients and have not consistently found improvement in health outcomes. Moreover, a 2012 meta-analysis that pooled results of studies evaluating FeNO in the management of asthma found a high degree of variability among studies and did not recommend routine use of FeNO in clinical practice. A 2011 RCT of pregnant women with asthma found better outcomes in the group managed using a FeNO algorithm than standard care. However, two subsequent RCTs, one in children with asthma and the other in adults with asthma, reported no improvement in outcomes associated with FENO-based treatment algorithms.

There is less evidence on the utility of FeNO for the diagnosis and management of other respiratory disorders. There are also few studies on exhaled breath condensate evaluation for the diagnosis and treatment of asthma and other conditions. Thus, the evidence is insufficient to determine the effect of exhaled nitric oxide and exhaled breath condensate tests on health outcomes, and these tests are therefore considered investigational.

Practice Guidelines and Position Statements

American Thoracic Society: In 2011, the ATS published a clinical practice guideline on interpretation of FeNO levels. (9) The guideline was critically appraised using criteria developed by the Institute of Medicine (IOM) which includes 8 standards. (39) The guideline was judged to not adequately meet the following standards: Standard 3: guideline development group composition; Standard 4: clinical practice guideline-systematic review intersection; Standard 5: Establishing evidence foundation for and rating strength of recommendations; and Standard 7: external review.

The ATS guideline included the following strong recommendations (if not otherwise stated, the recommendations apply to asthma patients):

- 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 recommend accounting for age as a factor affecting FENO in children younger than 12 years of age (strong recommendation, high quality of evidence).
- We recommend that low FENO less than 25 ppb (<20 ppb in children) be used to indicate that eosinophilic inflammation and responsiveness to corticosteroids are less likely (strong recommendation, moderate quality of evidence).
- We recommend that FENO greater than 50 ppb (>35 ppb in children) be used to indicate that eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids are likely (strong recommendation, moderate quality of evidence).
- We recommend that FENO values between 25 ppb and 50 ppb (20–35 ppb in children) should be interpreted cautiously and with reference to the clinical context. (strong recommendation, low quality of evidence).
- We recommend accounting for persistent and/or high allergen exposure as a factor associated with higher levels of FENO (strong 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).

American Thoracic Society/European Respiratory Society: A 2009 statement includes the following key points on exhaled nitric oxide:
"The clinical utility of FeNO-based management strategies has not been explored extensively. Currently available evidence suggests a role in identifying the phenotype in airways disease, particularly in the identification of corticosteroid responsiveness. Due to logistic and cost issues, FeNO is the only biomarker likely to have a role in primary care-based asthma studies, although it is possible that with technological improvements, other techniques including sputum induction could have a role in the medium term." (1)

National Heart Lung and Blood Institute (NHLBI): Their 2007 expert panel guidelines for the diagnosis and management of asthma state:
"Use of minimally invasive markers ("biomarkers") to monitor asthma control and guide treatment decisions for therapy is of increasing interest. Some markers, such as spirometry measures, are currently and widely used in clinical care; others, such as sputum eosinophils and FeNO, may also be useful, but they require further evaluation in both children and adults before they can be recommended as clinical tools for routine asthma management (Evidence D)."

"The Expert Panel recommends some minimally invasive markers for monitoring asthma control, such as spirometry and airway hyper-responsiveness, that are appropriately used, currently and widely, in asthma care (Evidence B). 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 (Evidence D)." (40)

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

83987	pH, exhaled breath condensate
94799	Unlisted pulmonary service or procedure
95012	Nitric oxide expired gas determination

- Effective in 2010, there is a CPT code to describe the collection of exhaled breath condensate with measurement of the pH: 83987.
  - A variety of substances has been analyzed in a collected sample of exhaled breath condensate, including but not limited to leukotrienes, cytokines, and other substances reflecting oxidative stress. The above CPT code would not apply to this expanded analysis of exhaled breath condensate. It is likely that specific CPT codes describing the underlying laboratory technique for analysis would be used.
- There is a CPT code specific to direct determination of exhaled nitric oxide (e.g., using the NIOX system): 95012.
- Effective in 2010, the CPT book instructs that the unlisted code 94799 should be used for services previously coded as 0064T: Spectroscopy, expired gas analysis (e.g., nitric oxide/carbon dioxide test).

REVISIONS

06-30-2009	Policy added to the bcbsks.com web site. No policy changes were made.
01-01-2010	In Coding Section: ▪ Added CPT Code: 83987 ▪ Removed CPT Codes: 0064T, 0140T
03-07-2011	Description section updated
	In Policy section: ▪ To be clearer, the policy wording was split from one policy statement reading: "Measurement of exhaled or nasal nitric oxide, or collection and analysis of exhaled breath condensate, is considered experimental / investigational in the diagnosis and management of asthma and other respiratory disorders." to two separate policy statements, reading: "A. Measurement of exhaled or nasal nitric oxide is considered investigational in the diagnosis and management of asthma and other respiratory disorders

	including but not limited to chronic obstructive pulmonary disease and chronic cough. B. Measurement of exhaled breath condensate is considered investigational in the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough." The policy intent was not changed.
	In Coding section: ▪ Added CPT code: 94799
	Rationale section updated
	References section updated
03-13-2012	Revised Title from "Exhaled Nitric Oxide and Exhaled Breath Condensate pH Measurement for Respiratory Disorders" to "Measurement of Exhaled Nitric Oxide and Exhaled Breath Condensate in the Diagnosis and Management of Asthma and Other Respiratory Disorders"
	Description section updated
	Rationale section updated
	References section updated
03-19-2013	Description section updated
	In Coding section: ▪ Coding notations updated
	Rationale section updated
	References section updated

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