Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

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Type of Submission – Check all that apply:

- [ ] New Policy
- [x] Revised Policy*
- [ ] Annual Review – No Revisions
- [ ] Statewide PDL

*All revisions to the policy must be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below:

**CPB 0691 Exhaled Breath Tests**

This CPB has been revised to state that the following are considered experimental and investigational: (i) hydrogen breath testing for prediction of bowel preparation adequacy prior to colonoscopy, (ii) exhaled nitric oxide as a biomarker for pulmonary hypertension and systemic sclerosis lung disease and; (iii) exhaled breath temperature as a biomarker for pulmonary hypertension; and (iv) measurement of exhaled volatile organic compounds for diagnosis and monitoring of sarcoidosis.

Name of Authorized Individual (Please type or print):

Dr. Bernard Lewin, M.D.

Signature of Authorized Individual:

[Signature]

Revised July 22, 2019
Exhaled Breath Tests

Number: 0691

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers hydrogen breath testing (HBT) medically necessary for evaluation of suspected lactose intolerance/deficiency after a 2-week trial of a lactose-free diet and symptoms of lactose intolerance persist.

Aetna considers HBT experimental and investigational for all other indications because of insufficient evidence of its effectiveness (not an all-inclusive list):

- Irritable bowel syndrome (IBS)
- Prediction of bowel preparation adequacy prior to colonoscopy
- Small intestinal bacterial overgrowth (SIBO)
- Small bowel transit time/gastroparesis.

Aetna considers measurement of exhaled nitric oxide medically necessary for evaluation of asthma and for monitoring response to long-term control therapy in members aged 5 years and older.

Aetna considers measurement of exhaled nitric oxide experimental and investigational for all other indications including the assessment of the following indications because of insufficient evidence of its effectiveness (not an all-inclusive list):

- Acute mountain sickness
- Airway inflammation due to bioaerosol exposures
- Biomarker for pulmonary hypertension and systemic sclerosis lung disease
- Chronic cough due to non-asthmatic eosinophilic bronchitis
- Chronic tonsillitis
- Lung cancer
- Pulmonary diseases (e.g., chronic obstructive pulmonary disease, pulmonary tuberculosis, sino-nasal disease)
- Sickle cell airway disease.

Aetna considers measurement of exhaled breath condensate (EBC) pH experimental and investigational for assessment of the following indications because of insufficient evidence of its effectiveness (not an all-inclusive list):

- Airway inflammation due to bioaerosol exposures
- Asthma
- Inflammatory bowel diseases
- Lung cancer
- Obstructive sleep apnea
- Pulmonary diseases (e.g., chronic obstructive pulmonary disease, pulmonary tuberculosis, sino-nasal disease).

Aetna considers the gastric emptying breath test (GEBT) experimental and investigational for gastroparesis and for all other indications because of insufficient evidence of its effectiveness.

Aetna considers exhaled breath temperature experimental and investigational for lung diseases and all other indications (e.g., as a biomarker for pulmonary hypertension) because its effectiveness has not been established.

Aetna considers measurement of exhaled volatile organic compounds for diagnosis and monitoring of sarcoidosis experimental and investigational because of insufficient evidence of its effectiveness.

Background
Exhaled breath tests are noninvasive techniques designed to be utilized as markers for airway inflammation. Though the tests were introduced primarily for the management of asthma, exhaled breath tests have been proposed for use to evaluate other respiratory disorders that
have an inflammatory component such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, pulmonary hypertension and are also suggested for gastrointestinal (GI) use. Marker identification is purported to be useful for physicians to verify a diagnosis, adherence to anti-inflammatory therapy or for predicting upcoming exacerbations in individuals. Exhaled breath markers for airway inflammation include the measurement of nitric oxide and/or breath condensate pH. Gastric emptying breath testing (GEBT) and hydrogen breath testing are examples of tests used to diagnose certain gastrointestinal conditions.

Exhaled Nitric Oxide

Nitric oxide (NO) is normally produced by the human respiratory tract mucosa (lining) and is supposedly a powerful mediator involved in airway inflammation. It has been suggested that elevated levels of NO in exhaled air, referred to as fractional exhaled NO (FeNO), could serve as markers of airway inflammation. Measurement changes in FeNO in expired breath purportedly aids in evaluating an asthmatic individual’s response to anti-inflammatory therapy and serve as an adjunct (addition) to established criteria and laboratory assessments of asthma.

Exhaled nitric oxide testing involves breathing through a mouthpiece that is connected to a computer by a tube. The individual begins by breathing in nitric oxide free air to total lung capacity. Air is then slowly exhaled into the mouthpiece. The computer screen immediately displays the nitric oxide concentration.

Examples of nitric oxide testing systems include, but may not be limited to: NIOX Breath Nitric Oxide Test System; NIOX MINO Nitric Oxide Test System.

A number of studies have investigated the relationship between exhaled nitric oxide (NO) and airway inflammation in asthma. These studies have found that levels of exhaled NO are elevated in people with asthma who are not taking inhaled glucocorticosteroids compared to people without asthma, yet these findings are not specific for asthma. Exhaled NO is thought to reflect eosinophilic airway inflammation in asthma.

Levels of exhaled NO have been suggested as non-invasive markers of airway inflammation in asthma, as an alternative to invasive methods such as examination of spontaneously produced or hypertonic-saline induced sputum for eosinophils and metachromatic cells. Measurement of exhaled NO may prove to be useful in diagnosing asthma, assessing adherence to treatment with inhaled corticosteroids, or in the identification of patients in whom respiratory symptoms are associated with eosinophilic airway inflammation. A number of methods have been developed to measure exhaled NO, including laser spectroscopy and chemiluminescence.
Current studies on exhaled NO in asthma have focused on the technical feasibility of measurement and correlations with pulmonary function and invasive methods of assessing airway inflammation. The evidence for assessment of exhaled NO for other pulmonary conditions is more limited. However, well-designed, long-term studies are needed to evaluate whether the addition of exhaled NO measurements to clinical and lung function assessment results in improved asthma control.

An assessment on a NO measurement system (NIOX) for monitoring response to asthma treatment prepared by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) (Hailey, 2004) concluded that no information was found on the extent to which the use of this device improves patients’ compliance with medication use or ensures appropriate prescribing. Comparative studies to obtain such measures of efficacy would be desirable. This is in agreement with the observation of Zeidler et al (2004) who stated that exhaled NO may be a useful parameter for monitoring asthmatic inflammation, adjusting therapy, and diagnosing asthma, although prospective longitudinal trials investigating the correlation between exhaled NO and clinical outcomes are necessary to determine its utility.

An assessment by the BlueCross BlueShield Association (BCBSA) Technology Evaluation Center (TEC) (2006) concluded that use of fractional exhaled NO (FENO) levels for monitoring patients with chronic asthma does not meet the TEC criteria. The TEC assessment found that available evidence does not permit the conclusion that use of FENO monitoring to guide treatment decisions in asthma leads to improved outcomes. The assessment stated that the 7 studies that evaluated the predictive ability of FENO, and its potential to provide prognostic information that could influence management decisions, had considerable methodologic limitations and variability in study methodology that precluded synthesis of their results and definitive conclusions. The assessment stated that the 2 randomized, controlled trials included in the review suggest possible benefits for FENO monitoring, but are not sufficient to conclude that outcomes are improved. The assessment explained that each study reported different benefits that have not been reproduced. The assessment noted that differences in the control management strategy raise questions about the optimal management strategy to which FENO monitoring should be compared.

In a randomized-controlled trial, Smith et al (2005) reported a reduction in use of inhaled corticosteroids in asthma patients (n = 46) using FENO measurements to adjust their doses compared to asthma patients (n = 48) using conventional guidelines to adjust their doses. Patients were followed for 12 months. The final mean daily doses of fluticasone were 370 µg for the FENO group versus 641 µg for the control group, a difference of 270 µg per day. The rates of exacerbation were 0.49 episodes per patient in the FENO group and 0.90 in the control group, representing a non-significant reduction of 45.6 % in the FENO group. The authors reported no
significant differences in other markers of asthma control, use of oral prednisone, pulmonary function, or levels of airway inflammation (sputum eosinophils). Earlier studies, however, have demonstrated that control can be maintained through a standardized approach involving a uniform dose reduction. Smith’s findings may reflect over treatment in the control group rather than more appropriately targeted treatment in the FENO group. It is also unclear what effects multiple medications may have on the relationship between asthma control and FENO measurements.

van Mastrigt et al (2007) stated that there is still much uncertainty about the potential clinical utility of measurement of fractional FENO in infants. There is a need for clinical studies showing the merits and limitations of different methodologies, to standardize measurements of fractional FENO in infants, and to obtain normal reference values for this age group. Turner (2007) stated that over a relatively short time FENO has become recognized as an useful objective tool for diagnosing and monitoring asthma. However, more clinical studies are needed in order for FENO to become fully established in the diagnosis and management of asthma.

Shaw and co-workers (2007) tested the hypothesis that titrating corticosteroid dose using the concentration of FENO in exhaled breath results in fewer asthma exacerbations and more efficient use of corticosteroids, when compared with traditional management. A total of 118 subjects with a primary care diagnosis of asthma were randomized to a single-blind trial of corticosteroid therapy based on either FENO measurements (n = 58) or British Thoracic Society guidelines (n = 60). Participants were assessed monthly for 4 months and then every 2 months for a further 8 months. The primary outcome was the number of severe asthma exacerbations. Analyzes were by intention-to-treat. The estimated mean exacerbation frequency was 0.33 per patient per year (0.69) in the FENO group and 0.42 (0.79) in the control group (mean difference, -21 %; 95 % confidence interval [CI]: -57 % to 43 %; p = 0.43). Overall, the FENO group used 11 % more inhaled corticosteroid (95 % CI: -17 % to 42 %; p = 0.40), although the final daily dose of inhaled corticosteroid was lower in the FENO group (557 versus 895 microg; mean difference, 338 microg; 95 % CI: -640 to -37; p = 0.028). The authors concluded 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 a 12-month period, when compared with current asthma guidelines.

Travers and associates (2007) attempted to develop reference ranges for FENO and ascertained which factors in health and disease influence FENO levels. Subjects aged between 25 and 75 years were drawn from a random sample of the predominantly white population of Wellington, New Zealand. Exhaled NO was measured using an online NO monitor in accordance with international guidelines. A detailed respiratory questionnaire and pulmonary function tests were performed. The geometric mean FENO was 17.9 parts per billion (ppb) with a 90 % CI for an
individual prediction (reference range) for normal subjects of 7.8 to 41.1 ppb. Sex, atopy, and smoking status significantly affected FENO levels, and several reference ranges were presented adjusting for these factors. Asthma and allergic rhinitis were associated with higher FENO. Measurement of FENO had poor discriminant ability to identify steroid-naive subjects with asthma.

Ramser and colleagues (2008) evaluated FENO as a surrogate for bronchial hyper-responsiveness (BHR) in children with possible reactive airway disease. Exhaled NO was measured using the single-breath method in 169 successive outpatients 11 +/- 5 years of age before lung function testing and subsequent bronchial provocation by exercise (n = 165) and methacholine (n = 134). Baseline forced expiratory volume in 1 second (FEV1) less than 80% of predicted and/or BHR were seen in 59%. Exhaled NO correlated weakly with PD(20) to methacholine (r = -0.24, p < 0.05), but not with the change in FEV1 due to exercise-induced bronchoconstriction (EIB) (r = 0.1, p > 0.05). The negative predictive value of FENO less than 10 ppb for EIB was 94%, but overall accuracy for predicting BHR was low. The authors concluded that measurement of FENO is not a substitute for bronchial provocation in children.

A study by Szefler et al (2008) found that measurement of FENO did not improve asthma outcomes. In a randomized clinical trial, 546 adolescents and young adults with persistent or uncontrolled asthma were assigned to receive computer-protocol-driven care, with or without measurement of FENO. During the 46-week study, patients returned for visits every 6 to 8 weeks, and their medicines were adjusted as required. Mean numbers of days with asthma symptoms during the 2 weeks before each visit was similar in the NO and control groups (1.93 versus 1.89). No differences between groups were noted in secondary outcomes, including measures of pulmonary function and asthma exacerbations.

Guidelines from the National Asthma Education Program (NIH, 2007) state that NO expired gas determination is among several biomarkers that may potentially be used for asthma management in the future. The guidelines note that fractional FENO concentration is one of many biomarkers that have been proposed. "Few studies, however, have validated or 'anchored' assessment of these markers by analyzing their relationship to the rate of adverse events or decline in pulmonary function over time. Further complicating the matter is that the relationship between normalization of a biomarker and normalization of risk of an adverse event may depend on the specific treatment given. What is found true for treatment with an [inhaled corticosteroid] ICS may not be true for treatment with a leukotriene receptor antagonist (LTRA) or an inhaled long-acting beta2-agonist (LABA), or vice versa." The guidelines concluded that, "[i]n the future, assessment of a combination of historical features and of biomarkers may allow accurate
estimation of the risk of future adverse events, but it must be kept in mind that laboratory tests only indirectly estimate control of risk. In the end, only symptoms, exacerbations, and quality of life over time are the measures of asthma control."

The American Thoracic Society (ATS) guidelines on evaluation of chronic cough in gastro-esophageal reflux disease (GERD) (Irwin, 2006) stated that FENO measurements are not routinely recommended, because they do not appear to be helpful in diagnosing cough due to GERD.

Kowk et al (2009) examined the feasibility of obtaining FENO concentrations in 133 children aged 2 to 18 years, who were treated in the emergency department for acute asthma exacerbation and to examine the association between FENO concentrations and other measures of acute asthma severity. The investigators measured FENO concentrations before and 1 hour after the administration of corticosteroids and at discharge from the emergency department. Outcome measures included pulmonary index score (PIS), hospital admission, and short-term outcomes (e.g., missed days of school). The investigators reported that 68 % of the subjects provided adequate breaths for FENO measurement. The investigators found no difference in the median initial FENO concentration among subjects, regardless of the severity of their acute asthma. Most subjects showed no change in their FENO concentrations from the start to the end of treatment. The investigators stated that FENO concentrations were not significantly associated with other short-term outcomes. The investigators concluded that measurement of FENO is difficult for a large proportion of children with acute asthma exacerbation, and that FENO concentration during an asthma exacerbation does not correlate with other measures of acute severity and has limited utility in the emergency department management of acute asthma in children.

de Jongste et al (2009) found no added value of daily FENO monitoring with symptom monitoring versus symptom monitoring only. Children with atopic asthma (n = 151) were randomly assigned to 2 groups: (i) FENO monitoring plus symptom monitoring, or (ii) monitoring of symptoms only. All patients scored asthma symptoms in an electronic diary over 30 weeks; 77 received a portable NO analyzer. Data were transmitted daily to the coordinating centers. Patients were phoned every 3 weeks and their steroid dose was adapted according to FENO and symptoms, or according to symptoms. Children were seen at 3, 12, 21, and 30 weeks for examination and lung function testing. The primary end point was the proportion of symptom-free days in the last 12 study weeks. The investigators reported that both groups showed an increase in symptom-free days, improvement of FEV1 and quality of life, and a reduction in steroid dose. None of the changes from baseline differed between groups.
A randomized clinical study of step-up therapy in children (n = 182) with uncontrolled asthma despite corticosteroids (Lemanske et al, 2010) found that patterns of differential response were not predicted by the fraction of FENO, either dichotomized at the median baseline value or examined as a continuous covariate. The authors stated that more expensive and labor-intensive measures of physiological factors (e.g., methacholine PC20) and biomarkers (e.g., the fraction of ENO) did not have predictive value.

Powell et al (2011) concluded that asthma exacerbations during pregnancy can be significantly reduced with a validated FENO-based treatment algorithm. The investigators reported on a double-blind, parallel-group, controlled trial in two antenatal clinics in Australia. The investigators randomly assigned 220 pregnant, non-smoking women with asthma to treatment adjustment at monthly visits by an algorithm using clinical symptoms (control group) or FENO concentrations (active intervention group). The primary outcome was total asthma exacerbations. The investigators reported that the exacerbation rate was lower in the FENO group than in the control group (0·288 versus 0·615 exacerbations per pregnancy; incidence rate ratio 0·496, 95% CI 0·325-0·755; p=0·001). In the FENO group, quality of life was improved (score on short form 12 mental summary was 56·9 [95% CI 50·2-59·3] in FENO group versus 54·2 [46·1-57·6] in control group; p=0·037) and neonatal hospitalizations were reduced (eight [8%] versus 18 [17%]; p=0·046). A limitation of this study is that the control group's algorithm differed from current guidelines and that significantly more women in the FENO group were receiving corticosteroids than in the control group.

Commenting on the study by Powell, et al. (2011), a Cochrane review (Bain, et al., 2014) of interventions for managing asthma in pregnancy concluded that, "while a FENO-based algorithm reduced exacerbations, the effects on perinatal outcomes were less certain, and thus widespread implementation is not yet appropriate."

Using a similar treatment algorithm, Pike et al (2012) concluded that FENO-guided inhaled corticosteroid titration did not reduce corticosteroid usage or exacerbation frequency in children with moderate to severe asthma. The investigators conducted a randomized controlled clinical trial to evaluate whether monitoring FENO can improve outpatient management of children aged 6 to 17 years with moderate to severe asthma. Ninety children were randomized to FENO-driven therapy or to a standard management group where therapy was driven by conventional markers of asthma control. Inhaled corticosteroids or long-acting bronchodilator therapies were altered according to FENO levels in combination with reported symptoms in the FENO group. Subjects were assessed twice monthly for 12 months. Inhaled corticosteroid dose and exacerbation frequency change were compared between groups in an intention to treat analysis. The
investigators reported that no difference was found between the two groups in either change in corticosteroid dose or exacerbation frequency. The investigators stated that results were similar in a planned secondary analysis of atopic asthmatics.

Calhoun et al (2012) reported the results of the use of FENO in adults from the Best Adjustment Strategy for Asthma in the Long Term (BASALT) trial, a randomized controlled clinical trial conducted by the Asthma Clinical Research Network at 10 academic medical centers in the United States. The investigators found that, among adults with mild to moderate persistent asthma controlled with low-dose inhaled corticosteroid therapy, the use of either FENO-based or symptom-based adjustment of inhaled corticosteroids was not superior to physician assessment-based adjustment of inhaled corticosteroids in time to treatment failure. The investigators reported on the results of a randomized, parallel, 3-group, placebo-controlled, multiply-blinded trial of 342 adults with mild to moderate asthma controlled by low-dose inhaled corticosteroid therapy who were assigned to physician assessment-based adjustment, FENO-based adjustment, and symptom-based adjustment. For physician assessment-based adjustment and FENO-based adjustment, the dose of inhaled corticosteroids was adjusted every 6 weeks; for symptom-based adjustment, inhaled corticosteroids were taken with each albuterol rescue use. The primary outcome was time to treatment failure. The investigators reported that there were no significant differences in time to treatment failure. The 9-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 FENO-based adjustment, and 15% (97.5% CI, 9%-25%; 16 events) for symptom-based adjustment. The hazard ratio for physician assessment-based adjustment versus FENO-based adjustment was 1.2 (97.5% CI, 0.6-2.3). The hazard ratio for physician assessment-based adjustment versus symptom-based adjustment was 1.6 (97.5% CI, 0.8-3.3).

An editorial accompanying the BASALT trial (O'Connor and Reibman, 2012) concluded that dose adjustment based on exhaled nitric oxide measurements has not been shown to improve outcomes in routine asthma management. The editorialist commented that the result of the BASALT trial is consistent with prior evidence that routine exhaled nitric oxide monitoring is not warranted for managing most patients with asthma. The editorialist noted that the recent ATS practice guideline recommends the use of exhaled nitric oxide measurement “in monitoring airway inflammation in patients with asthma (strong recommendation, low quality of evidence),” but that, in light of the BASALT findings, it is difficult to justify additional health care expenditures for routinely monitoring exhaled nitric oxide in adults with mild to moderate asthma. The editorialist noted that there may be a role for exhaled nitric oxide measurement, however, when the diagnosis of asthma is not clear or for specific patient subgroups, but that further research is needed to identify the clinical scenarios in which exhaled nitric oxide measurement may improve clinical outcomes.
Lester et al (2012) reported on the use of a comprehensive asthma management program by an urban community health center. The program included serial FeNO measurements among several program components. Other components of the program were: use of asthma management guidelines; use of a team approach to asthma management; use of a standardized tool for screening for asthma risk factors, symptoms, and level of asthma control; use of a workflow algorithm and chart form incorporated into an electronic health record to collect data and track clinical measures for an asthma registry; use of asthma health educators to assist patients in setting asthma self-management goals and educate them in asthma self-management; use of community resources (visiting nurses, a state-funded pest control program, and durable medical equipment vendors for products such as aerochambers and nebulizers); and regular followup, with frequency based upon asthma severity. The authors reported that 95.8 percent of patients enrolled in the program had an asthma severity assessment, 95.4 percent of persistent asthmatics were on anti-inflammatory medications, 68.2 percent of asthma patients have documented asthma self-management goals, and 5.2 percent of asthma patients have a self-reported visit to the emergency room in the six months preceding their most recent visit. Because the program includes multiple components, the contribution of FeNO measurements to these outcomes cannot be determined.

Guidelines from the British Thoracic Society and the Scottish Intercollegiate Guidelines Network (2008) stated that "more research needs to be done before recommendations can be made for the use of exhaled nitric oxide concentration". Updated guidelines from the Scottish Intercollegiate Guidelines Network (2009) stated that more experience with FENO and more information on the long-term response to corticosteroid in patients who do not have a raised FENO is needed before this approach can be recommended to identify patients who are going to respond to corticosteroid therapy. Updated guidelines from the British Thoracic Society and the Scottish Intercollegiate Guidelines Network (2012) stated that studies in children have shown that routine serial measurements of exhaled nitric oxide do not provide additional benefit when added to a symptom based management strategy. The guidelines (2012) stated that a better understanding of the natural variability of biomarkers independent of asthma is required and studies are needed to establish whether subgroups of patients can be identified in which biomarker guided management is effective.

Puckett and George (2008) stated that the airway NO flux and alveolar NO concentration can be elevated in adults and children with asthma and have been correlated with markers of airway inflammation and airflow obstruction in cross-sectional studies. They noted that longitudinal studies that specifically address the clinical potential of partitioning FENO for diagnosis, managing therapy, and predicting exacerbation are needed.
In a review on FENO in the diagnosis and management of asthma, Rodway and colleagues (2009) stated that further evidence of the clinical utility of FENO in asthma management is needed. The authors stated that, "[r]egardless of the rapid, convenient, and noninvasive nature of this test, additional well-designed, long-term longitudinal studies are necessary to fully evaluate the clinical utility of eNO in asthma management".

In a review on the utility of FENO in the diagnosis and management of asthma, Majid and Kao (2010) noted that "FeNO shows promise as a tool in the diagnosis and treatment of asthma. However, further studies are needed to address outstanding questions about its exact role in guiding asthma management".

An International Consensus on Pediatric Asthma (ICON) (Papadopoulos, et al., 2012) stated that "monitoring FENO is not recommended by the referenced pediatric asthma guidelines; however, it has been recently favorably reevaluated. The consensus concluded that the role of FENO in monitoring should be re-evaluated in guidelines.

Donohue and Jain (2013) evaluated the evidence for FeNO as a predictor of corticosteroid responsive airway inflammation. The authors conducted a meta-analysis of three adult studies comparing asthma exacerbation rates with FeNO-based versus clinically based asthma management algorithms, including one study that was not included in the Cochrane metaanalysis. The authors reported that the results indicate that the rate of asthma exacerbations was significantly reduced in favor of FeNO-based asthma management (mean treatment difference - 0.27; 95% CI [0.42,0.12] as was the relative rate of asthma exacerbations (relative rate - 0.57; 95% CI [0.41, 0.80]).

An ATS ad hoc committee was organized by the committee chairman to devise "interpretive strategies" for the different potential uses and applications of FENO (Dweik et al, 2011). The committee identified a number of potential uses of FENO, which were graded by the committee members on the strength of the recommendation and strength of the evidence. Several potential uses of FENO were identified, each of which were related to the use of FENO to identify steroid responsiveness. One of the recommendations, identification of eosinophilic airway inflammation, was judged by the Committee to be supported by "strong consensus" and "moderate quality evidence." The report stated that the importance of identifying eosinophilic airway inflammation rests on its correlation with steroid responsiveness: “the finding that FENO correlates with eosinophilic inflammation suggests its use as indirect indicator not only of eosinophilic inflammation, but more importantly of the potential for steroid responsiveness.” However, the evidence cited to support the recommendation found widely varying correlations between FENO and other recognized measures of eosinophilic airway inflammation (biopsy, sputum, and bronchiolar lavage). Another potential use recommended by the Committee, the use of FENO to
support the diagnosis of asthma in situations in which objective evidence is needed, was a “weak recommendation” based upon “moderate quality evidence.” The report explained that “the importance of FENO lies in its potential to identify steroid responsiveness, rather than the exact clinical diagnosis.” Other potential uses of FENO identified by the Committee were judged to have “low quality evidence”, including use of FENO to determine the likelihood of steroid responsiveness in individuals with chronic respiratory symptoms possibly due to airway inflammation, and use of FENO in monitoring airway inflammation in patients with asthma. Also, the summary of this ATS position paper (Dweik et al, 2011) stated that “the use of exhaled nitric oxide levels (FENO) in COPD and pulmonary hypertension and the use of nasal NO in diagnosis and monitoring of other respiratory disorders (e.g., allergic rhinitis, sinusitis, nasal polyposis, CF) are potentially of interest, but more research is needed before we know how clinically useful these tests can be for these disorders”.

A systematic evidence review of the literature on the usefulness of exhaled nitric oxide in childhood asthma conducted by the Andalusian Agency for Health Technology Assessment (AETSA) (García Estepa, et al., 2011) identified four clinical trials, one systematic evidence review and two health technology assessment reports that met inclusion criteria. The review found that the selected trials, with the exception of one, had some methodological weaknesses, as did the health technology assessment reports. However, the systematic evidence review, despite several limitations, was of high methodological quality. The AETSA review found that the selected studies do not provide significant correlations between FENO levels and clinically relevant outcomes such as optimal therapy, reduction of inhaled corticosteroid doses or more appropriate drug combinations, reduced exacerbations, or decrease in symptoms. Furthermore, in the variety of secondary outcomes in each study, significant differences were detected only in some of them, from which it might be concluded that the usefulness of FENO levels for the control of childhood asthma has not been demonstrated. The authors of the systematic evidence review concluded that the clinical validity of using FENO levels to control childhood asthma has not been conclusively established. The report concluded that, according to available evidence, the use of the determination of FENO levels does not improve important outcomes in asthma such as: reduction of symptoms and prevention of crisis or exacerbations, improved lung function and reduction or better management of inhaled corticosteroid treatment, compared to the usual practice, based on symptoms with or without spirometry. The authors stated that the studies analyzed did not demonstrate the clinical usefulness of determining FENO levels in the control of childhood asthma.

Jartti et al (2012) noted that FENO has gained interest as a non-invasive tool to measure airway inflammation in asthma since it reflects allergic inflammation. The authors stated that recent controlled clinical studies have, however, questioned its role in the management of asthma in children. To assess the clinical value of FENO in pediatric asthma management, the authors
performed a meta-analysis on the controlled studies of childhood asthma management guided by repeated FENO measurements, and relevant publications on the confounders of FENO were reviewed. The authors concluded that the data suggested that utilizing FENO to tailor the dose of inhaled corticosteroids in children can not be recommended for routine clinical practice since there is a danger of excessive inhaled corticosteroid doses in children without meaningful changes in clinical outcomes. Many disease and non-disease related factors (most importantly atopy, height/age and infection) affect FENO levels that can easily confound the interpretation.

Petsky et al (2012) evaluated 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) for asthma-related outcomes in children and adults. Cochrane Airways Group Specialised Register of Trials, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and reference lists of articles were searched. The last searches were in February 2009. All 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 selected. Results of searches were reviewed against pre-determined criteria for inclusion. Relevant studies were selected, assessed and data extracted independently by at least 2 people. The trial authors were contacted for further information. Data were analysed as "intervention received" and sensitivity analyses performed. Six (2 adults and 4 children/adolescent) studies utilising FENO and 3 adult studies utilizing sputum eosinophils were included. These studies had a degree of clinical heterogeneity including definition of asthma exacerbations, duration of study and variations in cut-off levels for percentage of sputum eosinophils and FENO to alter management in each study. Adults who had treatment adjusted according to sputum eosinophils had a reduced number of exacerbations compared with the control group (52 versus 77 patients with greater than or equal to 1 exacerbation in the study period; p = 0.0006). There was no significant difference in exacerbations between groups for FENO compared with controls. The daily dose of inhaled corticosteroids at the end of the study was decreased in adults whose treatment was based on FENO in comparison with the control group (mean difference -450.03 μg, 95 % CI: -676.73 to -223.34; p < 0.0001). However, children who had treatment adjusted according to FENO had an increase in their mean daily dose of inhaled corticosteroids (mean difference 140.18 μg, 95 % CI: 28.94 to 251.42; p = 0.014). It was concluded that tailoring of asthma treatment based on sputum eosinophils is effective in decreasing asthma exacerbations. However, tailoring of asthma treatment based on FENO levels has not been shown to be effective in improving asthma outcomes in children and adults. The authors concluded that, 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.
Malby Schoos et al (2012) stated that elevated FENO and bronchial hyper-responsiveness are used as surrogate markers of asthma. These traits may be continuous in the population. The objective of this study was to investigate whether FENO and bronchial responsiveness are associated in both children with and children without a history of asthma symptoms. A total of 196 children (6-year old) with no asthma symptoms, intermittent asthma symptoms, and persistent asthma were randomly included from the Copenhagen Prospective Study on Asthma in Childhood prospective clinical birth cohort of mothers with asthma. Bronchial responsiveness was assessed as the relative change in specific airway resistance after cold dry air hyperventilation. FENO measurements were performed prior to the hyperventilation test. The association between FENO and bronchial responsiveness was assessed by generalized linear models. Bronchial responsiveness and FENO exhibited a significant and linear association in the population. A doubling of FENO corresponded to an 8.4 % (95 % CI: 3.7 % to 13.1 %; p = 0.0006) increase in airway resistance after challenge testing and remained significant after adjustment for sex, allergic rhinitis, current asthma, inhaled corticosteroid treatment, and upper respiratory tract infections prior to testing. Stratified analyses showed similar associations in children with and without asthma. The authors concluded that FENO and bronchial responsiveness are associated and continuous traits in young children regardless of asthma symptoms, suggesting a continuous subclinical to clinical process underlying asthma. The authors stated that these findings also suggested caution against the use of these surrogate markers for a dichotomized approach to asthma diagnosis.

Gelb and colleagues (2012) noted that the up-regulation of NO by inflammatory cytokines and mediators in central and peripheral airway sites can be easily monitored in exhaled air FENO. It is now possible to estimate the predominant airway site of increased FENO, i.e., large versus peripheral airway/alveoli, and its potential pathologic and physiologic role in obstructive lung disease. In asthma, 6 double-blind, randomized, controlled algorithm trials have reported only equivocal benefits of add-on measurements of FENO to usual clinical guideline management including spirometry. Significant design issues, as emphasized by Gibson, may exist. However, meta-analysis of these 6 studies (Petsky et al, 2012) concluded that routine serial measurements of FENO for clinical asthma management does not appear warranted. In COPD including chronic bronchitis and emphysema, despite significant expiratory airflow limitation, when clinically stable as well as during exacerbation, FENO, j'(awNO) and C(ANO) may all be normal or increased. Furthermore, the role of add-on monitoring of exhaled NO to GOLD management guidelines is less clear because of the absence of conclusive double-blind, randomized, control trial studies concerning potential clinical benefits in the management of COPD.

Guidelines from the Canadian Thoracic Society (Lougheed et al, 2012) concluded: “there is still insufficient evidence to recommend the use of FeNO to tailor the dose of ICS compared with titrating ICS dose based on clinical symptoms alone. As such, the routine use of FeNO
measurements as a guide to tailor the dose of ICS in asthma cannot be endorsed for clinical practice at this time."

Guidance from the National Institute for Health and Clinical Excellence (2013) states that fractional exhaled nitric oxide (FeNO) testing is recommended as an option to help with diagnosing asthma and as an option to support asthma management in people who are symptomatic despite using inhaled corticosteroids.

Harnan et al. (2015) conducted a systematic review and economic evaluation for the National Institute for Health and Care Excellence (NICE) to assess the diagnostic accuracy, clinical effectiveness, and cost-effectiveness of three hand-held FeNO analyzers. The review, which included 27 studies, concluded that FeNO-guided management has the potential to be cost-effective. However, the evidence for using FeNO for diagnosis and management was deemed inconclusive.

A British Thoracic Society guideline on the management of asthma (2014) stated: "At present, there is insufficient evidence to support a role for markers of eosinophilic inflammation in the diagnosis of asthma in children. They may have a role in assessing severity of disease or response to treatment."

Guidelines on work-related asthma from the European Respiratory Society (Bauer et al, 2012) state that "in the clinical setting, a finding of a normal exhaled nitric oxide fraction cannot be used to exclude occupational asthma." The guideline explained that exhaled nitric oxide is not sufficiently sensitive to be used to exclude occupational asthma suggested by history. Guidelines from the British Occupational Health Research Foundation (Nicholson, et al., 2010) concluded that the measurement of exhaled nitric oxide "has not been fully validated as an effective diagnostic test for occupational asthma." The guidelines explain that exhaled nitric oxide is increased in other inflammatory lung disorders, and levels are lower in persons who smoke and in those using inhaled corticosteroids.

See and Christiani (2013) stated that elevated FENO reflects airway inflammation, but few studies have established its normal values. This study aimed to establish the normal values and thresholds for the clinical interpretation of FENO in the U.S. general population. A total of 13,275 subjects aged 6 to 80 years sampled for the National Health and Nutrition Examination Survey (NHANES) 2007-2010 underwent interviews, physical examination, and FENO analysis at 50 ml/s using an online chemiluminescence device according to ATS/European Respiratory Society (ERS) guidelines. After excluding subjects with self-reported asthma and subjects with wheeze in the prior 12 months, prediction equations for the natural logarithm (ln) of FENO were
constructed using age, sex, ethnicity, height, body mass index (BMI), active/passive smoke exposure, and hay fever episodes as co-variates. The 5th to 95th percentile values of FENO were 3.5 to 36.5 ppb for children less than 12 years of age and 3.5 to 39 ppb for subjects 12 to 80 years of age. Using multiple linear regression, prediction equations explained only 10.3 % to 15.7 % of the variation in the general population. In the general population, 39 % to 45 % had ln(FENO) levels greater than 2 standard deviations of the predicted means. When applied to the general population inclusive of subjects who reported asthma but who did not have attacks within the past year, nearly identical results were obtained. The authors concluded that assuming 95 % of the healthy U.S. general population had no clinically significant airway inflammation as assessed by FENO, values exceeding the 95th percentiles indicated abnormality and a high-risk of airway inflammation. A large variation of normal FENO values existed in the general population, which was poorly predicted by multiple linear regression models.

Columbo et al (2013) studied the role of serial measurements of FENO in elderly subjects with asthma. A total of 30 stable asthmatics 65 years old and older were followed for 1 year with evaluations at baseline and every 3 months. These researchers looked for associations between FENO and subjects’ demographics, co-morbidities, asthma treatment, spirometric values and asthma control test (ACT) scores. Fractional exhaled nitric oxide was not elevated in these subjects throughout the study period (mean less than 30 ppb); FENO significantly increased and FEV1 % decreased between first and last study visit, while ACT scores and steroid dose remained unchanged. No significant correlation was found between FENO and FEV1/forced vital capacity (FVC), other spirometric values, inhaled steroid dose or ACT scores at any time point. No associations of FENO were found with age, sex, BMI, atopic status, disease duration, presence of rhinitis or GERD, or other medications used. Moderate asthma exacerbations did not consistently cause an increase of FENO. The authors concluded that in stable elderly asthmatic patients, FENO was not elevated and did not correlate with subjects’ demographics, co-morbidities, treatment, symptoms or spirometric values. They stated that routine measurements of FENO may not be clinically valuable in elderly asthmatics.

Hanania et al (2013) assessed the potential of FENO, peripheral blood eosinophil count, and serum periostin as biomarkers of Th2 inflammation and predictors of treatment effects of omalizumab. The EXTRA omalizumab study enrolled patients (aged 12 to 75 years) with uncontrolled severe persistent allergic asthma. Analyses were performed evaluating treatment effects in relation to FENO, blood eosinophils, and serum periostin at baseline. Patients were divided into low- and high-biomarker subgroups. Treatment effects were evaluated as number of protocol-defined asthma exacerbations during the 48-week treatment period (primary endpoint). A total of 850 patients were enrolled. Data were available from 394 (46.4 %), 797 (93.8 %), and 534 (62.8 %) patients for FENO, blood eosinophils, and serum periostin, respectively. After 48 weeks of omalizumab, reductions in protocol-defined exacerbations were greater in high versus
low subgroups for all 3 biomarkers: FENO, 53 % (95 % CI: 37 to 70; p = 0.001) versus 16 % (95 % CI: -32 to 46; p = 0.45); eosinophils, 32 % (95 % CI: 11 to 48; p = 0.005) versus 9 % (95 % CI: -24 to 34; p = 0.54); and periostin, 30 % (95 % CI: -2 to 51; p = 0.07) versus 3 % (95 % CI: -43 to 32; p = 0.94). The authors concluded that the difference in exacerbation frequency between omalizumab and placebo was greatest in the 3 high-biomarker subgroups, probably associated with the greater risk for exacerbations in high subgroups. Moreover, they stated that additional studies are needed to explore the value of these biomarkers in clinical practice.

In order to evaluate the clinical usefulness of FENO assessment for monitoring asthma during pregnancy, Nittner-Marszalska et al (2013) monitored 72 pregnant asthmatics who underwent monthly investigations including: the level of asthma control according to Global Initiative for Asthma (GINA), the occurrence of exacerbations, Asthma Control Test (ACT), as well as FENO and spirometry measurements. In 50 women, during all visits, asthma was well-controlled. In the remaining 22 women, asthma was periodically uncontrolled. FENO measured at the beginning of the study did not show significant correlation with retrospectively evaluated asthma severity (r=0.07; p=0.97). An analysis of data collected during all 254 visits showed that FENO correlated significantly but weakly with ACT scores (r=0.25; p=0.0004) and FEV1 (r=0.21; p=0.0014).

FENO at consecutive visits in women with well-controlled asthma (N=50) showed large variability expressed by median coefficient of variation (CV)=32.0% (Min 2.4%, Max 121.9%). This concerned both: atopic and nonatopic groups (35.5%; and 26.7%, respectively). Large FENO variability (35.5%) was also found in a subgroup of women (N=11) with ACT=25 constantly throughout the study. FENO measured at visits when women temporarily lost control of asthma (N=22; 38 visits), showed an increasing tendency (64.2ppb; 9.5ppb-188.3ppb), but did not differ significantly (p=0.13) from measurements taken at visits during which asthma was well-controlled (27.6ppb; 6.2ppb-103.4ppb). The authors observed that the comparison of FENO in consecutive months of pregnancy in women who had well-controlled asthma did not show significant differences in FENO values during the time of observation. The authors concluded that assessment of asthma during pregnancy by means of monitoring FENO is of limited practical value due to this parameter's considerable intrasubject variability, regardless of the degree of asthma control.

Piersman et al (2013) reported that FeNO measurements in childhood asthma management did not improve the proportion of symptom-free days, but did result in fewer asthma exacerbations associated with an increased leukotriene receptor antagonist use and an augmentation of the inhaled corticosteroid doses. The authors investigated the potential yield of incorporating FeNO measurements in childhood allergic asthma management. Ninety-nine children with persistent allergic asthma were included in this multicentre, single-blind, randomized controlled trial. Treatment was based on the Global Initiative for Asthma (GINA) guidelines. In the FeNO group, asthma management was also guided by FeNO measurements. Health outcomes were
evaluated over a 52-week timeframe. Results: Fewer asthma exacerbations were registered in the FeNO group. 24% of the children in the FeNO group experienced one or more exacerbations per year, compared with 48% in the clinical group (P = 0.017). The proportion of symptom-free days did not differ between groups. In the FeNO group, more months of leukotriene receptor antagonist use (median (interquartile range)) were observed: 12 (9–12) months, compared with 9 (3–12) months in the clinical group (P = 0.019). The evolution of inhaled corticosteroid doses between visits 1 and 5 (median change (interquartile range)) showed a significant increase of -100 micrograms (0, -400) in the FeNO group and a change of 0 mg (+200, -80) in the clinical group (p = 0.016).

Commenting on this study, Lee (2015) stated that the randomized controlled parallel study published by Peirsman et al combined GINA guidelines and FeNO level in guiding drug treatment in children with mild to severe asthma. Their target was to control the FeNO level below 20 ppb. The FeNO group resulted in increasing the dosage of inhaled corticosteroid and the usage of leukotriene receptor antagonist. However, the study was not truly randomized and drug adherence was not reported. The FeNO-guided algorithm failed to improve the primary outcome, the symptom-free days, but did result in decreasing the number of acute exacerbations and unscheduled contacts. Unfortunately the authors did not demonstrate a persistent and significant difference in FeNO levels between both groups. As the final FeNO levels were not reported, it remains unclear whether their target was met.

Syk et al (2013) reported on the results of a study where 187 patients with asthma and who were nonsmokers (age range of 18 to 64 years) with perennial allergy and who were on regular inhaled corticosteroid treatment were recruited at 17 primary health care centers, randomly assigned to 2 groups and followed up for 1 year. For the controls (n = 88), FENO measurement was blinded to both operator and patient, and anti-inflammatory treatment was adjusted according to usual care. In the active group (n = 93), treatment was adjusted according to FENO. Patients in both groups were not allowed to use long-acting beta agonists. Questionnaires on asthma-related quality of life (Mini Asthma Quality of Life Questionnaire) and asthma control (Asthma Control Questionnaire) were completed, and asthma events were noted. The Asthma Control Questionnaire score change over 1 year improved statistically significantly more in the FENO-guided group (e0.17 [interquartile range {IQR}, L0.67 to 0.17] versus 0 [L0.33 to 0.50]; p < 0.045), although of questionable clinical significance. The Mini Asthma Quality of Life Questionnaire score did not improve significantly more in the FENO-guided group (0.23 [IQR, 0.07 to 0.73] versus 0.07 [IQR, L0.20 to 0.80]; p < 0.197). The change in Asthma Control Questionnaire was clinically important in subpopulations with poor control at baseline (p < 0.03). Furthermore, the exacerbation rate (exacerbations/patient/y) was reduced by almost 50 % in the FENO-guided group (0.22 [CI: 0.14 to 0.34] versus 0.41 [CI: 0.29 to 0.58]; p < 0.024). Mean overall inhaled corticosteroid use was similar in both groups (p < 0.95).
Limitations of the study include that the control group was provided "usual care" and not assigned to best available guideline supported care, whereas patients assigned to the active treatment group was managed by protocol. Treatments deviated from current guideline supported care in that long-acting beta-agonists were not allowed to be used. Other limitations of the study included the lack of participant personnel blinding, incomplete outcome data and selective reporting.

McCormack et al (2013) noted that little is known about use of FENO to predict asthma exacerbations among high-risk, urban, minority populations receiving usual care. A total of 138 children with persistent asthma were enrolled in a prospective observational cohort study and skin tested at baseline (wheal greater than or equal to 3 mm = +SPT). Fractional exhaled nitric oxide levels, lung function, and asthma-related health care use were assessed at baseline and every 3 months thereafter for 1 year. Relationships between FENO and health care utilization in the subsequent 3 months were examined. Final models accounted for repeated outcome measures and were adjusted for age, gender and lung function. The mean age was 11 years (range of 5 to 17), and most were male (57 %), African American (91 %), and atopic (90 %). At baseline, FENO was (median IQR: 31.5 ppb [16 to 61]) and FEV1/FVC was (mean +/- SD: 80.7 +/- 9.6 %). There were 237 acute asthma-related health care visits, 105 unscheduled doctor (UD) visits, 125 ED visits, and 7 hospitalizations during the follow-up period. Fractional exhaled nitric oxide was not a significant predictor of acute visits, ED visits, UD visits, or hospitalization in either unadjusted or adjusted analyses. Use of recommended cut-off points did not improve the predictive value of FENO (positive-predictive value [PPV]: 0.6 to 32.8 %), nor did application of the guideline-based algorithm to assess change over time. The authors concluded that FENO may not be a clinically useful predictor of health care use for asthma exacerbations in urban minority children with asthma.

To evaluate the association between FeNO levels and the asthma control status in children, Visitsunthorn, et al. (2014) conducted a cross-sectional clinical trial in children with atopic asthma aged ≥ 7 years. The levels of asthma control were assessed by using the criteria from the GINA Guideline. FeNO levels and spirometry were measured. Asthma medications were recorded. The association between FeNO levels and asthma control status and the usage of asthma medications were analyzed. The investigators recruited 114 asthmatic children aged 12.1 ± 3.5 years into the study. Most of the patients had mild persistent asthma (79.8%). The administration of inhaled corticosteroid (ICS) was reported in 82.4% of cases. According to the GINA Guideline, 34.2% of cases were controlled, 44.7% were partly controlled and 21.1% were uncontrolled. The investigators found that there was no significant difference in the median FeNO levels in the controlled, partly controlled and uncontrolled groups [19.2 (95% CI 5.1-108.9), 24.9 (2.2-85.7), and 39.2 (2.4-192.3) ppb, respectively (p = 0.24)]. However, in 20 cases who did not receive ICS treatment, the median FeNO levels showed a significant difference among controlled, partly
controlled and uncontrolled groups [31.8 (95% CI 11.1-108.9), 34.1 (5.3-81.8), 92.0 (46.3-192.3) ppb, respectively; p <0.05]. The investigators concluded that FeNO levels were increased in ICS-treated asthmatic patients with less asthma control, albeit with no statistically significance. However, FeNO levels correlated with poor asthma control status in ICS untreated cases.

A trial by Petsky et al (2015) found that taking atopy into account when using FeNO to tailor asthma medications is likely beneficial in reducing the number of children with severe exacerbations at the expense of increased inhaled corticosteroid use. However, the investigators concluded that this strategy is unlikely beneficial for improving asthma control. The investigators stated that controversy remains of the benefits of use of FeNO for routine asthma management, and the appropriate FeNO cut-off remains elusive. The investigators noted that there are four published randomized controlled trials that have evaluated the benefit of an FeNO-based strategy in adjusting medications for asthma in children, and none of these had shown any significant benefit of using FeNO compared to controls with respect to exacerbations, but none of the studies used exacerbation as their primary end-point. The authors noted that adult-based studies used exacerbations as their primary endpoint, but none showed any benefit in reducing asthma exacerbations. The investigators conducted the first clinical trial to evaluated the use of FeNO cut-offs adjusted for atopy to improve asthma outcomes. In a randomized controlled clinical trial conducted at two centers, the investigators assessed whether a treatment strategy based on FeNO levels, adjusted for atopy, reduces asthma exacerbations compared with the symptoms-based management (controls). Children with asthma from hospital clinics of two hospitals were randomly allocated to receive an a-priori determined treatment hierarchy based on symptoms or FeNO levels. There was a 2-week run-in period and they were then reviewed 10 times over 12-months. The primary outcome was the number of children with exacerbations over 12-months. Sixty-three children were randomized (FeNO = 31, controls = 32); 55 (86%) completed the study. The investigators reported that, although they did achieve their planned sample size, significantly fewer children in the FeNO group (6 of 27) had an asthma exacerbation compared to controls (15 of 28), p = 0.021; number to treat to prevent one child from having any exacerbation in 12 months was 4 (95% CI 3-24). There was a trend toward fewer exacerbations in the FeNO group (0.39 per person-year) compared to controls (0.78 per person-year that did not reach statistical significance. When the groups were subanalyzed into those with 2 or more exacerbations per year, they found no significant difference between the groups. At the end of the 12-month study, the total cumulative dose of inhaled corticosteroid per child-year was significantly higher in the FeNO group compared to the control group. The investigators found no difference between groups for any secondary outcomes (quality of life, symptoms, FEV1). The final daily inhaled corticosteroids (ICS) dose was significantly (p = 0.037) higher in the FeNO group (median 400 µg, IQR 250-600) compared to the controls (200, IQR 100-400). The authors concluded that a larger study is required to confirm or refute their findings.
Korevaar et al (2015) conducted a systematic review and searched Medline, Embase, and PubMed for studies assessing the diagnostic accuracy of markers against a reference standard of induced sputum, bronchoalveolar lavage, or endobronchial biopsy in patients with asthma or suspected asthma (for inception to Aug 1, 2014). Unpublished results were obtained by contacting authors of studies that did not report on diagnostic accuracy, but had data from which estimates could be calculated. The investigators assessed risk of bias with QUADAS-2. They used meta-analysis to produce summary estimates of accuracy. The investigators included 32 studies: 24 in adults and 8 in children. Of these, 26 (81 %) showed risk of bias in at least 1 domain. In adults, 3 markers had extensively been investigated: FENO (17 studies; 3,216 patients; summary area under the receiver operator curve [AUC] 0.75 [95 % CI: 0.72 to 0.78]); blood eosinophils (14 studies; 2,405 patients; 0.78 [0.74 to 0.82]); total IgE (7 studies; 942 patients; 0.65 [0.61 to 0.69]). In children, only FENO (6 studies; 349 patients; summary AUC 0.81 [0.72 to 0.89]) and blood eosinophils (3 studies; 192 patients; 0.78 [0.71 to 0.85]) had been investigated in more than 1 study. Induced sputum was most frequently used as the reference standard. Summary estimates of sensitivity and specificity in detecting sputum eosinophils of 3 % or more in adults were: 0.66 (0.57 to 0.75) and 0.76 (0.65 to 0.85) for FENO; 0.71 (0.65 to 0.76) and 0.77 (0.70 to 0.83) for blood eosinophils; and 0.64 (0.42 to 0.81) and 0.71 (0.42 to 0.89) for IgE. The investigators concluded that FENO, blood eosinophils, and IgE had moderate diagnostic accuracy. Their use as a single surrogate marker for airway eosinophilia in patients with asthma will lead to a substantial number of false positives or false negatives.

Van Beek et al (2011) evaluated the potential usefulness of measuring FENO as a screening tool for pulmonary tuberculosis (TB). These researchers compared 90 consecutive smear-positive, culture-confirmed TB patients presenting at a referral hospital with office workers (no X-ray confirming TB) at a hospital (n = 52) and at a construction firm (n = 84). Exhaled NO levels were analysed using a validated hand-held analyser. Exhaled NO levels among TB patients (median 15 parts per billion [ppb], inter-quartile range [IQR] 10 to 20) were equal to those among construction firm workers (15 ppb, IQR 12-19, p = 0.517) but higher than those among hospital workers (8.5 ppb, IQR 5 to 12.5, p < 0.001). Taking the hospital workers as the comparison group, best performance as a diagnostic tool was at a cut-off of 10 ppb, with sensitivity 78 % (95 % CI: 68 to 86) and specificity 62 % (95 % CI: 47 to 75). Test characteristics could be optimized to 84 % versus 67 % by excluding individuals who had recently smoked or consumed alcohol. The authors concluded that while FENO measurement has limited value in the direct diagnosis of pulmonary TB, it may be worth developing and evaluating as a cost-effective replacement of chest X-ray in screening algorithms of pulmonary TB where X-ray is not available.

Phillips et al (2011) reviewed the data available on the sino-nasal application of nasal NO measurement, particularly its use as a diagnostic, prognostic, or treatment effect indicator.

EMBASE 1980 to February 10, 2010; Medline 1950 to February 10, 2010; Cochrane
Collaboration database; NHS Evidence Health Information Resources database were searched using a search strategy designed to include manuscripts relevant both to NO measurement and sinus or nasal problems. A title search was performed on these manuscripts to select those relevant to clinical or basic science aspects of NO measurement. A subsequent abstract search selected those manuscripts concerning the application of NO measurement to sino-nasal problems. The manuscripts selected were subject to a full-text review to extract data sets of nasal NO readings for different patient groups. Initially, 1,088 manuscripts were selected. A title search found 335 manuscripts of basic scientific or clinical interest. An abstract search found 35 manuscripts directly relating to NO measurement in sino-nasal disease. Full-text analysis produced 20 studies with extractable data on nasal NO levels in clearly defined patient groups. Studies did not show sufficient homogeneity to enable substantial meta-analysis of aggregated data. The authors stated that the literature concerning nasal NO is marked by many theories concerning its role in the nose. However, clinical studies show a wide range of measurement methods, the presence of various confounding factors, and heterogeneity of study populations. Although both the presence of nasal polyps and opening of the sinuses surgically seem to have an effect on nasal NO levels, there is no evidence in any population that low nasal NO causes harmful effects. They concluded that current evidence shows that nasal NO is not a clinically useful measure for sino-nasal disease.

Yoon and Sin (2011) stated that chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality in the world. None of the current treatments, except for smoking cessation and supplemental domiciliary oxygen for hypoxemic patients, can modify its natural course or alter survival. The pipeline for new compounds is not very promising owing to repeated failures, and many large pharmaceutical companies have abandoned COPD drug discovery altogether. One major barrier to new drug discovery is the lack of modifiable biomarkers that can be used as surrogates of clinical outcomes such as exacerbation and mortality. The only accepted marker in COPD is FEV1. However, by definition, COPD is a non-reversible or poorly reversible condition with respect to FEV1. Thus, very few drugs except for bronchodilators have been able to address this endpoint. Of many candidate molecules, sputum neutrophil counts, FENO and proline-glycine-proline (PGP) and N-\(\alpha\)-PGP, which are breakdown products of collagen, are promising lung-based biomarkers. However, their clinical utility has not been validated in large clinical trials. Promising blood biomarkers include surfactant protein D, and pulmonary- and activation-regulated chemokine (PARC/CCL-18). However, the clinical data have been inconsistent. Non-specific inflammatory biomarkers such as C-reactive protein and interleukin-6 lack specificity for COPD and thus are of limited clinical usefulness.

In a pilot study, Donohue et al (2014) identified increases in FENO in a subset of patients with COPD. The investigators conducted a single-visit, outpatient study in 200 patients aged 40 years and older with COPD. All patients underwent spirometry and FENO testing. COPD
severity was classified according to the Global initiative for chronic Obstructive Lung Disease (GOLD) 2010 guidelines. Patients who participated in the study had a mean age of 63.9 ± 11.3 years and a mean smoking history of 46 ± 29 pack years. Patients had a mean forced expiratory volume in 1 second percent predicted of 53.9% ± 22.1%. The percentage of patients classified with COPD severity Stage I, II, III, and IV was 13 %, 40 %, 39 %, and 8 %, respectively. In addition, according to current procedural terminology codes, 32 % of patients were classified as mixed COPD/asthma, 26 % as COPD/emphysema, and 42 % as all other codes. The mean FENO level for all patients was 15.3 ± 17.2 parts per billion (ppb). Overall, 89 % of patients had a FENO less than 25 ppb, 8 % had a FENO 25 to 50 ppb, and 3 % had a FENO greater than 50 ppb. The percentages of patients with FENO in the intermediate or high ranges of FENO were greatest among patients with mixed COPD/asthma (intermediate, 11.5%; high, 6.6 %) compared with COPD/emphysema (intermediate, 8 %; high, 0) and all other codes (intermediate, 6.3 %; high, 1.3 %).

In a review on “Biomarkers in chronic obstructive pulmonary disease”, Rosenberg and Kalhan (2012) concluded that "So far, no single biomarker in COPD warrants wide acceptance emphasizing the need for future investigation of biomarkers in large-scale longitudinal studies”.

See and Christiani (2013) stated that elevated FENO reflects airway inflammation, but few studies have established its normal values. This study aimed to establish the normal values and thresholds for the clinical interpretation of FENO in the U.S. general population. A total of 13,275 subjects aged 6 to 80 years sampled for the National Health and Nutrition Examination Survey (NHANES) 2007-2010 underwent interviews, physical examination, and FENO analysis at 50 ml/s using an online chemiluminescence device according to ATS/European Respiratory Society (ERS) guidelines. After excluding subjects with self-reported asthma and subjects with wheeze in the prior 12 months, prediction equations for the natural logarithm (ln) of FENO were constructed using age, sex, ethnicity, height, body mass index (BMI), active/passive smoke exposure, and hay fever episodes as co-variates. The 5th to 95th percentile values of FENO were 3.5 to 36.5 ppb for children less than 12 years of age and 3.5 to 39 ppb for subjects 12 to 80 years of age. Using multiple linear regression, prediction equations explained only 10.3 % to 15.7 % of the variation in the general population. In the general population, 39 % to 45 % had ln(FENO) levels greater than 2 standard deviations of the predicted means. When applied to the general population inclusive of subjects who reported asthma but who did not have attacks within the past year, nearly identical results were obtained. The authors concluded that assuming 95 % of the healthy U.S. general population had no clinically significant airway inflammation as assessed by FENO, values exceeding the 95th percentiles indicated abnormality and a high-risk of airway inflammation. A large variation of normal FENO values existed in the general population, which was poorly predicted by multiple linear regression models.
Columbo et al (2013) studied the role of serial measurements of FENO in elderly subjects with asthma. A total of 30 stable asthmatics 65 years old and older were followed for 1 year with evaluations at baseline and every 3 months. These researchers looked for associations between FENO and subjects’ demographics, co-morbidities, asthma treatment, spirometric values and asthma control test (ACT) scores. Fractional exhaled nitric oxide was not elevated in these subjects throughout the study period (mean less than 30 ppb); FENO significantly increased and FEV1 % decreased between first and last study visit, while ACT scores and steroid dose remained unchanged. No significant correlation was found between FENO and FEV1/FVC, other spirometric values, inhaled steroid dose or ACT scores at any time point. No associations of FENO were found with age, sex, BMI, atopic status, disease duration, presence of rhinitis or GERD, or other medications used. Moderate asthma exacerbations did not consistently cause an increase of FENO. The authors concluded that in stable elderly asthmatic patients, FENO was not elevated and did not correlate with subjects’ demographics, co-morbidities, treatment, symptoms or spirometric values. They stated that routine measurements of FENO may not be clinically valuable in elderly asthmatics.

Hanania et al (2013) assessed the potential of FENO, peripheral blood eosinophil count, and serum periostin as biomarkers of Th2 inflammation and predictors of treatment effects of omalizumab. The EXTRA omalizumab study enrolled patients (aged 12 to 75 years) with uncontrolled severe persistent allergic asthma. Analyses were performed evaluating treatment effects in relation to FENO, blood eosinophils, and serum periostin at baseline. Patients were divided into low- and high-biomarker subgroups. Treatment effects were evaluated as number of protocol-defined asthma exacerbations during the 48-week treatment period (primary endpoint). A total of 850 patients were enrolled. Data were available from 394 (46.4 %), 797 (93.8 %), and 534 (62.8 %) patients for FENO, blood eosinophils, and serum periostin, respectively. After 48 weeks of omalizumab, reductions in protocol-defined exacerbations were greater in high versus low subgroups for all 3 biomarkers: FENO, 53 % (95 % CI: 37 to 70; p = 0.001) versus 16 % (95 % CI: -32 to 46; p = 0.45); eosinophils, 32 % (95 % CI: 11 to 48; p = 0.005) versus 9 % (95 % CI: -24 to 34; p = 0.54); and periostin, 30 % (95 % CI: -2 to 51; p = 0.07) versus 3 % (95 % CI: -43 to 32; p = 0.94). The authors concluded that the difference in exacerbation frequency between omalizumab and placebo was greatest in the 3 high-biomarker subgroups, probably associated with the greater risk for exacerbations in high subgroups. Moreover, they stated that additional studies are needed to explore the value of these biomarkers in clinical practice.

McCormack et al (2013) noted that little is known about use of FENO to predict asthma exacerbations among high-risk, urban, minority populations receiving usual care. A total of 138 children with persistent asthma were enrolled in a prospective observational cohort study and skin tested at baseline (wheal greater than or equal to 3 mm = +SPT). Fractional exhaled nitric oxide levels, lung function, and asthma-related health care use were assessed at baseline and
every 3 months thereafter for 1 year. Relationships between FENO and health care utilization in the subsequent 3 months were examined. Final models accounted for repeated outcome measures and were adjusted for age, gender and lung function. The mean age was 11 years (range of 5 to 17), and most were male (57 %), African American (91 %), and atopic (90 %). At baseline, FENO was (median IQR: 31.5 ppb [16 to 61]) and FEV1/FVC was (mean +/- SD: 80.7 +/- 9.6 %). There were 237 acute asthma-related health care visits, 105 unscheduled doctor (UD) visits, 125 ED visits, and 7 hospitalizations during the follow-up period. Fractional exhaled nitric oxide was not a significant predictor of acute visits, ED visits, UD visits, or hospitalization in either unadjusted or adjusted analyses. Use of recommended cut-off points did not improve the predictive value of FENO (positive-predictive value [PPV]: 0.6 to 32.8 %), nor did application of the guideline-based algorithm to assess change over time. The authors concluded that FENO may not be a clinically useful predictor of health care use for asthma exacerbations in urban minority children with asthma.

An UpToDate review on “Exhaled nitric oxide analysis and applications” (Dweik, 2017) states that “While FENO levels correlate with the presence of asthma and with eosinophilic airway inflammation and rise with exposure to asthma triggers, the exact role of FENO measurement in the diagnosis and characterization of asthma has not been defined. ... While FENO levels generally predict which patients will respond to inhaled glucocorticoid therapy, the largest trials and systematic reviews did not find sufficient evidence to support routine use of FENO to guide asthma therapy.”

Guidelines from the ATS and the ERS (Chung et al, 2014) concluded that “We suggest that clinicians do not use FeNO to guide therapy in adults or children with severe asthma (conditional recommendation, very low quality evidence)”.

A European Respiratory Society Statement on monitoring asthma in children (Pijnenburg, et al., 2015) stated: "Studies incorporating FeNO into management algorithms have used many different protocols, not only in terms of the frequency of measurements but also in the inclusion of other indices of asthma control. The results are variable, with only some showing significant effects such as reduced BHR and higher maximal expiratory flow at 25% of FVC, and the outcome measures are not consistent across studies. There is a view that the potential of this technique has not been fully evaluated and more work is required that evaluates FeNO-based management in appropriate patients and clinical settings. In preschool children, there is no published data that considers the utility of FeNO in monitoring asthma control, adjusting therapy or predicting exacerbations. However, some studies imply that elevated FeNO in preschool children is associated with a risk of future wheezing or later asthma, and predicts a decline in lung function in infants with recurrent wheeze. FeNO measurements in preschool children have not been standardised and there is insufficient evidence to support the use of such
measurements when monitoring preschool children. A Cochrane review concluded that based on current evidence, FeNO cannot be recommended for routine monitoring of asthma in children. Most Task Force members support this recommendation; however, in children with difficult or uncontrolled asthma, FeNO is sometimes used for monitoring disease in specialist centres. Persistently high FeNO should alert the physician of reduced adherence to treatment, a faulty inhalation technique, ongoing allergen exposure or severe airways inflammation." The ERS statement also concluded that "the evidence indicates that ... monitoring FeNO at home do[es] not improve asthma outcomes compared with symptom monitoring."

A review to support the ERS Statement (Moeller, et al., 2015) found: "based on current evidence FeNO is not useful for routine monitoring of children with asthma, although most task force members use FeNO in children with difficult or uncontrolled asthma especially in specialist centres. Clinical trials that assess the utility of FeNO in adjusting treatment or in predicting exacerbations in preschool children have not been performed. It is still unclear what represents a significant change in FeNO in a longitudinal setting."

Bjermer et al (2014) stated that although not yet widely implemented, FENO has emerged in recent years as a potentially useful biomarker for the assessment of airway inflammation both in undiagnosed patients with non-specific respiratory symptoms and in those with established airway disease. Research to date essentially suggested that FENO measurement facilitates the identification of patients exhibiting T-helper cell type 2 (Th2)-mediated airway inflammation, and effectively those in whom anti-inflammatory therapy, particularly ICS, is beneficial. In some studies, FENO-guided management of patients with established airway disease is associated with lower exacerbation rates, improvements in adherence to anti-inflammatory therapy, and the ability to predict risk of future exacerbations or decline in lung function. Despite these data, concerns regarding the applicability and utility of FENO in clinical practice still remain. These investigators reviewed the current evidence, both supportive and critical of FENO measurement, in the diagnosis and management of asthma and other inflammatory airway diseases. It additionally provided suggestions regarding the practical application of FENO measurement: how it could be integrated into routine clinical practice, how its utility could be assessed and its true value to both clinicians and patients could be established. The authors concluded that although some unanswered questions remain, current evidence suggested that FENO is potentially a valuable tool for improving the personalized management of inflammatory airway diseases.

Chaudry et al (2014) noted that asthma and airway hyper-responsiveness are reportedly more common in children with sickle cell disease (SCD). In a prospective, single-center study, these researchers determined airway responsiveness, airway inflammation and clinical features of asthma in SCD. A total of 50 SCD children without overt pulmonary vascular disease and 50
controls were included in this study. Exhaled nitric oxide and total serum IgE were measured and spirometry and methacholine challenge were performed. The methacholine dose-response slope (DRS) was calculated. Doctor diagnosis of asthma was made in 7 (14%) SCD versus 12 (24%) control subjects (p = 0.203). FENO levels were similar in SCD and controls (p = 0.250), and were higher in those with atopy and an asthma diagnosis (OR 4.33, 95% CI: 1.7 to 11.1; p < 0.05). zFEV1 (p = 0.002) and zFVC/FVC (p = 0.003) but not zFVC (p = 0.098) were lower in SCD versus controls. The methacholine dose-response slope was higher in those with asthma (p = 0.006) but not in SCD versus controls (p = 0.403). The methacholine dose-response slope correlated with FENO and blood eosinophil count in controls but not SCD. In SCD, DRS was higher in those admitted to hospital with respiratory symptoms (n = 27) versus those never admitted (n = 23) (p = 0.046). The methacholine dose-response slope was similar in those with at least 1 acute chest syndrome episode (n = 12) versus those with none (n = 35) (p = 0.247). The authors concluded that SCD children have airflow obstruction despite having minimal evidence of pulmonary vascular disease. Airflow obstruction is not associated with increased methacholine sensitivity or eosinophilic inflammation, at least as judged by FENO. Airflow obstruction in SCD does not appear to be related to childhood eosinophilic asthma, but its pathophysiology remains ill understood.

In a meta-analysis, Lu and colleagues (2015) evaluated the potential benefit of incorporating the use of monitoring FENO with guideline-based management in treating children with asthma. PubMed and Cochrane CENTRAL databases were searched until November 2013 for randomized control trials (RCTs) that investigated the use of FENO compared with conventional monitoring in managing asthma in children. Included studies had at least 2 intervention groups: one that utilized FENO and the other that utilized only conventional or standard methods (e.g., spirometry, symptoms, and others) to guide treatment. A total of 6 studies were included in the meta-analysis comprising 506 subjects whose treatment was monitored using FENO and 511 subjects who were managed using conventional methods. These investigators found no difference between the FENO and the conventional groups in FENO value (95% CI: -0.31 to 0.1), change from baseline in FEV1 (95% CI: -0.07 to 0.20), or steroid use (95% CI: -0.67 to 1.80). However, the FENO group was associated with a lower frequency of greater than 1 asthma exacerbation (95% CI: 0.532 to 0.895). The authors concluded that the findings of this meta-analysis suggested that using FENO to guide treatment decisions has little clinical benefit, although it may result in a decrease in asthma exacerbations.

Maniscalco et al (2015) evaluated the usefulness of an extended exhaled NO measurement and nasal NO for an initial evaluation of chronic cough. These researchers studied 52 non-smoker patients with prolonged cough lasting more than 8 weeks. Etiologies of cough were identified. Nasal NO and FENO were assessed using multiple single-breath NO analysis at different constant expiratory flow-rates. From the fractional NO concentration measured at each flow-
rate, the total NO flux between tissue and gas phase in the bronchial lumen (J'awNO), and the alveolar NO concentration (Cano) were extrapolated. The patients were classified in 4 categories: (i) cough variant asthma (CVA), (ii) non-asthmatic eosinophilic bronchitis (NAEB), (iii) upper airway cough syndrome (UACS) and (iv) GERD. Compared with UACS and GERD, both exhaled NO and J'awNO were higher in CVA and NAEB, and no differences were found in Cano and nasal NO level among the 4 groups. The authors concluded that the findings of this study suggested a potentially useful role for FENO measurement in the etiological diagnosis of chronic cough. Moreover, they did not find any additive value of performing exhaled NO at multiple flow-rates and nasal NO measurements.

Ren et al (2015) stated that acute mountain sickness (AMS) is a common disabling condition observed in people ascending to high altitudes. However, a simple predictive test for AMS is not known. These researchers assessed the relationship between baseline FENO and AMS occurrence. A total of 80 healthy lowland Chinese adults were recruited for this study. Fractional exhaled NO was measured at baseline, as well as 6 and 24 hours after arrival in Tibet. The standard Lake Louise Score (LLS) consensus symptoms questionnaire was used to assess the incidence and severity of AMS. Individuals with a high LLS (greater than 3) had higher FENO levels at baseline and after arrival in Tibet than people with a low LLS (less than or equal to 3) (baseline: 22.9 ± 11.9 versus 16.7 ± 6.4; 6 hours: 26.2 ± 16.7 versus 17.9 ± 5.7; 24 hours: 24.9 ± 13.1 versus 16.3 ± 1.7; all p < 0.01). Evaluation of risk factors revealed that female gender, diabetes and not smoking were associated with a high AMS score (all p < 0.05), but that hypertension showed no association (p > 0.05). The authors concluded that the findings of this prospective observational study suggested that baseline FENO levels may be positively correlated with AMS in healthy Chinese lowlanders.

Torretta et al (2015) stated that it has been suggested that bacterial biofilms may be a causative factor in the etiopathogenesis of chronic tonsillitis. Involvement of exhaled NO has been previously considered, with conflicting findings. In a pilot study, these researchers examined the relationship between exhaled NO levels and the presence of tonsillar biofilm-producing bacteria in children with chronic tonsillitis. Tonsillar biofilm-producing bacteria on bioptic specimens taken during tonsillectomy were assessed by means of spectrophotometry. Analysis was based on 24 children aged 5 to 10 years (median of 7.5 years). Biofilm-producing bacteria were found in 40.9% of specimens. The median exhaled NO level was 11.6 ppb (range of 3.2 to 22.3 ppb). There was a significant relationship between the presence of biofilm-producing bacteria and increased exhaled NO levels (p = 0.03). Children with exhaled NO levels of more than 8 ppb were at 3 times greater risk of developing tonsillar biofilm-producing bacteria than those with lower levels.
The authors concluded that these findings suggested the possibility of discriminating children with chronic biofilm-sustained tonsillar infections on the basis of exhaled NO levels. These preliminary findings need to be validated by well-designed studies.

Hoffmeyer et al (2015) stated that occupational bioaerosol exposures are capable to cause respiratory diseases. These researchers studied the relationship between exposure to bioaerosols and biomarkers’ concentration in EBC and FENO in 119 bioaerosol-exposed compost workers taking into account atopy and smoking habits. Atopy was classified according to specific IgE concentrations to common inhalant allergens (sx1). Bioaerosol exposure was estimated according to job title, duration of employment, results of ambient monitoring at the work-places, and shift time worked under protection of filtered air supply. Concentrations of 8-iso-prostaglandin F2α (8-iso-PGF2α), prostaglandin E2 (PGE2), leukotriene B4 (LTB4), and acid-base balance (pH) in EBC and FENO were assessed in 59 never-smoking (NS) and 60 smoking (S) compost workers. These investigators found that atopic subjects were equally distributed among NS and S (n = 16 each). Levels of 8-iso-PGF2α were significantly higher in workers considered highly exposed to bioaerosols than in low exposed workers (86.6 (66.1; 128.8) pg/ml versus 74.4 (56.3; 96.7) pg/ml, p = 0.047). No associations could be observed between exposures and biomarkers concerning compost workers in total, but there were some in atopic workers (duration of employment and FENO: r = 0.376, p = 0.041; filtered air supply and FENO: r = -0.335, p = 0.071). Smokers had significantly lower pH values compared to NS (non-atopic, p = 0.041; atopic p = 0.050). The authors concluded that EBC and FENO might be useful tools for monitoring of inflammation due to bioaerosol exposures, especially in atopic subjects.

Yi and colleagues (2016) stated that whether FENO measurement alone or combined with sputum eosinophil and atopy is useful in predicting corticosteroid-responsive cough (CRC) and non-CRC (NCRC) is unclear. In this study, a total of 244 patients with chronic cough and 59 healthy subjects as control were enrolled. The causes of chronic cough were confirmed according to a well-established diagnostic algorithm; FENO measurement and induced sputum for differential cell were performed in all subjects. Corticosteroid-responsive cough occurred in 139 (57.0 %) patients and NCRC occurred in 105. The FENO level in CRC significantly correlated with sputum eosinophils (Spearman Rank-order Coefficient [rs] = 0.583, p < 0.01). The median (quarter) of FENO level in CRC was significantly higher than NCRC (32.0 ppb [19.0 to 65.0 ppb] versus 15.0 ppb [11.0 to 22.0 ppb], p < 0.01). FENO of 31.5 ppb had a sensitivity and specificity of 54.0 % and 91.4 %, respectively, in predicting CRC from chronic cough, with a PPV of 89.3 % and a negative predictive value (NPV) of 60.0 %. If the patients had a combination of low level of FENO (less than 22.5 ppb), normal sputum eosinophil (less than 2.5 %), and absence of atopy, the sensitivity and specificity would be 30.3 % and 93.5 % for predicting NCRC. The authors concluded that in this cohort, a high level (greater than or equal
to 31.5 ppb) of FENO indicated more likelihood of CRC, but the sensitivity is insufficient to rule out a diagnosis of CRC. A combination of low-level FENO, normal sputum eosinophil, and absence of atopy suggested a lower likelihood of CRC.

Gomersal and colleagues (2016) evaluated the available evidence on the effectiveness of FeNO-guided management of childhood asthma. Databases including Medline and the Cochrane Library were searched, and RCTs comparing FeNO-guided management with any other monitoring strategy were included. Study quality was assessed using the Cochrane risk of bias tool for RCTs, and a number of outcomes were examined, including: exacerbations, medication use, quality of life (QOL), adverse events (AES), and other markers of asthma control. Meta-analyses were planned if multiple studies with suitable heterogeneity were available. However, due to wide variations in study characteristics, meta-analysis was not possible. A total of 7 RCTs were identified. There was some evidence that FeNO-guided monitoring resulted in improved asthma control during the 1st year of management, although few results attained statistical significance. The impact on severe exacerbations was unclear. Similarly, the impact on use of anti-asthmatic drugs was unclear, and appeared to depend on the step-up/step-down protocols, and the clinical characteristics of patients. The authors concluded that the potential benefit of FeNO monitoring is equivocal. Trends toward reduced exacerbation and increased medication use were seen, but typically failed to reach statistical significance. There are a number of issues that complicate data interpretation, including differences in the likely severity of included cohorts and variations in treatment algorithms. They stated that further work is needed to examine the impact of these parameters.

In a Cochrane review, Petsky and associates (2016) evaluated the effectiveness of tailoring asthma interventions based on FeNO, in comparison to not using FeNO, i.e., management based on clinical symptoms (with or without spirometry/peak flow) or asthma guidelines (or both), for asthma-related outcomes in children. The authors concluded that in this updated review with 5 new included studies, tailoring asthma medications based on FeNO levels (in comparison with primarily guideline management) significantly decreased the number of children who had 1 or more exacerbations (defined as any exacerbation or rescue oral corticosteroid courses but not hospitalizations) over the study period. However, use of the FeNO strategy was not beneficial for exacerbation rates, or the secondary outcomes of forced expiratory volume in one second (FEV1), FeNO levels, inhaled corticosteroid doses or symptom scores. Thus, the use of FeNO to guide therapy decisions for medication in children with asthma cannot be universally advocated. The author suggested that the intervention may be most useful in a subset of children with asthma. The authors stated that further double-blind, parallel group, randomized controlled trials are required. Studies should be conducted in primary care and consider various cut-offs for FeNO levels and other significant influences of FeNO levels such as atopy, sex and
ethnicity. The effect of tailoring asthma medications based on different levels of asthma severity should also be considered. Further cost analyses and adverse events of inhaled and oral corticosteroids would provide additional important information.

Petsky, et al. (2016) conducted a Cochrane review to evaluate the efficacy of tailoring asthma interventions based on exhaled nitric oxide (FeNO), in comparison to not using FeNO, that is management based on clinical symptoms (with or without spirometry/peak flow) or asthma guidelines or both, for asthma-related outcomes in adults. The authors searched the Cochrane Airways Group Specialised Register of Trials, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and reference lists of articles. The last searches were undertaken in June 2016. The review included all randomized controlled trials (RCTs) comparing adjustment of asthma medications based on exhaled nitric oxide levels compared to not using FeNO, that is management based on clinical symptoms (with or without spirometry/peak flow) or asthma guidelines or both. The authors reviewed results of searches against predetermined criteria for inclusion. The authors independently selected relevant studies in duplicate. Two review authors independently assessed trial quality and extracted data. The investigators contacted study authors for further information, receiving responses from four. The review included seven adult studies; these studies differed in a variety of ways including definition of asthma exacerbations, FeNO cutoff levels used (15 to 35 ppb), the way in which FeNO was used to adjust therapy, and duration of study (4 to 12 months). Of 1700 randomized participants, 1546 completed the trials. The mean ages of the participants ranged from 28 to 54 years old. The inclusion criteria for the participants in each study varied, but all had a diagnosis of asthma and required asthma medications. In the meta-analysis, there was a significant difference in the primary outcome of asthma exacerbations between the groups, favoring the FeNO group. The number of people having one or more asthma exacerbations was significantly lower in the FeNO group compared to the control group (odds ratio (OR) 0.60, 95% confidence interval (CI) 0.43 to 0.84). The number needed to treat to benefit (NNTB) over 52 weeks was 12 (95% CI 8 to 32). Those in the FeNO group were also significantly more likely to have a lower exacerbation rate than the controls (rate ratio 0.59, 95% CI 0.45 to 0.77). The authors, however, did not find a difference between the groups for exacerbations requiring hospitalization (OR 0.14, 95% CI 0.01 to 2.67) or rescue oral corticosteroids (OR 0.86, 95% CI 0.50 to 1.48). There was also no significant difference between groups for any of the secondary outcomes (FEV1, FeNO levels, symptoms scores, or inhaled corticosteroid doses at final visit). The authors considered three included studies that had inadequate blinding to have a high risk of bias. However, when these studies were excluded from the meta-analysis, the difference between the groups for the primary outcomes (exacerbations) remained statistically significant. The GRADE quality of the evidence ranged from moderate (for the outcome 'exacerbations') to very low (for the outcome 'inhaled corticosteroid dose at final visit') based on the lack of blinding and statistical heterogeneity. Six of the seven studies were industry supported, but the company
had no role in the study design or data analyses. The authors concluded that, with new studies included since the last version of this review, which included adults and children, this updated meta-analysis in adults with asthma showed that tailoring asthma medications based on FeNO levels (compared with primarily on clinical symptoms) decreased the frequency of asthma exacerbations but did not impact on day-to-day clinical symptoms, end-of-study FeNO levels, or inhaled corticosteroid dose. Thus, 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. The authors concluded that further RCTs encompassing different asthma severity, ethnic groups in less affluent settings, and taking into account different FeNO cutoffs are required.

A statement by the American Academy of Pediatrics Section on Allergy and Immunology (Dinakar, et al., 2017) noted that some specialists may consider evaluation of airway inflammation by using FENO to be useful, but concluded that "[t]he value of additional FENO monitoring in children whose asthma is appropriately managed using guideline-based strategies is unproven ..."

Guidelines on asthma from the Global Initiative for Asthma (GINA, 2017) states: "Measurement of the fractional concentration of exhaled nitric oxide (FENO) is becoming more widely available. It is modestly associated with eosinophilic airway inflammation. FENO has not been established for ruling or ruling out a diagnosis of asthma.....FENO is higher in eosinophilic asthma but also in non-asthma conditions (e.g., eosinophilic bronchitis, atopy, allergic rhinitis, eczema), and it is not elevated in some asthma phenotypes (e.g., neutrophilic asthma). Several other factors affect FENO levels: it is lower in smokers and is decreased during bronchoconstriction and in the early stages of allergic response; it may be increased or decreased during viral respiratory infections. In adult steroid naive patients (mainly non-smokers) with non-specific respiratory symptoms, a finding of FENO > 50 parts per billion (ppb) was associated with a good short-term response to ICS. However, there are no long-term studies examining the safety of withholding ICS in patients with low initial FENO. Consequently, in patients with a diagnosis or suspected diagnosis of asthma, FENO can support the decision to start ICS, but cannot be recommended at present for deciding against treatment for ICS." The guidelines continue that "Fractional concentration of exhaled oxygen (FENO) treatment guided by FENO has not generally been found to be effective. In several of these studies, there have been problems with the design of the intervention and/or control algorithms, that make comparisons and conclusions difficult. Results of FENO measurement at a single point in time should be interpreted with caution. ....At present, neither sputum- nor FENO-guided treatment is recommended for the general asthma population."
The updated 2018 guidelines also include results of a new meta-analysis that separately analyzed studies in which the control algorithm was reasonably close to current guidelines-based treatment, and provided a clinically relevant comparator. In studies involving children and young adults, the analyses showed that FENO-guided treatment significantly reduces exacerbation rates compared with guidelines-based treatment (Evidence A). No significant difference was seen in adults with FENO-guided treatment compared with guidelines-based treatment. The guidelines concluded that further studies are needed to identify the populations most likely to benefit from sputum-guided or FENO-guided treatment, and the optimal frequency of FENO monitoring.” (GINA, 2018).

The Agency for Healthcare Research and Quality (AHRQ) conducted a comparative effectiveness review to examine the clinical utility of fractional exhaled nitric oxide (FeNO) in asthma management (Wang et al. 2017). The authors concluded that FeNO has moderate accuracy to diagnose asthma in people ages 5 years and older. 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. At this time, 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.

Exhaled Nitric Oxide for COPD

Lu and colleagues (2018) stated that FENO is a useful and non-invasive biomarker for eosinophilic airway inflammation, particularly in asthma. However, its utility in COPD remains controversial. These researchers carried out a systematic review and meta-analysis to examine FENO levels in COPD. A search of PubMed, Embase, Cochrane Library, and clinical trial registry was conducted from inception to January 2018. Studies were included if they reported FENO levels in patients with COPD and healthy controls. These investigators then extracted relevant information and analyzed data. Standard mean difference (SMD) with 95% CI was applied in this meta-analysis. A total of 2,073 studies were reviewed for eligibility, with 24 studies pooled for analysis. The FENO levels in patients with COPD were elevated mildly compared with healthy controls (SMD 1.28, 95% CI: 0.60 to 1.96). A similar result was also observed in stable COPD, with an SMD of 1.21 (95% CI: 0.47 to 1.96). On the other hand, these researchers found no association between FENO levels and exacerbated COPD. Additionally, for patients with COPD, ex-smokers had higher levels of FENO than current smokers (SMD 2.05, 95% CI: 1.13 to 2.97). The authors concluded that the findings of this review demonstrated a mild elevation of FENO in COPD, and the association between exacerbated COPD and FENO levels needs to be further explored. The potential mechanism is still unknown and conflicting. These researchers stated that the usefulness of FENO measurement in clinical
management of COPD still needs to be evaluated in a long-term of practice and requires more high-quality studies. More importantly, the association between exacerbated COPD and FENO levels and the underlying mechanism in COPD exacerbation should be further examined.

Exhaled Nitric Oxide and Exhaled Breath Temperature as Biomarkers for Pulmonary Hypertension

Carpagnano and colleagues (2018) stated that pulmonary hypertension (PH) is a progressive fatal disease thus, non-invasive prognostic tools are needed to follow these patients. These researchers evaluated FeNO and EBT values in patients with PH from different causes and correlated them with respiratory functional data. A total of 24 PH patients underwent spirometry, carbon monoxide diffusion (DLCO) test, trans-thoracic echocardiography (TTE), right-heart catheterization, and FeNO and EBT measurements. These investigators studied 3 groups according to the type of PH: 10 patients with pulmonary arterial hypertension (PAH) (group A), 11 patients with PH due to COPD (group B), and 3 patients with PH associated with left heart disease (group C). Mean FeNO values tend to be higher in group B (15.0 ± 9.3 ppb) compared with other groups (9.9 ± 5.7 and 8.5 ± 5.2 ppb in groups A and C; respectively, p = 0.271); but no statistical significance has been reached. Mean values of alveolar NO concentration (CANO) were higher in groups A and B compared to group C (16.9 ± 12.6; 13.9 ± 6.8; and 6.7 ± 2.0 ppb, respectively) (p = 0.045). EBT mean values were significantly lower in group C when compared with other groups (group C: 29.0 ± 1.3° C, groups A and B: 30.9 ± 1.3 and 31.2 ± 1.2° C, respectively: p = 0.041). EBT levels were inversely correlated to mean pulmonary artery pressure (PAPm) levels (Spearman coefficient -0.481; p = 0.017). The authors concluded that eNO, CANO, and EBT have been evaluated in 3 groups of PH patients. Interestingly, EBT reduction was correlated with PAPm increase, whereas FeNO was higher in COPD patients and CANO in PAH and COPD groups. These researchers stated that further studies are needed to clarify EBT, FeNO, and CANO roles as biomarkers in the monitoring of patients with PH.

Exhaled Nitric Oxide as a Biomarker for Systemic Sclerosis Lung Disease

Kozij and colleagues (2017) stated that eNO is a potential biomarker to distinguish systemic sclerosis (SSc) associated pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD). These researchers evaluated the discriminative validity, feasibility, methods of eNO measurement, and magnitude of differences across lung diseases, disease-subsets (SSc, systemic lupus erythematosus [SLE]), and healthy-controls. Consecutive subjects in the UHN Pulmonary Hypertension Program were recruited. Exhaled nitric oxide was measured at 50 ml/s intervals using chemiluminescent detection. Alveolar and conducting airway NO were partitioned using a 2-compartment model of axial diffusion (CMAD) and the trumpet model of axial diffusion (TMAD). A total of 60 subjects were evaluated. Using the CMAD model, control subjects had
lower median (IQR) alveolar NO than all PAH subjects (2.0 (1.5, 2.5) versus 3.14 ppb (2.3, 4.0), p = 0.008). SSC-ILD had significantly lower median conducting airway NO compared to controls (1,009.5 versus 1,342.1 ml/ppb/s, p = 0.04). SSc-PAH had increased median (IQR) alveolar NO compared to controls (3.3 (3.0, 5.7) versus 2.0 ppb (1.5, 2.5), p = 0.01). SSc-PAH conducting airway NO inversely correlated with DLCO (r -0.88 (95 % CI: -0.99 to -0.26)). The authors concluded that they have demonstrated feasibility, identified that CMAD modeling was preferred in SSc, and reported the magnitude of differences across cases and controls. They noted that these findings supported discriminative validity of eNO in SSc lung disease. Moreover, these researchers stated that currently, the performance of eNO determination at multiple flow rates is experimental and only suitable for academic centers with the equipment and knowledge needed to carry out these measures. They noted that the integration of eNO as a marker in scleroderma pulmonary disease will require further validation and dissemination of knowledge.

Exhaled Breath Condensate pH

Exhaled breath condensate (EBC) is a non-invasive method for studying the composition of the fluid lining the airway. Researchers have reported abnormalities in EBC concentrations of at least 12 markers in individuals with inflammatory lung disorders.

The measurement of EBC pH is one EBC marker that is currently being investigated as a method for assessing asthma and other chronic pulmonary diseases. EBC pH is being investigated as a biomarker for airway inflammation. Acidic or low pH measurements have been demonstrated in individuals with asthma and COPD. Exhaled breath condensation pH testing involves breathing into a tube that is surrounded by a cold metal sleeve for ten to 15 minutes. The pH is obtained and measured from the collection of water vapors created by the lungs.

Investigators have found that EBC pH values of individuals with respiratory disease (e.g., asthma and other chronic pulmonary diseases) are lower compared with those of healthy controls and that pH levels increase towards control levels after steroid treatment (Kharitonov, 2004; Carpagnano et al, 2004, 2005; Carraro et al, 2005; Effros et al, 2005).

In a study presented at the 2004 Annual Meeting of the American Academy of Allergy, Asthma and Immunology (AAAAI), researchers reported that the pH of EBC in acute asthmatic children was significantly lower than those with stable asthma. Brunetti and colleagues tested 104 asthmatic children with skin prick tests, lung function tests, and EBC pH measurements. The children experiencing asthma exacerbations received steroid and beta-2 agonist treatment for one week before the pH test was repeated. Thirty-four children (34.7 %) showed evidences of acute asthma and 70 children (67.3 %) had stable asthma. After treatment, the EBC pH of patients with acute asthma was significantly higher than before therapy.
Several researchers, however, have raised concerns regarding the standardization of EBC collection and measurement methods. A recent consensus panel convened by the American Thoracic Society/European Respiratory Society Task Force on EBC (Horvath, 2005) provided general recommendations for both EBC collection and measurement. However, the Task Force stated that more studies are necessary before EBC can be recommended for clinical practice. The following areas for future research were identified: (i) mechanisms and site of EBC particle formation; (ii) determination of dilution markers; (iii) improvement of reproducibility; (iv) longitudinal studies are needed; and (v) determination of the utility of EBC measures in the management of individual patients.

In a review of EBC in chronic obstructive pulmonary disease, Effros et al (2005) stated that EBC pH measurements may not provide accurate estimates of airway pH. Data interpretation is complicated by uncertainty regarding the source of condensate solutes and by variable dilution of respiratory droplets from condensed water vapor, which represents more than 99.9 % of condensate volumes. Furthermore, the Guidelines from the Global Initiative for Asthma (GINA) (2004) stated that neither sputum eosinophilia nor exhaled gases have been evaluated prospectively as an aid in the diagnosis of asthma. The guidelines state that there is a need to develop further noninvasive discriminate measurements of airway inflammation.

Exhaled breath condensate pH is a novel, noninvasive research approach to monitor lung diseases; however, well-designed controlled studies are needed to establish the clinical utility of EBC pH for the assessment of asthma and other chronic pulmonary diseases.

Baraldi and Carraro (2006) stated that EBC is still only a research tool. Ko et al (2007) stated that there is some evidence that certain markers in EBC differ between patients with asthma and controls, and some markers may correlate with asthma severity and lung function, but there are many methodologic pitfalls with EBC assessment that limit its clinical applicability at present. The authors concluded that more studies are needed before this technique can be recommended for clinical use.

Cepelak and Dodig (2007) stated that in spite of many scientific studies involving lung disease patients, methodology for EBC collection and analysis has not yet been realized for daily utilization. Additional studies of the exact origin of condensate constituents and standardization of the overall analytical process, including collection, storage, analysis and result interpretation, are needed. Irrespective of these limitations, further investigation of this sample type is fully justified by the fact that classical specimens used in the management of pulmonary diseases are either obtained by invasive procedures (e.g., induced sputum, biopsy, broncho-alveolar lavage) or can not provide appropriate information (e.g., urine, serum). Analysis of EBC in the future
might contribute significantly to the understanding of the physiological and pathophysiological processes in lungs, to early detection, diagnosis and follow-up of disease progression, and to evaluation of therapeutic response.

Guidelines from the National Asthma Education Program (NIH, 2007) stated that many biomarkers have been proposed, including concentration of hydrogen ions and various other metabolites in an exhaled breath condensate, but that few studies have validated these markers. The guidelines stated that these biomarkers may have a role in asthma management in the future.

Chan and colleagues (2009) stated that breath analysis, which includes gaseous phase analysis that measures volatile organic compounds using electronic noses, FENO, and EBC, has been proposed as a non-invasive and simple technique to investigate neoplastic processes in the airways. Exhaled breath condensate can be easily collected by breathing into a cooling system that condenses the water vapor in the breath. It has already been suggested to be a useful method to monitor severity of diseases such as asthma and to act as a surrogate measure of compliance to medical therapy. Presently, there still remains a relative paucity of lung cancer research involving EBC. However, since EBC is a simple, non-invasive technique that can be easily performed, even in ill patients, it has the potential to be validated for use in screening for the early diagnosis of lung cancer.

Dalaveris and associates (2009) evaluated the levels of vascular endothelial growth factor (VEGF), 8-isoprostane and tumor necrosis factor (TNF)-alpha in EBC and serum of patients with primary lung cancer prior to the initiation of any treatment, in order to evaluate their possible diagnostic role. Furthermore, associations between VEGF, 8-isoprostane and TNF-alpha levels in EBC and serum with clinicopathologic factors were examined. These researchers enrolled 30 patients with lung cancer (mean age of 65.2 +/- 10.5 years) and 15 age- and gender-matched healthy smokers as controls. Serum and EBC were collected before any treatment; TNF-alpha, VEGF and 8-isoprostane levels in EBC and serum were analyzed by an immunoenzymatic method. A statistically significant difference was observed between lung cancer patients and the control group regarding the values of TNF-alpha, both in EBC (52.9 +/- 5.0 pg/ml versus 19.4 +/- 3.9 pg/ml, p < 0.0001) and serum (44.5 +/- 6.3 pg/ml versus 22.2 +/- 4.3 pg/ml, p = 0.035). Moreover, EBC VEGF levels were higher in patients with T3-T4 tumor stage compared to T1-T2 (9.3 +/- 2.8 pg/ml versus 2.3 +/- 0.7 pg/ml, p = 0.047). A statistically significant correlation was also observed between serum and EBC values of VEGF (r = 0.52, p = 0.019). In addition, serum levels of VEGF were higher in lung cancer patients than in controls (369.3 +/- 55.1 pg/ml versus 180.5 +/- 14.7 pg/ml, p = 0.046). Serum VEGF levels were also higher in patients with advanced stage of disease (IIIB-IV) and distant nodal metastasis (N2-N3). No differences were observed in 8-isoprostane in EBC between lung cancer patients and controls. In contrast, serum 8-
isoprostane levels were higher in lung cancer patients compared to controls (24.9 +/- 3.6 pg/ml versus 12.9 +/- 1.6 pg/ml, p = 0.027) and were higher in patients with advanced disease. All 3 biomarkers presented acceptable reproducibility in the EBC on 2 consecutive days. The authors concluded that TNF-alpha, VEGF and 8-isoprostane are elevated in the serum of lung cancer patients and increased serum VEGF and 8-isoprostane levels are related to advanced disease. In EBC, increased TNF-alpha levels were observed in lung cancer patients, whereas increased VEGF levels were observed in advanced T-stage. They stated that further longitudinal studies are needed for the evaluation of the prognostic role of these biomarkers in lung cancer.

Fila and Musil (2010) stated that examination of EBC belongs to experimental methods that are used in many pulmonary diseases and it can take part in the study of their pathophysiology. Many biomarkers of inflammation and oxidative stress were studied in EBC in cystic fibrosis. Examination of pH of EBC is considered to be useful in evaluation of inflammatory acidification of airways, together with evaluation of response to antibiotic treatment of pulmonary exacerbation, due to immediately accessible result. Other important biomarkers include 8-isoprostane and 3-nitrotyrosine as markers of oxidative stress (both with negative correlation with pulmonary function) and leukotriene B4 as marker of neutrophilic inflammation. Opposite to other pulmonary diseases, hydrogen peroxide does not belong to useful markers of oxidative stress in cystic fibrosis, due to abundant reduced thiols and glutathione peroxidase in sputum of these patients. Attempts to detect bacterial DNA in EBC in cystic fibrosis also failed. In spite of mentioned progress, examination of EBC remains a research method and it has not been introduced into clinical practice.

Teng et al (2011) examined if EBC hydrogen peroxide (H(2)O(2)) is elevated in people with asthma and if it reflects disease severity and disease control or responds to corticosteroid treatment. Studies were identified by searching PubMed, Embase, Cochrane Database, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and for relevant reports published before September 2010. Observational studies comparing levels of EBC H(2)O(2) between patients with asthma who were non-smokers and healthy subjects were included. Data were independently extracted by 2 investigators and analyzed using Stata 10.0 software. A total of 8 studies (involving 728 participants) were included. EBC H(2)O(2) concentrations were significantly higher in patients with asthma who were non-smokers compared with healthy subjects, and higher values of EBC H(2)O(2) were observed at each level of asthma, classified either by severity or control level, and the values were negatively correlated with FEV1. In addition, EBC H(2)O(2) concentrations were lower in patients with asthma treated with corticosteroids than in patients with asthma not treated with corticosteroids. The authors concluded that H(2)O(2) might be a promising biomarker for guiding asthma treatment; however, further investigation is needed to establish its role.
Thomas et al (2013) performed a systematic review to identify studies of EBC markers in childhood asthma. Most of the studies were cross-sectional in design, and the results suggested that simple chemical entities such as hydrogen ions (as pH), hydrogen peroxide, and oxides of nitrogen are associated with pediatric allergic asthma and exacerbations. In addition, more complex molecules including leukotrienes, prostaglandins, and cytokines such as the interleukins IL-4 and IL-5 are also elevated in the breath of those with asthma. The authors concluded that EBC has the potential to aid diagnosis, and to evaluate the inflammatory status of asthmatic children. They stated that future studies may be able to refine further how best to collect EBC samples, to interpret them, and the technique has the potential to allow repeated sampling that will allow studies of natural history, pathogenesis and response to treatment to be undertaken.

Kurada and colleagues (2015) stated that there is an urgent need for cheap, reproducible, easy to perform and specific biomarkers for diagnosis, differentiation and stratification of inflammatory bowel disease (IBD) patients. Technical advances allow for the determination of volatile organic compounds in the human breath to differentiate between health and disease. These investigators reviewed and discussed medical literature on volatile organic compounds in exhaled human breath in gastro-intestinal disorders, focusing on diagnosis and differentiation of IBD. They performed a systematic search in PubMed, Ovid Medline and Scopus using appropriate keywords. In addition, a bibliography search of each article was performed. Mean breath pentane, ethane, propane, 1-octene, 3-methylhexane, 1-decene and NO levels were elevated ($p < 0.05$ to $p < 10^{-7}$) and mean breath 1-nonene, (E)-2-nonene, hydrogen sulphide and methane were decreased in IBD compared to healthy controls ($p = 0.003$ to $p < 0.001$). A combined panel of 3 volatile organic compounds (octene, (E)-2-nonene and decene) showed the best discrimination between pediatric IBD and controls (AUC 0.96). Breath condensate cytokines were higher in IBD compared to healthy individuals ($p < 0.008$). Breath pentane, ethane, propane, isoprene and NO levels correlated with disease activity in IBD patients. Breath condensate IL-1β showed an inverse relation with clinical disease activity. The authors concluded that breath analysis in IBD is a promising approach that is not yet ready for routine clinical use, but data from other gastro-intestinal diseases suggested the feasibility for use of this technology in clinical practice. Moreover, they stated that well-designed future trials, incorporating the latest breath detection techniques, need to determine the exact breath metabolome pattern linked to diagnosis and phenotype of IBD.

In a systematic review, De Luca Canto et al (2015) evaluated the diagnostic value of biological markers (EBC, blood, salivary and urinary) in the diagnosis of obstructive sleep apnea (OSA) in comparison to the gold standard of nocturnal polysomnography (PSG). Studies that differentiated OSA from controls based on PSG results, without age restriction, were eligible for inclusion. The sample of selected studies could include studies in obese patients and with known cardiac disease. A detailed individual search strategy for each of the following...
bibliographic databases was developed: Cochrane, EMBASE, MEDLINE, PubMed, and LILACS. The references cited in these articles were also cross-checked and a partial grey literature search was undertaken using Google Scholar. The methodology of selected studies was evaluated using the 14-item Quality Assessment Tool for Diagnostic Accuracy Studies. After a 2-step selection process, 9 articles were identified and subjected to qualitative and quantitative analyses. Among them, only 1 study was conducted in children and 1 study in adults found biomarkers that exhibit sufficiently satisfactory diagnostic accuracy that enabled application as a diagnostic method for OSA. The authors concluded that kallikrein-1, uromodulin, uroctin-3, and orosomucoid-1 when combined have enough accuracy to be an OSA diagnostic test in children. Plasma levels of IL-6 and IL-10 have potential to be good biomarkers in identifying or excluding the presence of OSA in adults.

Lee and colleagues (2015) noted that acid gastro-esophageal reflux is a common problem in non-cystic fibrosis bronchiectasis and COPD. Invasive methods are used to diagnose gastro-esophageal reflux, but the ability to detect pulmonary microaspiration of gastric contents using this method is unclear. A non-invasive option to detect pulmonary microaspiration is to measure pepsin in EBC, but this has not been related to esophageal pH monitoring in these lung conditions. This study aimed to measure pepsin concentrations and pH in EBC and to determine the relationship to gastro-esophageal reflux in bronchiectasis or COPD. Subjects with bronchiectasis (n = 10) or COPD (n = 10) and control subjects (n = 10) completed 24-hour esophageal pH monitoring for detection of acid gastro-esophageal reflux, measuring the percentage of reflux time in the proximal esophagus and the DeMeester score (DMS). Concurrently, 3 samples of EBC were collected from each subject, and pH was measured and pepsin concentrations were analyzed by enzyme-linked immunosorbent assay. Exhaled breath condensate pepsin was detected in subjects with bronchiectasis (44 %) or COPD (56 %) and in control subjects (10 %). A diagnosis of gastro-esophageal reflux was not associated with a higher concentration of EBC pepsin in bronchiectasis (p = 0.21) or COPD (p = 0.11); EBC pepsin concentration did not correlate with DMS (rs = 0.36) or proximal reflux index (rs = 0.25) in subjects with bronchiectasis or with DMS (rs = 0.28) or proximal reflux index (rs = 0.21) in patients with COPD. Exhaled breath condensate and sputum pepsin concentrations were moderately correlated in bronchiectasis (rs = 0.56) and in COPD (rs = 0.43). The authors concluded that pepsin is detectable in EBC samples in bronchiectasis and COPD. Although no association was found between pepsin concentrations and a diagnosis of gastro-esophageal reflux, a moderate relationship between sputum and EBC pepsin concentrations suggested that EBC pepsin may be a useful non-invasive marker of pulmonary microaspiration.

Canto Gde et al (2015) noted that the overall validity of biomarkers in the diagnosis of OSA remains unclear. These investigators conducted a review to evaluate biomarkers characteristics in the context of OSA and to identify gaps in the literature. A review of studies in humans without
age restriction that evaluated the potential diagnostic value of biological markers (blood, EBC, salivary, and urinary) in the OSA diagnosis was undertaken. Retained articles were those focused on the identification of biomarkers in subjects with OSA, the latter being confirmed with a full overnight or home-based PSG. Search strategies for 6 different databases were developed. The methodology of selected studies was classified using an adaptation of the evidence quality criteria from the American Academy of Pediatrics. Additionally the biomarkers were classified according to their potential clinical application. These researchers identified 572 relevant studies, of which 117 met the inclusion criteria; 82 studies were conducted in adults, 34 studies involved children, and 1 study had a sample composed of both adults and children. Most of the studies evaluated blood biomarkers. Potential diagnostic biomarkers were found in 9 pediatric studies and in 58 adults studies. Only 9 studies reported sensitivity and specificity, which varied substantially from 43 % to 100 %, and from 45 % to 100 %, respectively. Studies in adults have focused on the investigation of IL-6, TNF-alpha, and high-sensitivity C-reactive protein (hsCRP). The authors concluded that there was no specific biomarker that was tested by a majority of authors in pediatric studies, and combinatorial urine biomarker approaches have shown preliminary promising results. In adults IL-6 and IL-10 appeared to have a favorable potential to become a good biomarker to identify OSA.

Aldakheel et al (2016) performed a systematic review of oxidative stress markers measured in EBC of adult asthma; studies were identified by searching Medline and Scopus databases. A total of 16 papers met the inclusion criteria. Concentrations of exhaled hydrogen ions, nitric oxide products, hydrogen peroxide and 8-isoprostanes were generally elevated and related to lower lung function tests in adults with asthma compared to healthy subjects. Assessment of EBC markers may be a non-invasive approach to evaluate airway inflammation, exacerbations, and disease severity of asthma, and to monitor the effectiveness of anti-inflammatory treatment regimens. Moreover, the authors concluded that longitudinal studies, using standardized analytical techniques for EBC collection, are needed to establish reference values for the interpretation of EBC markers in the context of asthma.

In a systematic review and meta-analysis, Peel and colleagues (2017) evaluated the evidence for the use of 8-isoprostane in EBC as a biomarker in adult asthma. These investigators searched a number of online databases (including PubMed, Embase and Scopus) in January 2016. They included studies of adult non-smokers with EBC collection and asthma diagnosis conducted according to recognized guidelines. They pooled data using random effects meta-analysis and assess heterogeneity using I2. These researchers included 20 studies, the findings from which were inconsistent; 7 studies (n = 329) reported 8-isoprostane levels in asthma to be significantly higher than that of control groups, whilst 6 studies (n = 403) did not. Only 4 studies were appropriate for inclusion in a random effects meta-analysis of mean difference. This found a statistically significant between-groups difference of 22 pg/ml. Confidence in the result was
limited by the small number of studies and by substantial statistical heterogeneity ($I^2 = 94$). The authors concluded that the clinical value of EBC 8-isoprostane as a quantitative assessment of oxidative stress in asthma remains unclear due to variability in results and methodological heterogeneity. They stated that it is essential to develop a robust and standardized methodology if the use of EBC 8-isoprostane in asthma is to be properly evaluated.

**Gastric Emptying Breath Testing**

Gastric emptying breath testing (GEBT) was developed to purportedly aid in the diagnosis of delayed gastric emptying, known as gastroparesis. This condition is characterized by slow or nonmovement of food from the stomach to the small intestine due to improper contractions of stomach muscles. Gastroparesis may result from conditions such as Parkinson’s disease, diabetes or following intestinal surgery. Gastric scintigraphy is considered the gold standard for diagnosing gastroparesis.

The GEBT is conducted over a four hour period after an overnight fast and reportedly measures how fast the stomach empties solids by measuring carbon dioxide in an individual's breath. Before the test begins, baseline breath tests are conducted and the individual eats a specially made protein test meal enriched with carbon-13. This substance is then measured via breath testing at multiple time points after the meal to determine the rate of gastric emptying.

**Hydrogen Breath Testing (HBT)**

Lactose intolerance or deficiency is caused by the inability to digest lactose, which is found in milk and other dairy products. This condition typically involves symptoms such as abdominal bloating, diarrhea or gas. Individuals with suspected lactose intolerance are generally advised to follow a dairy-free diet for a period of time to determine if symptoms will resolve. Further testing, such as HBT, may be indicated if symptoms continue. HBT involves measuring breath hydrogen (H2) before and at timed intervals after ingesting a solution containing lactose. The individual blows into balloon-like bags from which the exhaled breath is tested for the presence of H2. The exhalations are captured and tested every 15 minutes during a 2-hour testing period. Normally, very little H2 is detected in exhaled breath; however, when undigested lactose becomes fermented in the colon, H2 is produced. Raised levels of H2 found in exhaled breath may aid in diagnosis of lactose intolerance or deficiency.

Pimentel (2016) stated that the HBT based on following breath H2 levels after the administration of a carbohydrate (most commonly lactulose) to a patient with suspected small intestinal bacterial overgrowth (SIBO). The test is based on the interaction between the administered carbohydrate and the intestinal bacteria. The resulting fermentation produces H2. A positive
breath test is based on a breath H2 rise prior to the expected arrival time in the highly microbial cecum. Despite renewed enthusiasm for breath testing in recent years due to associations with conditions such as irritable bowel syndrome, breath testing poses many challenges.

Hydrogen Breath Testing for Prediction of Bowel Preparation Adequacy Prior to Colonoscopy

In a systematic review, Sondhi and colleagues (2018) examined the accuracy of HBT as a predictor of bowel preparation. Studies were identified from Medline, Embase, Web of Science, Cochrane Library and clinicaltrials.gov. Two investigators evaluated abstracts for inclusion criteria -- report of correlation between hydrogen breath levels and bowel preparation quality, prospective design and non-emergent colonoscopy in adults. Included studies underwent duplicate data extraction using a standardized approach. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool assessed quality of the studies. A total of 159 publications were identified, and 6 unique studies met inclusion criteria. The number of patients analyzed ranged from 61 to 127; 3 studies were performed in the U.S., 1 in Japan and 2 in Italy; 3 studies used a prebiotic in addition to a purgative, with the intention of enhancing the discriminating ability of hydrogen breath levels; 3 studies assessed baseline hydrogen levels. In 5 of the 6 studies, hydrogen breath levels were predictive of inadequate bowel preparation. Suggested absolute hydrogen levels to distinguish adequate from inadequate bowel preparation ranged from 3 to 10 parts per million. Depending on the cut-off value, sensitivity ranged from 71 % to 100 % and specificity from 87 % to 100 %. There was significant heterogeneity among studies in HBT protocol and breath analyzer used. Full-text studies had low risk of bias in most assessed domains. The authors concluded that hydrogen breath levels predicted bowel preparation adequacy but existing studies had significant limitations. These researchers stated that further research in this area could potentially lead to a more proactive, effective and safer means to ensure every patient achieves adequate bowel preparation.

The authors stated that a principal drawback of this review was that multiple studies were unclear in their patient selection process and endoscopist blinding. Another drawback was that meta-analysis with summary estimates of results could not be conducted given the significant heterogeneity of study designs. Lastly, these findings were subject to the same threats to validity that exist in the constituent studies.

Exhaled Breath Temperature

Hamill and associates (2016) noted that exhaled breath temperature (EBT) reflects airways (both eosinophilic and neutrophilic) inflammation in asthma and thus may aid the management of children with asthma that are treated with anti-inflammatory drugs. A new EBT monitor has
become available that is cheap and easy to use and may be a suitable monitoring device for airways inflammation. Little is known about how EBT relates to asthma treatment decisions, disease control, lung function, or other non-invasive measures of airways inflammation, such as ENO. These researchers determined the relationships between EBT and asthma treatment decision, current control, pulmonary function, and ENO. This was a cross-sectional prospective study on 159 children aged 5 to 16 years attending a pediatric respiratory clinic; EBT was compared with the clinician's decision regarding treatment (decrease, no change, increase), asthma control assessment (controlled, partial, uncontrolled), level of current treatment (according to British Thoracic Society guideline, BTS step), ENO, and spirometry; EBT measurement was feasible in the majority of children (25 of 159 could not perform the test) and correlated weakly with age \( r = 0.33, p < 0.01 \); EBT did not differ significantly between the 3 clinician decision groups \( p = 0.42 \), the 3 asthma control assessment groups \( p = 0.9 \), or the current asthma treatment BTS step \( p = 0.57 \). The authors concluded that EBT measurement was not related to measures of asthma control determined at the clinic. Thus, the routine intermittent monitoring of EBT in children prescribed inhaled corticosteroids who attend asthma clinics cannot be recommended for adjusting anti-inflammatory asthma therapy.

Carpagnano and colleagues (2017) stated that EBT is a new non-invasive method for the study of lung diseases (e.g., asthma, airway inflammation and inflammatory respiratory diseases) with a potential to reach clinical practice. However, few studies are available regarding the validation of this method, and they were mainly derived from small, pediatric populations; thus, the range of normal values is not well-established. These researchers measured EBT values in an Italian population of 298 subjects (mean age of 45.2 ± 15.5 years; 143 men; FEV1, 97.2 % ± 5.8 %; FVC, 98.4 % ± 3.9 %) selected from 867 adult volunteers to define reference values in healthy subjects and analyzed the influence of individual and external variables on this parameter; EBT was measured with an X-halo PRO device to different ambient temperature ranging from 0°C to 38°C. These investigators reported reference values of EBT in healthy white subjects who had never smoked; EBT values were strongly influenced by the external temperature and to a lesser extent according to sex. The authors concluded that in a large population of healthy subjects who never smoked, these data provided reference values for measuring EBT as a basis for future studies; these findings contributed to the promotion of EBT from "bench" to "bedside".

Exhaled Volatile Organic Compounds for Diagnosis and Monitoring of Sarcoidosis

Terrington and colleagues (2019) noted that sarcoidosis is a chronic granulomatous disease of unknown etiology with a variable clinical course and prognosis. There is a growing need to identify non-invasive biomarkers to differentiate between clinical phenotypes, identify those at risk of disease progression and monitor response to treatment. In a systematic review and meta-analysis, these investigators carried examined the utility of breath-based biomarkers in
discriminating sarcoidosis from healthy controls, alongside correlation with existing non-breath based biomarkers used in clinical practice, radiological stage, markers of disease activity and response to treatment. Electronic searches were undertaken during November 2017 using PubMed, Ebsco, Embase and Web of Science to capture relevant studies evaluating breath-based biomarkers in adult patients with sarcoidosis. A total of 353 papers were screened; 21 met the inclusion criteria and assessed 25 different biomarkers alongside volatile organic compounds (VOCs) in exhaled breath gas or condensate. Considerable heterogeneity existed among the studies in terms of participant characteristics, sampling and analytical methods. Elevated biomarkers in sarcoidosis included 8-isoprostan, carbon monoxide, neopterin, TGF-beta1, TNF-alpha, CysLT and several metallic elements including chromium, silicon and nickel; 3 studies exploring VOCs were able to distinguish sarcoidosis from controls. Meta-analysis of 4 studies assessing alveolar NO showed no significant difference between sarcoidosis and healthy controls (2.22 ppb; 95 % CI: -0.83 to 5.27) however, a high degree of heterogeneity was observed with an I2 of 93.4 % (p < 0.001). Inconsistent or statistically insignificant results were observed for correlations between several biomarkers and radiological stage, markers of disease activity or treatment. The authors concluded that the evidence for using breath biomarkers to diagnose and monitor sarcoidosis remains inconclusive with many studies limited by small sample sizes and lack of standardization; VOCs have shown promising potential but further research is needed to evaluate their prognostic role.

CPT Codes / HCPCS Codes / ICD-10 Codes

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":*

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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</thead>
<tbody>
<tr>
<td>Hydrogen breath testing (HBT):</td>
<td></td>
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<tr>
<td>CPT codes covered if selection criteria are met:</td>
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<tr>
<td>91065</td>
<td>Breath hydrogen or methane test (eg, for detection of lactase deficiency, fructose intolerance, bacterial overgrowth, or oro-cecal gastrointestinal transit)</td>
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<td>Other CPT codes related to the CPB:</td>
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<tr>
<td>44388–44408</td>
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<td>45378–45398</td>
<td>Colonoscopy, flexible;</td>
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<td>Encounter for screening for malignant neoplasm of colon</td>
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<td><em>Measurement of exhaled nitric oxide:</em></td>
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<td></td>
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<td>Nitric oxide expired gas determination</td>
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<tr>
<td>D57.00 - D57.819</td>
<td>Sickle-cell disorders [airway]</td>
</tr>
<tr>
<td>I27.0</td>
<td>Primary pulmonary hypertension</td>
</tr>
<tr>
<td>I27.20 - I27.29</td>
<td>Other secondary pulmonary hypertension</td>
</tr>
<tr>
<td>D72.1</td>
<td>Eosinophilia [non-asthmatic bronchitis]</td>
</tr>
<tr>
<td>J30.0 - J37.1</td>
<td>Other diseases of upper respiratory tract [sino-nasal disease]</td>
</tr>
<tr>
<td>J40 - J47.9</td>
<td>Chronic lower respiratory diseases [asthma, lung cancer, and other pulmonary diseases]</td>
</tr>
<tr>
<td>J67.0 - J67.9</td>
<td>Hypersensitivity pneumonitis due to organic dust [asthma, lung cancer, and other pulmonary diseases]</td>
</tr>
<tr>
<td>J68.2</td>
<td>Upper respiratory inflammation due to chemicals, gases, fumes and vapors, not elsewhere classified</td>
</tr>
<tr>
<td>M34.81</td>
<td>Systemic sclerosis with lung involvement</td>
</tr>
<tr>
<td>R05</td>
<td>Cough [chronic, due to non-asthmatic eosinophilic bronchitis]</td>
</tr>
<tr>
<td>R09.81</td>
<td>Nasal congestion</td>
</tr>
<tr>
<td>T70.29x+</td>
<td>Other effects of high altitude [mountain sickness]</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Z12.2</td>
<td>Encounter for screening for malignant neoplasm of respiratory organs</td>
</tr>
</tbody>
</table>

**Measurement of exhaled breath condensate (EBC) pH:**

CPT codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>CPT codes not covered for indications listed in the CPB:</th>
</tr>
</thead>
<tbody>
<tr>
<td>83987</td>
<td>pH; exhaled breath condensate</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):</th>
</tr>
</thead>
<tbody>
<tr>
<td>A15.0</td>
<td>Tuberculosis of lung, larynx, trachea and bronchus</td>
</tr>
<tr>
<td>A15.5</td>
<td></td>
</tr>
<tr>
<td>C34.00</td>
<td>Malignant neoplasm of bronchus and lung [screening or diagnosing lung cancer]</td>
</tr>
<tr>
<td>C34.92</td>
<td></td>
</tr>
<tr>
<td>G47.33</td>
<td>Obstructive sleep apnea (adult) (pediatric)</td>
</tr>
<tr>
<td>J30.0</td>
<td>Other diseases of upper respiratory tract [sino-nasal disease]</td>
</tr>
<tr>
<td>J47.9</td>
<td>Chronic lower respiratory diseases [asthma, lung cancer, and other pulmonary</td>
</tr>
<tr>
<td>J67.0</td>
<td>Hypersensitivity pneumonitis due to organic dust [asthma, lung cancer, and other</td>
</tr>
<tr>
<td>J67.9</td>
<td>pulmonary diseases]</td>
</tr>
<tr>
<td>J68.2</td>
<td>Upper respiratory inflammation due to chemicals, gases, fumes and vapors, not</td>
</tr>
<tr>
<td>K50.00</td>
<td>Crohn's disease [regional enteritis]</td>
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<td>K50.919</td>
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</tr>
</tbody>
</table>

CPT codes not covered for indications listed in the CPB:

**Gastric emptying breath test (GEBT), Exhaled breath temperature (EBT), Exhaled volatile organic compounds** - no specific code:

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):</th>
</tr>
</thead>
<tbody>
<tr>
<td>D86.0</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>D86.89</td>
<td></td>
</tr>
<tr>
<td>I27.0</td>
<td>Primary pulmonary hypertension</td>
</tr>
<tr>
<td>I27.20</td>
<td>Other secondary pulmonary hypertension</td>
</tr>
<tr>
<td>J00 - J99</td>
<td>Respiratory diseases</td>
</tr>
<tr>
<td>K31.84</td>
<td>Gastroparesis</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:

Exhaled Nitric Oxide


87. Dweik RA. Exhaled nitric oxide analysis and applications. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed September 2017.


114. Dinakar C, Chipps BE; Section on Allergy and Immunology; Section on Pediatric Pulmonology and Sleep Medicine. Clinical tools to assess asthma control in children. Pediatrics. 2017;139(1).


Exhaled Breath Condensate pH


Hydrogen Breath Test


Gastric Emptying Breath Test


Exhaled Breath Temperature


Exhaled Volatile Organic Compounds

Amendment to
Aetna Clinical Policy Bulletin Number: 0691
Exhaled Breath Tests

There are no amendments for Medicaid.