Exhaled Nitric Oxide and Exhaled Breath Condensate

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DESCRIPTION

Evaluation of exhaled nitric oxide (NO) and exhaled breath condensate (EBC) are proposed as techniques to diagnose and monitor asthma as well as other respiratory conditions (e.g., chronic cough and chronic obstructive pulmonary disease (COPD)). Existing techniques for monitoring the status of underlying inflammation in the respiratory tract have focused on bronchoscopy, with lavage and biopsy, analysis by induced sputum. Given the cumbersome nature of these techniques and current standards, the ongoing assessment focuses not on the status of the underlying chronic inflammation, but rather on regular assessments of respiratory parameters such as forced expiratory volume in one second (FEV1) and peak flow. Therefore, there has been an interest in noninvasive techniques to assess the underlying pathogenic chronic inflammation as reflected by measurements of inflammatory mediators. Two proposed strategies are the measurement of exhaled nitric oxide (NO) and the evaluation of exhaled breath condensate.

(*Note: There are commercially available devices for measuring NO in expired breath and various laboratory techniques for evaluating components of EBC.*)

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

Several articles note before routine clinical use in the diagnosis and management of respiratory disorders can be considered the following issues must be resolved:

- Standardization of collection and storage techniques
- Effect of dilution of respiratory droplets by water vapor
- Techniques of measuring concentrations of nonvolatile substances in EBC; in most cases these concentrations are very low, which may be at the lower limits of detection of conventional analytic techniques
- Variability in exhaled breath condensate assays for certain substances
- Further investigation of levels of compounds in health and disease

Measurement of NO and EBC has been investigated in the diagnosis and management of asthma. Potential uses in management of asthma include assessing response to anti-inflammatory treatment, monitoring compliance with treatment, and predicting exacerbations. Aside from asthma, they have also been proposed in the management of patients with chronic obstructive pulmonary disease (COPD), cystic fibrosis, allergic rhinitis, and primary ciliary dyskinesia.

The following clinical roles for measurement of nitric oxide and EBC have been investigated in the diagnosis and management of asthma:

- Diagnosis of asthma – as an alternative or adjunct to spirometry;
- Response to anti-inflammatory treatment – declining levels suggest declining inflammation;
- Monitoring compliance of anti-inflammatory treatment – persistent elevation may suggest poor compliance with long-term therapy;
- Detection of corticosteroid resistance – reflected by persistently high nitric oxide levels despite corticosteroid treatment;
- Prediction of exacerbation – increasing levels of nitric oxide may precede onset of clinical symptoms or changes in peak flow values; and
- Dose optimization – to guide dosing of anti-inflammatory medications.

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

Fractional Exhaled Nitric Oxide (FeNO)
One proposed strategy is the measurement of fractional exhaled nitric oxide (FeNO). Nitric oxide (NO) is an important endogenous messenger and inflammatory mediator that is widespread in the human body, with functions including the regulation of peripheral blood flow, platelet function, immune reactions, neurotransmission, and the mediation of inflammation. Patients with asthma have been found to have high levels of FeNO, which decreases with treatment with corticosteroids. In biologic tissues, NO is unstable, limiting measurement. However, in the gas phase, NO is fairly stable, permitting its measurement in exhaled air. Fractional exhaled NO is typically measured during single breath exhalations. First, the subject inspires NO-free air via a mouthpiece until total lung capacity is achieved, followed immediately by exhalation through the mouthpiece into the measuring device. Devices measuring FeNO are commercially available in the U.S. According to a joint statement by the American Thoracic Society and European Respiratory Society (2009), there is a consensus that FeNO is best measured at an exhaled rate of 50 mL per second maintained within 10% for more than 6 seconds at an oral pressure between 5 and 20 cm H2O.1, Results are expressed as the NO concentration in parts per billion, based on the mean of 2 or 3 values.

Asthma
Asthma is characterized by airway inflammation that leads to airway obstruction and hyper-responsiveness, which in turn lead to characteristic clinical symptoms including wheezing, shortness of breath, cough, and chest tightness.

Guidelines for the management of persistent asthma stress the importance of long-term suppression of inflammation using inhaled corticosteroids as primary treatment but may also use other anti-inflammatory drugs.

Type 2 inflammation is present in about half of patients with severe asthma and is characterized by elevated levels of cytokines, eosinophils, and/or increased FeNO. In patients with elevated type 2 biomarkers despite receipt of high dose ICS, type 2 phenotypes should be elucidated to determine the best add-on therapy. Eosinophilic asthma is an asthma phenotype associated with responsiveness to ICS and later onset time. Currently, 4 drugs approved by the U.S. Food and Drug Administration (FDA) are available to treat asthma with an eosinophilic phenotype (mepolizumab, reslizumab, and benralizumab, anti-IL-5 therapies, and dupilumab, an anti-IL-4 receptor alpha subunit antibody), which makes the identification of eosinophilic asthma of potential clinical importance. Studies demonstrating the efficacy of these treatments generally used blood or sputum eosinophilic measurements to determine eligibility when eligibility was limited to eosinophilic asthma.

Severe allergic asthma is another asthma phenotype where the underlying inflammation is activated by allergens or other irritants. Currently, there is 1 drug approved by the FDA for moderate-to-severe persistent asthma with a positive skin test or in vitro reactivity to a perennial aeroallergen: omalizumab, an anti-IgE therapy.

(2017) Agency for Healthcare Research and Quality (AHRQ) includes the following key messages in the clinical utility of fractional exhaled nitric oxide (FeNO) in asthma management: evidence summary

- Depending on the FeNO cutoff, the likelihood of having asthma in people ages 5 years and older increases by 2.8 to 7.0 times given a positive FeNO test result.
- FeNO is modestly more accurate in diagnosing steroid-naïve asthmatics, children (ages 5-18), and nonsmokers than other patients suspected to have asthma.
- FeNO results can predict which patients will respond to inhaled corticosteroid therapy.
- Using FeNO to manage long-term control medications including dose titration, weaning, and monitoring of adherence, reduces the frequency of exacerbations.
- There is insufficient evidence supporting the use of FeNO in children (ages 0-4) for predicting a future diagnosis of asthma.

Conclusions. This systematic review provides the diagnostic accuracy measures of FeNO 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, and treatment adherence. At this time, evidence is insufficient to support the measurement of FeNO in children under the age of 5 as a means for predicting a future diagnosis of asthma.

Exhaled Breath Condensate: Clinical Context and Test Purpose

The purpose of exhaled breath condensate (EBC) testing in individuals who have symptoms of asthma or other respiratory conditions is to aid in diagnosis and treatment decisions. To evaluate the test performance, the position on the diagnostic or management pathway as well as the specification of whether EBC is meant to be used as a triage, add-on, or replacement test with respect to existing diagnostic tests or procedures are needed. For asthma, potential uses of EBC may be similar to those listed for FeNO.

The published literature suggests that EBC is at an earlier stage of development than FeNO. A review by Davis et al (2012) noted that this is due, in part, to the fact that FeNO is a single biomarker and EBC is a matrix that contains so many potential biomarkers that research efforts have thus far been spread across numerous markers. In addition, several review articles have noted that before routine clinical use in the diagnosis and management of respiratory disorders can be considered, the following issues must be resolved:

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

The question addressed in this evidence review is: Does measurement of EBC improve the net health outcome in individuals with suspected or confirmed respiratory disorders?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with suspected or confirmed respiratory conditions. A precise explication of the population of interest depends on the position of the EBC test in the diagnostic or management pathway.

Interventions

The test being considered is measurement of EBC.

Comparators

The following practice is currently being used to diagnose and treat respiratory disorders: standard clinical diagnosis and management. The appropriate comparator depends on the position of the EBC in the diagnostic or management pathway.

Outcomes
The general outcomes of interest are test validity, symptoms, change in disease status, morbid events, and functional outcomes. Specific o utcomes of interest might be diagnostic accuracy, rates of exacerbations, symptoms, hospitalizations, use of medications, and quality of life.

(2017) Blue Cross Blue Shield Association (BCBSA) sought clinical input was to help determine whether measurement of fractional exhaled nitric oxide (FeNO) and exhaled breath condensate in the diagnosis and management of individuals with respiratory disorders would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from three physician-level respondents identified through two specialty societies including physicians with academic medical center affiliations. For individuals who have suspected or confirmed respiratory disorders who receive measurement of FeNO or exhaled breath condensate, clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice. For both FeNO and exhaled breath condensate, limitations of the published evidence preclude determining the effects of the technology on net health outcome.

Exhaled Breath Condensate Markers of Asthma
(2016) Aldakheel et al. published a qualitative systematic review assessing the relations between adult asthma and oxidative stress markers and pH in EBC. Sixteen studies met the inclusion criteria and compared 832 patients with asthma and 556 healthy controls. In addition to measuring pH (n=6 studies), studies evaluated nitrite (n=1), nitrate (n=1), total NO (n=3), hydrogen peroxide (n=8), and 8-isoprostane (n=4). Most studies were cross-sectional (n=11) and the rest were longitudinal (n=5); 1 was double-blinded. A variety of EBC collecting devices were used, with a custom-made condensing device used in 7 studies. The association between pH or NO and asthma varied between studies, and in 1 study, the pH in the same subjects varied by collection device. Concentrations of hydrogen peroxide and 8-isoprostane were significantly higher in patients with asthma in most studies. Reviewers concluded EBC collection of oxidative stress markers is relatively robust despite variability in techniques, but to become a useful clinical tool, studies were needed to evaluate the ability of EBC biomarkers to predict future asthma exacerbations and tailor asthma treatment.

(2013) Thomas et al. conducted a systematic review of studies assessing the association between components of EBC and pediatric asthma. Reviewers identified 46 articles that measured at least 1 EBC marker in asthma, allergy, and atopy in children up to age 18 years. Most studies were cross-sectional, and there was wide variation in the definitions used to identify children with asthma and the collection devices and assays for EBC components. Studies in the review evaluated multiple specific EBC components, including hydrogen ions (pH), NO, glutathione and aldehydes, hydrogen peroxide, eicosanoids (including prostaglandins and leukotrienes), and cytokines (including interleukins in the Th2 pathway and interferon-gamma). Reviewers noted that hydrogen

ions and markers of oxidative stress, including hydrogen peroxide and oxides of nitrogen, were most consistently associated with asthma severity. Eicosanoids and cytokines demonstrated more variable results but were frequently elevated in the EBC of patients with asthma. Overall, reviewers concluded while EBC has the potential to aid diagnosis of asthma and to evaluate inflammation in pediatric asthma, further studies on EBC collection and interpretation techniques are needed.

Exhaled Breath Condensate Markers of Asthma Severity

(2011) Liu et al. completed a study not included in the systematic review of adults with asthma is by who reported on the Severe Asthma Research Program, a multicenter study funded by the NIH. This study had the largest sample size (N=572 patients). Study participants included 250 patients with severe asthma, 291 patients with nonsevere asthma, and 51 healthy controls. Samples of EBC were collected at baseline and analyzed for pH levels. Overall, the median pH of the 2 asthma groups combined (7.94) did not differ significantly from the median pH of controls (7.90; p=.80). However, the median pH of patients with nonsevere asthma (7.90) was significantly lower than that for patients with severe asthma (8.02; p not reported). The authors concluded; asthma is a complex syndrome. Subjects who are not experiencing an exacerbation but have low EBC pH appear to be a unique subpopulation.

Exhaled Breath Condensate Markers of Asthma Control

(2014) Navratil et al. evaluated the relation between EBC and asthma control in a cross-sectional study of 103 children (age range, 6 to 18 years) with asthma. Subjects were enrolled from a single clinic, had an established asthma diagnosis, and were on a stable dosage of their asthma treatment. Patients were considered to have controlled (n=50 [48.5%]) or uncontrolled asthma (n=53 [52.5%]) based on Global Initiative for Asthma guidelines. Controlled and uncontrolled asthmatics differed significantly in EBC urates (uncontrolled median EBC urate, 10 µmol/L vs controlled median EBC urate, 45 µmol/L; p<.001); EBC pH (uncontrolled mean pH, 7.2 vs controlled mean pH, 7.33; p=.002); and EBC temperature (uncontrolled mean EBT, 34.26°C vs controlled mean EBT, 33.9°C; p=.014). Also, EBC urate concentration was significantly associated with time from last exacerbation (p<.001), Asthma Control Test results (p<.001), and short-acting bronchodilator use (p<.001) within the entire cohort. In conclusion, different markers in condensate are of an additional value to exhaled nitric oxide and are needed in non-invasive inflammometry. They could be useful to diagnose asthma and to indicate asthma control and severity in childhood.

Exhaled Breath Condensate Components as Markers of Respiratory Disorders Other Than Asthma

(2010) Antus et al. evaluated EBC in 58 hospitalized patients (20 with asthma, 38 with COPD) and 36 healthy controls (18 smokers, 18 nonsmokers). The EBC pH was significantly lower in patients with asthma exacerbations (all nonsmokers) at hospital admission (6.2) than in nonsmoking controls (6.4; p<.001). The EBC pH in asthma patients increased during the hospital stay and was similar to that of nonsmoking controls at discharge. Contrary to investigators' expectations, EBC pH values in ex-smoking

COPD patients (n=17) did not differ significantly from nonsmoking controls, either at hospital admission or discharge. Similarly, pH values in EBC samples from smoking COPD patients (n=21) at admission and discharge did not differ significantly from smoking controls.

Exhaled Breath Condensate-Guided Treatment Decisions for Patients with Asthma or Other Respiratory Disorders

No controlled studies were identified evaluating the role of EBC tests in the management of asthma or other respiratory disorders.

Section Summary: Exhaled Breath Condensate

There is considerable variability in the particular EBC components measured and criteria for standardized measurements. There is also limited evidence on the use of EBC for determining asthma severity, diagnosing other respiratory conditions, or guiding treatment decisions for asthma or other respiratory conditions. The available evidence does not support conclusions on the utility of EBC for any indication.

Summary of Evidence: Exhaled Breath Condensate

For individuals who have suspected asthma who receive measurement of FeNO for diagnosis, the evidence includes multiple retrospective and prospective studies of diagnostic accuracy, along with systematic reviews of those studies. Relevant outcomes are test validity, symptoms, change in disease status, morbid events, and functional outcomes. There are multiple reports on the sensitivity and specificity of FeNO in asthma diagnosis; however, most studies are in the setting of patients with asthma symptoms without previous testing (or with unclear previous testing), which is unlikely to be how the test is used in a U.S. setting. The available evidence is limited by variability in FeNO cutoff levels used to diagnose asthma, lack of data on performance characteristics in challenging diagnostic settings, and lack of data on the incremental value of adding FeNO to existing diagnostic algorithms from studies with concurrent controls. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have asthma who receive medication management directed by FeNO, the evidence includes diagnostic accuracy studies, multiple RCTs, and systematic reviews of those trials. Relevant outcomes are symptoms, change in disease status, morbid events, and functional outcomes. The available RCTs evaluating the use of FeNO tests to guide step-up/step-down therapy in patients have not consistently found improvement in health outcomes. Two Cochrane reviews from 2016, 1 on adults and the other on children, found that FeNO-guided asthma management to guide step-up/step-down therapy reduced the number of individuals who had more than 1 exacerbation in children but not in adults compared with guidelines-driven therapy. However, it had no impact on day-to-day symptoms or hospitalizations. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.
For individuals who have severe asthma who receive measurement of FeNO to select treatment, the evidence includes diagnostic accuracy studies and subgroup analyses of

RCTs and observational studies. Relevant outcomes are test validity, symptoms, change in disease status, morbid events, and functional outcomes. For the use of FeNO to identify eosinophilic asthma for the purpose of selecting patients for therapy with anti-IL-5 therapy or an anti-IL-4 and -13 monoclonal antibody, subgroup analyses of RCTs are available. The evidence that points toward an interaction between baseline FeNO and treatment for the outcome of response suggests that there may be a quantitative but not necessarily a qualitative interaction between baseline FeNO and anti-IL-4 treatment (dupilumab), i.e., it is unclear if baseline FeNO can identify a group for whom there is no benefit from dupilumab. Similarly, a subgroup analysis for mepolizumab suggested a more pronounced effect compared to placebo in those with elevated levels of both blood eosinophils and FeNO. However, outcomes were not reported stratified based on FeNO alone precluding insight into the utility of using FeNO to predict response to treatment. For use of FeNO to predict response to therapy for patients with other severe asthma phenotypes, such as the allergic subtype, where anti-IgE therapy is used, a subgroup analysis of an RCT is available. Subgroup analysis of omalizumab showed an association with more favorable outcomes in patients with high FeNO levels, but as with dupilumab, a qualitative interaction has not been established. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.
For individuals who have suspected or confirmed respiratory disorders other than asthma who receive measurement of FeNO, the evidence includes a crossover trial, a pilot study, and observational studies. Relevant outcomes are test validity, symptoms, change in disease status, morbid events, and functional outcomes. The available evidence assessing the use of FeNO for respiratory disorders other than asthma is limited by heterogeneity in the conditions evaluated and uncertainty about how the test fits in defined clinical management pathways. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected or confirmed respiratory disorders who receive measurement of EBC, the evidence includes observational studies reporting on the association between various EBC components and disease severity. Relevant outcomes are test validity, symptoms, change in disease status, morbid events, and functional outcomes. There is considerable variability in the particular EBC components measured and criteria for standardized measurements. Also, there is limited evidence on the use of EBC for determining asthma severity, diagnosing other respiratory conditions, or guiding treatment decisions for asthma or other respiratory conditions. The available published evidence does not support conclusions on the utility of EBC for any indication. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Fractional Exhaled Nitric Oxide (FeNO) for Asthma

Clinical Context and Test Purpose
The purpose of FeNO testing and to aid in making treatment decisions in patients who have suspected or diagnosed asthma is to aid in the diagnosis and management of asthma.

National Heart, Lung, and Blood Institute (NHLBI) guidelines have suggested clinicians confirm the following to establish the diagnosis and management of asthma: (1) presence of episodic symptoms of airflow obstruction or hyperresponsiveness; (2) reversibility of airflow obstruction; and (3) exclusion of alternative diagnoses. In children younger than 5, spirometry often cannot be performed, and a trial of asthma medications may help establish the diagnosis.

The NHLBI guidelines have also suggested that management of patients with asthma includes routine monitoring of symptoms and lung function, patient education, controlling environmental trigger factors, controlling comorbid conditions, and pharmacologic therapy.

U.S. guidelines do not support FeNO as a replacement for spirometry when spirometry can be used.

Although patient education and identification and avoidance of asthma triggers are critical components of successful asthma management, this section focuses on pharmacologic maintenance therapy. In treatment-naive patients, the severity of symptoms is assessed and categorized as intermittent, mild, moderate, or severe based on reported symptoms, lung function, and exacerbations requiring systemic glucocorticoids. Treatment is initially based on asthma severity and then medications are increased or decreased in a stepwise approach ("step-up/step-down") based on the assessment of asthma control. The components of control are also described in guidelines and focus on impairment as determined by patient report or a validated questionnaire, a current forced expiratory volume in 1 second (FEV1) or peak flow and estimates of risk.

Populations
The relevant population of interest is individuals with a suspected or known asthma. The specific population of interest depends on when of the FeNO test is completed in the diagnosis or management process.

Interventions
The intervention being considered is medication management directed by FeNO testing and measurement of FeNO to select treatment. Several devices measuring FeNO are commercially available in the U.S.

Fractional exhaled NO measurement may be easier to perform than other tests used for diagnosing asthma, particularly in children. To measure FeNO, the patient exhales directly into the analyzer or container at a constant flow for several seconds so that the mean FeNO value over a 3 second plateau can be recorded.

Results are expressed as the NO concentration in parts per billion (ppb), based on the mean of 2 or 3 values.

Comparators
The following practice is currently being used to diagnose and treat asthma: standard clinical diagnosis. The appropriate comparator depends on the position of the FeNO test in the point of the diagnostic pathway asthma is being diagnosed/managed. At times appropriate comparator would be lung function tests (e.g., spirometry) given that FeNO would be a replacement for spirometry. In additional scenarios, the appropriate comparators are other tests or procedures used to rule in or rule out asthma after spirometry such as additional pulmonary function testing, bronchoprovocation testing, or tests used to rule-in other respiratory conditions.

There is no definitive reference standard for diagnosing asthma.

Currently to treat asthma and severe asthma the appropriate comparator depends on the position of the FeNO in the diagnostic pathway. At times the appropriate comparator would be a guidelines-driven assessment of control and therapy. One could also consider appropriate comparators are blood and sputum assessment of eosinophils.

Once a severe asthma diagnosis is established, consideration of appropriate add-on biologic targeted treatments is required. The appropriate comparator to predict response to therapy would be the guidelines-driven empiric selection of a type 2 inflammation-targeted biologic.

Outcomes
The general outcomes of interest are test validity, symptoms, change in disease status, morbid events, and functional outcomes. The performance characteristics of most interest depend on whether the test is used to rule in or rule out asthma or other respiratory disorders. The performance characteristics provide data needed to infer rates of true positives, true negatives, false positives, and false negatives.

Beneficial outcomes that can be a consequence of a true-positive FeNO test result are the avoidance of other diagnostic testing or treatment, which could reduce resource utilization and exposure to adverse events of other testing modalities, as well as undergoing correct treatment, which would lead to control of respiratory symptoms. The consequence of a true-negative result is avoiding unnecessary or incorrect treatment and other diagnostic testing and limiting exposure to their adverse events.

The harmful outcomes that can be a consequence of a false-positive or -negative FeNO test result are incorrect or unnecessary treatment or unnecessary additional diagnostic testing.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Fractional Exhaled Nitric Oxide in Asthma Diagnosis
(2018) Tang et al. completed a comparative study with clinical features in patients of cough variant asthma with normal and high level of exhaled fractional nitric oxide. The clinical history and pulmonary function data from 99 patients with newly diagnosed CVA were collected. Results noted newly diagnosed subjects with CVA were divided into a high FeNO group (FeNO value over or equal to 25 ppb, n = 52) and a normal FeNO group (FeNO lower than 25 ppb, n = 47). There were more patients with coexistent allergic rhinitis or with family histories of allergic diseases in the high FeNO group. More patients in the high FeNO group reported that their chronic cough was triggered by allergen exposure. In the high FeNO group, the patients were younger than in the normal FeNO group. It was shown that baseline lung function tests were normal in all subjects, apart from a reduced midexpiratory flow rate (FEF25-75). There was a significant decrease in FEF25-75 in the high FeNO group compared with the normal FeNO group. No difference was found in the PD20 or the maximal FEV1 drop between the two groups. The multi-factor logistic regression analysis showed that concomitant with allergic rhinitis was the high-risk factor of a high FeNO in these subjects with CVA (OR = 5.03, 95% CI, 1.88-13.49). In conclusion, CVA patients showed heterogeneity according to FeNO level. Patients with high FeNO level are more likely to experience symptoms associated with allergies.

(2018) Wang et al. completed a systemic review and meta-analyses on the diagnostic accuracy of fractional exhaled nitric oxide testing in asthma. It included 43 studies with a total of 13,747 patients. In adults, using FeNO cutoffs of less than 20, 20 to 29, 30 to 39, and 40 or more parts per billion, FeNO testing had sensitivities of 0.80, 0.69, 0.53, and 0.41, respectively, and specificities of 0.64, 0.78, 0.85, and 0.93, respectively. In children, using FeNO cutoffs of less than 20 and 20 to 29 parts per billion, FeNO testing had sensitivities of 0.78 and 0.61, respectively, and specificities of 0.79 and 0.89, respectively. Depending on the FeNO cutoff, the posttest odds of having asthma with a positive FeNO test result increased by 2.80- to 7.00-fold. Diagnostic accuracy was modestly better in corticosteroid-naive asthmatics, children, and nonsmokers than in the overall population. In conclusion fractional exhaled nitric oxide measurement has moderate accuracy to diagnose asthma in individuals aged 5 years and older. Test performance may be modestly better in corticosteroid-naive asthmatics, children, and nonsmokers than in the general population with suspected asthma.

(2017) Blue Cross Blue Shield Association (BCBSA) sought clinical input was to help determine whether measurement of fractional exhaled nitric oxide (FeNO) and exhaled breath condensate in the diagnosis and management of individuals with respiratory disorders would provide a clinically meaningful improvement in net health outcome and

whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from three physician-level respondents identified through two specialty societies including physicians with academic medical center affiliations. For individuals who have suspected or confirmed respiratory disorders who receive measurement of FeNO or exhaled breath condensate, clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice. For both FeNO and exhaled breath condensate, limitations of the published evidence preclude determining the effects of the technology on net health outcome.

(2017) Harnan et al. completed a systemic review on exhaled nitric oxide in the diagnosis of asthma in adults. Records were included if they recruited patients with the symptoms of asthma; used a single set of inclusion criteria; measured FE NO50 in accordance with American Thoracic Society guidelines, 2005 (off-line excluded); reported/allowed calculation of true-positive, true-negative, false-positive and false-negative patients as classified against any reference standard. Study quality was assessed using QUADAS II. Meta-analysis was planned where clinical study heterogeneity allowed. Rule-in and rule-out uses of FE NO were considered. A total of 4861 records were identified originally and 1312 in an update. Twenty-seven studies were included. Heterogeneity precluded meta-analysis. Results varied even within subgroups of studies. Cut-off values for the best sum of sensitivity and specificity varied from 12 to 55 p.p.b. but did not produce high accuracy. 100% sensitivity or 100% specificity was reported by some studies indicating potential use as a rule-in or rule-out strategy. In conclusion FE NO50 had variable diagnostic accuracy even within subgroups of studies with similar characteristics. Diagnostic accuracy, optimal cut-off values and best position for FE NO50 within a pathway remain poorly evidenced.

(2017) Karrasch et al. completed a systemic review for the accuracy of FeNO for diagnosing asthma with 26 studies with 4518 participants (median 113) were included. Risk of bias was considered low for six of seven items in five studies and for five items in seven studies. The overall sensitivity in the meta-analysis was 0.65 (95% CI 0.58 to 0.72), the overall specificity 0.82 (0.76 to 0.86), the diagnostic OR 9.23 (6.55 to 13.01) and the area under the curve 0.80 (0.77 to 0.85). In meta-regression analyses, higher cut-off values were associated with increasing specificity (OR 1.46 per 10 ppb increase in cut-off) while there was no association with sensitivity. Sensitivities varied significantly within the different FENO devices, but not specificities. Neither prevalence, age, use of bronchoprovocation in >90% of participants or as exclusive reference standard test, nor risk of bias were significantly associated with diagnostic accuracy. In conclusion there appears to be a fair accuracy of FENO for making the diagnosis of asthma. The overall specificity was higher than sensitivity, which indicates a higher diagnostic potential for ruling in than for ruling out the diagnosis of asthma.

(2017) Wang et al. completed a review on the clinical utility of fractional exhaled nitric oxide in asthma management in people aged 5 years and older with asthma; and the ability of FeNO measured at age 4 years or younger to predict a future diagnosis of

asthma. They included 175 studies. In adults (>18) and children (ages 5–18), 43 studies showed that FeNO results increased the odds of correctly diagnosing asthma between 5.85 and16.95 fold. Using FeNO cutoffs of <20, 20–30, 30–40, ≥40 part per billion (ppb); respectively, FeNO testing had sensitivities of 0.79, 0.64, 0.53 and 0.41; and specificities of 0.72, 0.81, 0.84, 0.94 (Strength of Evidence (SOE): Moderate). Depending on the FeNO cutoff, the posttest odds of having asthma given a positive FeNO test result increased by 2.80 to 7.00-fold. Diagnostic accuracy was modestly better in steroid-naïve asthmatics, children and nonsmokers than the overall population. Data from 58 studies showed that in adults and children (age 5–18), FeNO levels had a weak association with asthma control and the risk of subsequent and prior exacerbations (SOE: Low). Elevated FeNO levels were likely more predictive of exacerbation risk in those with atopy. In adults and children with acute asthma exacerbations, FeNO levels did not correlate with exacerbation severity and were poorly reproducible. In children and adolescents (ages 5–18), FeNO levels were inversely associated with adherence to inhaled corticosteroids (SOE: Low). Data from 14 randomized controlled trials showed that asthma management following algorithms that included FeNO monitoring, compared to no FeNO, reduced the risk of exacerbations (SOE: High) but did not affect other outcomes such as hospitalization, or quality of life. FeNO testing may identify patients who were more likely to respond to inhaled corticosteroids (SOE: Low). FeNO testing predicted exacerbations in patients undergoing ICS reduction or withdrawal. Data from 9 studies showed that althoughFeNO levels in children at age 0–4 years correlated with the Asthma Predictive Index and wheezing (SOE: Low), there was insufficient evidence to determine if FeNO results at age 0–4 years can reliably predict a future asthma diagnosis.

In conclusion, this systematic review provides the diagnostic accuracy measures of FeNO 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, and treatment adherence. At this time, evidence is insufficient to support the measurement of FeNO in children under the age of 5 as a means for predicting a future diagnosis of asthma.

Section Summary: Fractional Exhaled Nitric Oxide in Asthma Diagnosis
Systematic reviews of diagnostic accuracy of FeNO for asthma have assessed numerous observational studies with varying reference standards, cutoff values, study quality, and positions in the diagnostic pathway. The most useful position for FeNO in the diagnostic pathway is likely in the diagnosis of difficult cases (i.e., when spirometry to assess obstruction or reversibility and/or methacholine challenge testing is negative but suspicion for asthma remains). Very few studies have been conducted in those settings and populations; therefore, diagnostic accuracy is not well-characterized. Data on the incremental value of FeNO compared with spirometry or other tests and algorithms are limited.

Fractional Exhaled Nitric Oxide in Asthma Management

(2021) Heaney et al. completed a single-blind, parallel group, randomized controlled trial in adults (18–80 years of age) with severe asthma (at treatment steps 4 and 5 of the Global Initiative for Asthma) and FENO of less than 45 parts per billion at 12 specialist severe asthma centers across England, Scotland, and Northern Ireland. Patients were randomly assigned (4:1) to either the biomarker strategy group or the control group by an online electronic case-report form, in blocks of ten, stratified by asthma control and use of rescue systemic steroids in the previous year. Patients were masked to study group allocation throughout the entirety of the study. Patients attended clinic every 8 weeks, with treatment adjustment following automated treatment-group-specific algorithms: those in the biomarker strategy group received a default advisory to maintain treatment and those in the control group had their treatment adjusted according to the steps indicated by the trial algorithm. The primary outcome was the proportion of patients with corticosteroid dose reduction at week 48, in the intention-to-treat (ITT) population. Secondary outcomes were inhaled corticosteroid (ICS) dose at the end of the study; cumulative dose of ICS during the study; proportion of patients on maintenance oral corticosteroids (OCS) at study end; rate of protocol-defined severe exacerbations per patient year; time to first severe exacerbation; number of hospital admissions for asthma; changes in lung function, Asthma Control Questionnaire-7 score, Asthma Quality of Life Questionnaire score, and T2 biomarkers from baseline to week 48; and whether patients declined to progress to OCS. A secondary aim of our study was to establish the proportion of patients with severe asthma in whom T2 biomarkers remained low when corticosteroid therapy was decreased to a minimum ICS dose. This study is registered with ClinicalTrials.gov, NCT02717689 and has been completed. Of 549 patients assessed, 301 patients were included in the ITT population and were randomly assigned to the biomarker strategy group (n=240) or to the control group (n=61). 28·4% of patients in the biomarker strategy group were on a lower corticosteroid dose at week 48 compared with 18·5% of patients in the control group (adjusted odds ratio [aOR] 1·71 [95% CI 0·80–3·63]; p=0·17). In the per-protocol (PP) population (n=121), a significantly greater proportion of patients were on a lower corticosteroid dose at week 48 in the biomarker strategy group (30·7% of patients) compared with the control group (5·0% of patients; aOR 11·48 [95% CI 1·35–97·83]; p=0·026). Patient choice to not follow treatment advice was the principle reason for loss to PP analysis. There was no difference in secondary outcomes between study groups and no loss of asthma control among patients in the biomarker strategy group who reduced their corticosteroid dose. In conclusion, biomarker-based corticosteroid adjustment did not result in a greater proportion of patients reducing corticosteroid dose versus control. Understanding the reasons for patients not following treatment advice in both treatment strategies is an important area for future research. The prevalence of T2 biomarker-low severe asthma was low. Important limitations to noted are key exacerbation outcomes not reported and less than a 1 year follow up were not reported.

(2016) Petsky et al. completed a systemic 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. They viewed results of searches against predetermined criteria for inclusion. We independently selected relevant studies in duplicate. Two review authors independently assessed trial quality and extracted data. We contacted study authors for further information, receiving responses from four. They 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 randomised 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, favouring 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). However, we did not find a difference between the groups for exacerbations requiring hospitalisation (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). They 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 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. Further RCTs encompassing different asthma severity, ethnic groups in less affluent settings, and taking into account different FeNO cutoffs are required.

(2016) Pesky et al. completed a systemic review to evaluate the efficacy of tailoring asthma interventions based on fractional 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 children. They reviewed results of searches against predetermined criteria for inclusion. Two review authors independently selected relevant studies, assessed trial quality and extracted data. We contacted study authors for further information with responses provided from three. The review included nine studies; these studies differed in a variety of ways including definition of asthma exacerbations, FeNO cut-off levels used (12 parts per billion (ppb) to 30 ppb), the way in which FeNO was used to adjust therapy and duration of study (6 to 12 months). Of 1426 children randomised, 1329 completed the studies. The inclusion criteria for the participants in each study varied but all had a diagnosis of asthma. There was a significant difference in the number of children having one or more asthma exacerbations over the study period, they were significantly lower in the FeNO group in comparison to the control group (odds ratio (OR) 0.58, 95% confidence interval (CI) 0.45 to 0.75; 1279 participants; 8 studies). The number needed to treat for an additional beneficial outcome (NNTB) over 52 weeks was 9 (95% CI 6 to 15). There was no difference between the groups when comparing exacerbation rates (mean difference (MD) -0.37, 95% CI -0.8 to 0.06; 736 participants; 4 studies; I2 = 67%). The number of children in the FeNO group requiring oral corticosteroid courses was lower in comparison to the children in the control group (OR 0.63, 95% CI 0.48 to 0.83; 1169 participants; 7 studies; I2 = 0%). There was no statistically significant difference between the groups for exacerbations requiring hospitalisation (OR 0.75, 95% CI 0.41 to 1.36; 1110 participants; 6 studies; I2 = 0%). There were no significant differences between the groups for any of the secondary outcomes (forced expiratory volume in one second (FEV1), FeNO levels, symptom scores or inhaled corticosteroid doses at final visit). The included studies recorded no adverse events.Three studies had inadequate blinding and were thus considered to have a high risk of bias. However, when these studies were removed in subgroup analysis, the difference between the groups for the primary outcome (exacerbations) remained statistically significant. The GRADE quality of the evidence ranged from moderate (for the outcome 'Number of participants who had one or more exacerbations over the study period') to very low (for the outcome 'Exacerbation rates'), based on lack of blinding, statistical heterogeneity and imprecision.

The authors' concluded tailoring asthma medications based on FeNO levels (in comparison with primarily guideline management) significantly decreased the number of children who had one or more exacerbations over the study period but did not impact on the day-to-day clinical symptoms or inhaled corticosteroid doses. Therefore, the use of FeNO to guide asthma therapy in children may be beneficial in a subset of children, it cannot be universally recommended for all children with asthma. Further RCTs need to be conducted and these should encompass different asthma severities, different settings including primary care and less affluent settings, and consider different FeNO cut-offs.

(2014) Peirsman et al. completed a RTC for exhaled nitric ocide 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. 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). Next, the evolution of inhaled corticosteroid doses between visits 1 and 5 (median change (interquartile range)) showed a significant increase of +100 µg (0, +400) in the FeNO group and a change of 0 µg (-200, +80) in the clinical group (P = 0.016). In conclusion 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.

(2013) Pike et al. completed a randomized controlled trial Exhaled nitric oxide monitoring does not reduce exacerbation frequency or inhaled corticosteroid dose in pediatric asthma. They included children aged 6–17 years with moderate to severe asthma were recruited. Their asthma was stabilized before randomization to FENO-driven therapy or to a standard management group where therapy was driven by conventional markers of asthma control. ICS or long-acting bronchodilator therapies were altered according to FENO levels in combination with reported symptoms in the FENO group. Participants were assessed 2 monthly for 12 months. ICS dose and exacerbation frequency change were compared between groups in an intention to treat analysis. Ninety children were randomized. No difference was found between the two groups in either change in corticosteroid dose or exacerbation frequency. Results were similar in a planned secondary analysis of atopic asthmatics. The authors conclusion were FENO-guided ICS titration does not appear to reduce corticosteroid usage or exacerbation frequency in pediatric outpatients with moderate to severe asthma. This may reflect limitations in FENO-driven management algorithms, as there are now concerns that FENO levels relate to atopy as much as they relate to asthma control. Please note all key outcomes were not reported and there was less than a 1 year follow up.

(2012) Calhoun et al. completed a randomized controlled trial to determine if adjustment of inhaled corticosteroid therapy based on exhaled nitric oxide or day-to-day symptoms is superior to guideline-informed, physician assessment-based adjustment in preventing treatment failure in adults with mild to moderate asthma.
The RCT included parallel, 3-group, placebo-controlled, multiply-blinded trial of 342 adults with mild to moderate asthma controlled by low-dose inhaled corticosteroid therapy (n = 114 assigned to physician assessment-based adjustment [101 completed], n = 115 to biomarker-based [exhaled nitric oxide] adjustment [92 completed], and n = 113 to symptom-based adjustment [97 completed]), the Best Adjustment Strategy for Asthma in the Long Term (BASALT) trial was conducted by the Asthma Clinical Research Network at 10 academic medical centers in the United States for 9 months between June 2007 and July 2010. For physician assessment-based adjustment and biomarker-based (exhaled nitric oxide) 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.

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 biomarker-based adjustment, and 15% (97.5% CI, 9%-25%; 16 events) for symptom-based adjustment. The hazard ratio for physician assessment-based adjustment vs biomarker-based adjustment was 1.2 (97.5% CI, 0.6-2.3). The hazard ratio for physician assessment-based adjustment vs symptom-based adjustment was 1.6 (97.5% CI, 0.8-3.3). In conclusion, among adults with mild to moderate persistent asthma controlled with low-dose inhaled corticosteroid therapy, the use of either biomarker-based or symptom-based adjustment of inhaled corticosteroids was not superior to physician assessment-based adjustment of inhaled corticosteroids in time to treatment failure. Important limitations to note are key exacerbation outcomes were not reported and Less than 1 y follow-up were reported.

(2011) Hashimoto et al. completed a pragmatic RCT to investigate whether an internet-based management tool including home monitoring of symptoms, lung function and fraction of exhaled nitric oxide (FE(NO)) facilitates tapering of oral corticosteroids and leads to reduction of corticosteroid consumption without worsening asthma control or asthma-related quality of life. 95 adults with prednisone-dependent asthma from six pulmonary outpatient clinics were allocated to two tapering strategies: according to conventional treatment (n=43) or guided by a novel internet-based monitoring system (internet strategy) (n=52). Primary outcomes were cumulative sparing of prednisone, asthma control and asthma-related quality of life. Secondary outcomes were forced expiratory volume in 1 s (FEV1), exacerbations, hospitalisations and patient's satisfaction with the tapering strategy. The results noted median cumulative sparing of prednisone was 205 (25-75th percentile -221 to 777) mg in the internet strategy group compared with 0 (-497 to 282) mg in the conventional treatment group ($p = 0.02$). Changes in prednisone dose (mixed effect regression model) from baseline were -4.79 mg/day and +1.59 mg/day, respectively ($p < 0.001$). Asthma control, asthma-related quality of life, FEV1, exacerbations, hospitalizations and satisfaction with the strategy were not different between groups. In conclusion an internet-based management tool including home monitoring of symptoms, lung function and FE(NO) in severe asthma is superior to conventional treatment in reducing total corticosteroid consumption without compromising asthma control or asthma-related quality of life. There is very little information available in the literature on how to taper oral corticosteroids safely in asthma after prolonged use. The adjustment of ICS guided by objective parameters of airway disease has been addressed in several other studies. The use of airway responsiveness, eosinophils in induced sputum and FENO appear to be superior over usual care in most studies, although for FENO there has been some controversy. In contrast to these previous studies, the aim of the study was not to evaluate the use of ACQ or FENO in adjusting the corticosteroid dose but to use these measures as part of an integrated multifaceted approach including internet-supported monitoring and continuous supervision by a specialized asthma nurse. Netherlands Trial Register number 1146.

Section Summary: Efficacy of Fractional Exhaled Nitric Oxide-Guided Medication Management of Asthma

The most direct evidence related to the use of FeNO in the management of asthma comes from RCTs and systematic reviews of these RCTs comparing the management of asthma with and without FeNO. These studies are heterogeneous in terms of patient populations, FeNO cutoff levels, and protocols for managing patients in the control groups.

Two Cochrane reviews from 2016, 1 on adults and a second on children, found that FeNO-guided asthma management reduced the number of individuals who had more than one exacerbation but had no impact on day-to-day symptoms or hospitalizations. In adults, the benefit for FeNO on exacerbations was attenuated and no longer statistically significant when only studies using guidelines-driven controls were included.

Fractional exhaled NO-guided management significantly decreased exacerbations (and exacerbations requiring OCS) compared with guidelines-driven controls in children. In the Cochrane meta-analysis, the estimated pooled MD in rate of exacerbations was -0.27 (95% CI, -0.49 to -0.06) favoring FeNO and the estimated pooled OR for the percentage of patients with 1 or more exacerbations was 0.67 (95% CI, 0.51 to 0.90). The Szefler et al (2008) RCT, which was by far the largest RCT (N=546) and funded by NIH, used guidelines-driven control and a definition of exacerbation consistent with NIH and ATS recommendations .The percentage with 1 or more exacerbation in this trial was not statistically significant (MD, -6.5%; 95% CI, -14% to 1%; p=.11) but the percentage requiring OCS was statistically significant favoring FeNO (32% vs 42%; MD, -10%; 95% CI, -18% to -2%; p=.01). Use of FeNO-guided management did not impact day-to-day clinical symptoms, hospitalizations, or pulmonary function measures.

Fractional Exhaled Nitric Oxide for Selecting Treatments for Patients with Severe Asthma

(2019) Casake et al. noted omalizumab has demonstrated efficacy in clinical trials of patients with asthma, but real-world data are needed to assess outcomes after omalizumab initiation in patients with asthma in a real-world setting. Patients aged 12 years and older with allergic asthma who were candidates for omalizumab on the basis of physician-assessed need were enrolled in a US-based, prospective, single-arm, 48-week multicenter study, the Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab. Monthly assessments included exacerbations, health care utilization, asthma control test (ACT), and adverse events. At baseline, 6 months, and end of study, biomarkers (blood eosinophils and fractional exhaled nitric oxide) were collected, and spirometry performed. Of 806 enrollees, 801 (99.4%) received omalizumab and 622 (77.2%) completed the study. The exacerbation rate significantly improved from a mean of 3.00 ± 3.28 in the 12 months before baseline to 0.78 ± 1.37 through month 12 ($P < .001$) and was similar in adults and adolescents; there was a reduction of 81.9% in the percentage of patients with 1 or more hospitalizations. Lung function remained generally unchanged. A mean improvement of 4.4 ± 4.9 in ACT scores was observed. Eighty-seven percent of patients were responders on the basis of clinical

improvement in exacerbations, lung function, or ACT scores. Baseline biomarker status was associated with ACT scores and lung function improvement, but the magnitude of this improvement was not clinically relevant. No new safety signals emerged. The authors concluded omalizumab initiation in patients with asthma resulted in improved exacerbation rates, reduced hospitalizations, and improved ACT scores compared with pretreatment values, regardless of biomarker status.

(2019) Shrimanker et al. completed a post hoc analysis of prognostic and predictive value of blood eosinophil count, fractional exhaled nitric oxide, and their combination in severe asthma which included analysis of a phase 2b study of mepolizumab in patients with severe eosinophilic asthma (DREAM [Mepolizumab for Severe Eosinophilic Asthma: A Multicenter, Double-Blind, Placebo-controlled Trial]) (1). We selected this study as it was the only mepolizumab study to assess FeNO and blood eosinophils at baseline. DREAM evaluated placebo and three doses of mepolizumab (75, 250, and 750 mg i.v. once every 4 wk) for 52 weeks. Participants had a history of two or more exacerbations requiring oral corticosteroids in the previous year, and evidence of eosinophilic inflammation as reflected by one of more of the following: a PBE count ≥300 cells/μl, a sputum eosinophil count ≥3%, FeNO ≥ 50 ppb, and prompt deterioration of asthma control after a 25% or less reduction in regular maintenance inhaled or oral corticosteroids. As the DREAM study did not show a dose-related effect of active treatment or evidence of an interaction between dose and predictive value of biomarkers, our analysis is based on the combined effect of the different doses. Participants were divided into subgroups depending on their baseline PBE count and FeNO. PBEs were defined as high (≥150 cells/μl) or low (<150 cells/μl), and FeNO as high (≥25 ppb) or low (<25 ppb). We chose these cut points because of preexisting evidence linking them to eosinophilic airway inflammation and response to corticosteroids (5). Baseline demographics, clinical characteristics, and annualized exacerbation rates were calculated on the basis of four biomarker subgroups: PBE high–FeNO high, PBE high–FeNO low, PBE low–FeNO high, and PBE low–FeNO low. An additional analysis was performed using a PBE cut point of 300 cells/μl.The DREAM study was a multicenter, randomized, double-blind, placebo-controlled trial. Our primary interest was severe exacerbation rate, defined as the requirement for rescue oral corticosteroids, as the main benefit of mepolizumab treatment is to reduce the rate of exacerbations, and exacerbation rate was the primary outcome measure of the trial. We also present the change in prebronchodilator FEV_1 after 52 weeks of treatment.

A total of 606 DREAM participants had baseline blood eosinophil and FENO measurements. The study population had a mean of 3.6 exacerbations per patient per year in the year before study enrollment. Lung function was reduced, with a mean FEV_1 of 60% predicted, and there was a high symptom burden with a mean asthma control questionnaire 6 score of 2.3 (with ,1.5 indicating good control). The risk for exacerbations was highest in placebo-treated patients with high baseline PBE count and FENO. The efficacy of active treatment was most marked in this group, with mepolizumab showing 62% exacerbation rate reduction compared with 36% exacerbation rate reductions in the PBE high–FENO low group. Mepolizumab did not have a

significant effect on exacerbation rate in the PBE low subgroups, regardless of FENO. Similar findings were seen for change in prebronchodilator FEV_1 and when patients were stratified by a PBE count of 300 cells/ml.

(2018) Castro et al noted dupilumab is a fully human anti-interleukin-4 receptor α monoclonal antibody that blocks both interleukin-4 and interleukin-13 signaling. They assessed its efficacy and safety in patients with uncontrolled asthma. They randomly assigned 1902 patients 12 years of age or older with uncontrolled asthma in a 2:2:1:1 ratio to receive add-on subcutaneous dupilumab at a dose of 200 or 300 mg every 2 weeks or matched-volume placebos for 52 weeks. The primary end points were the annualized rate of severe asthma exacerbations and the absolute change from baseline to week 12 in the forced expiratory volume in 1 second (FEV_1) before bronchodilator use in the overall trial population. Secondary end points included the exacerbation rate and FEV_1 in patients with a blood eosinophil count of 300 or more per cubic millimeter. Asthma control and dupilumab safety were also assessed. The annualized rate of severe asthma exacerbations was 0.46 (95% confidence interval [CI], 0.39 to 0.53) among patients assigned to 200 mg of dupilumab every 2 weeks and 0.87 (95% CI, 0.72 to 1.05) among those assigned to a matched placebo, for a 47.7% lower rate with dupilumab than with placebo (P<0.001); similar results were seen with the dupilumab dose of 300 mg every 2 weeks. At week 12, the FEV_1 had increased by 0.32 liters in patients assigned to the lower dose of dupilumab (difference vs. matched placebo, 0.14 liters; P<0.001); similar results were seen with the higher dose. Among patients with a blood eosinophil count of 300 or more per cubic millimeter, the annualized rate of severe asthma exacerbations was 0.37 (95% CI, 0.29 to 0.48) among those receiving lower dose dupilumab and 1.08 (95% CI, 0.85 to 1.38) among those receiving a matched placebo (65.8% lower rate with dupilumab than with placebo; 95% CI, 52.0 to 75.6); similar results were observed with the higher dose. Blood eosinophilia occurred after the start of the intervention in 52 patients (4.1%) who received dupilumab as compared with 4 patients (0.6%) who received placebo. The authors concluded in this trial, patients who received dupilumab had significantly lower rates of severe asthma exacerbation than those who received placebo, as well as better lung function and asthma control. Greater benefits were seen in patients with higher baseline levels of eosinophils. Hypereosinophilia was observed in some patients. (NCT02414854).

(2018) Rabe et al. noted dupilumab is a fully human anti-interleukin-4 receptor α monoclonal antibody that blocks both interleukin-4 and interleukin-13 signaling. Its effectiveness in reducing oral glucocorticoid use in patients with severe asthma while maintaining asthma control is unknown. They randomly assigned 210 patients with oral glucocorticoid-treated asthma to receive add-on dupilumab (at a dose of 300 mg) or placebo every 2 weeks for 24 weeks. After a glucocorticoid dose-adjustment period before randomization, glucocorticoid doses were adjusted in a downward trend from week 4 to week 20 and then maintained at a stable dose for 4 weeks. The primary end point was the percentage reduction in the glucocorticoid dose at week 24. Key secondary end points were the proportion of patients at week 24 with a reduction of at least 50% in the glucocorticoid dose and the proportion of patients with a reduction to a glucocorticoid

dose of less than 5 mg per day. Severe exacerbation rates and the forced expiratory volume in 1 second (FEV_1) before bronchodilator use were also assessed. The percentage change in the glucocorticoid dose was -70.1% in the dupilumab group, as compared with -41.9% in the placebo group (P<0.001); 80% versus 50% of the patients had a dose reduction of at least 50%, 69% versus 33% had a dose reduction to less than 5 mg per day, and 48% versus 25% completely discontinued oral glucocorticoid use. Despite reductions in the glucocorticoid dose, in the overall population, dupilumab treatment resulted in a severe exacerbation rate that was 59% (95% confidence interval [CI], 37 to 74) lower than that in the placebo group and resulted in an FEV_1 that was 0.22 liters (95% CI, 0.09 to 0.34) higher. Injection-site reactions were more common with dupilumab than with placebo (9% vs. 4%). Transient blood eosinophilia was observed in more patients in the dupilumab group than in the placebo group (14% vs. 1%). The authors concluded in patients with glucocorticoid-dependent severe asthma, dupilumab treatment reduced oral glucocorticoid use while decreasing the rate of severe exacerbations and increasing the FEV_1. Transient eosinophilia was observed in approximately 1 in 7 dupilumab-treated patients. (NCT02528214).

(2016) Ortega et al. did a post-hoc analysis of data, which was completed on Sept 25, 2015, from two randomised, double-blind, placebo-controlled studies of at least 32 weeks duration (NCT01000506 [DREAM] and NCT01691521 [MENSA]) done between 2009 and 2014. In these studies, mepolizumab. Dream: 75 mg, 250 mg, or 750 mg intravenously; MENSA: 75 mg intravenously or 100 mg subcutaneously) versus placebo was given at 4-week intervals in addition to standard care (high-dose inhaled corticosteroids plus ≥1 additional controller with or without daily oral corticosteroids) to patients aged 12 years or older with a clinical diagnosis of asthma, a history of at least two exacerbations in the previous year that required systemic corticosteroid treatment, and evidence of eosinophilic airway inflammation. The primary endpoint in both studies was the annual rate of clinically significant exacerbations (defined as worsening of asthma that required the use of systemic corticosteroids, or admission to hospital, or an emergency-room visit, or a combination of these occurrences). In our analysis, the primary outcome was the annualized rate of exacerbations in patients stratified by baseline eosinophil counts (≥150 cells per μL, ≥300 cells per μL, ≥400 cells per μL, and ≥500 cells per μL) and baseline blood eosinophil ranges (<150 cells per μL, ≥150 cells per μL to <300 cells per μL, ≥300 cells per μL to <500 cells per μL, and ≥500 cells per μL). We based our analysis on the intention-to-treat populations of the two original studies, and all mepolizumab doses were combined for analysis. The findings included 1192 patients, 846 received mepolizumab and 346 received placebo. The overall rate of mean exacerbations per person per year was reduced from 1·91 with placebo to 1·01 with mepolizumab (47% reduction; rate ratio [RR] 0·53, 95% CI 0·44-0·62; p<0·0001). The exacerbation rate reduction with mepolizumab versus placebo increased progressively from 52%; 0·48, 0·39-0·58) in patients with a baseline blood eosinophil count of at least 150 cells per μL to 70%; 0·30, 0·23-0·40]) in patients with a baseline count of at least 500 cells per μL. At a baseline count less than 150 cells per μL, predicted efficacy of mepolizumab was reduced. Their analysis has shown a close relationship between baseline blood eosinophil count and clinical efficacy of mepolizumab in patients with

severe eosinophilic asthma and a history of exacerbations. We noted clinically relevant reductions in exacerbation frequency in patients with a count of 150 cells per μL or more at baseline. The use of this baseline biomarker will help to select patients who are likely to achieve important asthma outcomes with mepolizumab.

(2014) Ortega et al. completed a randomized, double-blind, double-dummy study, by assigning 576 patients with recurrent asthma exacerbations and evidence of eosinophilic inflammation despite high doses of inhaled glucocorticoids to one of three study groups. Patients were assigned to receive mepolizumab, a humanized monoclonal antibody against interleukin-5, which was administered as either a 75-mg intravenous dose or a 100-mg subcutaneous dose, or placebo every 4 weeks for 32 weeks. The primary outcome was the rate of exacerbations. Other outcomes included the forced expiratory volume in 1 second (FEV1) and scores on the St. George's Respiratory Questionnaire (SGRQ) and the 5-item Asthma Control Questionnaire (ACQ-5). Safety was also assessed. The rate of exacerbations was reduced by 47% (95% confidence interval [CI], 29 to 61) among patients receiving intravenous mepolizumab and by 53% (95% CI, 37 to 65) among those receiving subcutaneous mepolizumab, as compared with those receiving placebo (P<0.001 for both comparisons). Exacerbations necessitating an emergency department visit or hospitalization were reduced by 32% in the group receiving intravenous mepolizumab and by 61% in the group receiving subcutaneous mepolizumab. At week 32, the mean increase from baseline in FEV1 was 100 ml greater in patients receiving intravenous mepolizumab than in those receiving placebo (P=0.02) and 98 ml greater in patients receiving subcutaneous mepolizumab than in those receiving placebo (P=0.03). The improvement from baseline in the SGRQ score was 6.4 points and 7.0 points greater in the intravenous and subcutaneous mepolizumab groups, respectively, than in the placebo group (minimal clinically important change, 4 points), and the improvement in the ACQ-5 score was 0.42 points and 0.44 points greater in the two mepolizumab groups, respectively, than in the placebo group (minimal clinically important change, 0.5 points) (P<0.001 for all comparisons). The safety profile of mepolizumab was similar to that of placebo. The author’s concluded, mepolizumab administered either intravenously or subcutaneously significantly reduced asthma exacerbations and was associated with improvements in markers of asthma control. (Funded by GlaxoSmithKline; MENSA ClinicalTrials.gov number, NCT01691521.).

(2012) Pavord et al. completed a multicenter, double-blind, placebo-controlled trial for mepolizumab for severe eosinophilic asthma (DREAM) which included 81 centers in 13 countries between Nov 9, 2009, and Dec 5, 2011. Eligible patients were aged 12-74 years, had a history of recurrent severe asthma exacerbations, and had signs of eosinophilic inflammation. They were randomly assigned (in a 1:1:1:1 ratio) to receive one of three doses of intravenous mepolizumab (75 mg, 250 mg, or 750 mg) or matched placebo (100 mL 0·9% NaCl) with a central telephone-based system and computer-generated randomly permuted block schedule stratified by whether treatment with oral corticosteroids was required. Patients received 13 infusions at 4-week intervals. The primary outcome was the rate of clinically significant asthma exacerbations, which were defined as validated episodes of acute asthma requiring treatment with oral

corticosteroids, admission, or a visit to an emergency department. Patients, clinicians, and data analysts were masked to treatment assignment. Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01000506.

The findings included 621 patients were randomized: 159 were assigned to placebo, 154 to 75 mg mepolizumab, 152 to 250 mg mepolizumab, and 156 to 750 mg mepolizumab. 776 exacerbations were deemed to be clinically significant. The rate of clinically significant exacerbations was 2·40 per patient per year in the placebo group, 1·24 in the 75 mg mepolizumab group (48% reduction, 95% CI 31-61%; p<0·0001), 1·46 in the 250 mg mepolizumab group (39% reduction, 19-54%; p=0·0005), and 1·15 in the 750 mg mepolizumab group (52% reduction, 36-64%; p<0·0001). Three patients died during the study, but the deaths were not deemed to be related to treatment. The authors concluded mepolizumab is an effective and well tolerated treatment that reduces the risk of asthma exacerbations in patients with severe eosinophilic asthma.

Section Summary: Fractional Exhaled Nitric Oxide for Selecting Treatments for Patients with Severe Asthma

Anti-IL-5 and anti-IL-4 therapies to treat eosinophilic asthma and anti-IgE therapies to treat severe allergic asthma are available. Studies demonstrating the efficacy of anti-IL-5 treatments generally used blood or sputum eosinophilic measurements to determine eligibility. However, trials for anti-IL-4R therapy generally did not have minimum requirements of baseline eosinophil counts for inclusion. Subgroup analyses from 2 trials of dupilumab, 1 including patients with uncontrolled asthma and 1 including patients with oral glucocorticoid-treated asthma, reported conflicting results on whether baseline blood eosinophils could be used to identify a group of patients unlikely to benefit from dupilumab with respect to severe exacerbations. However, in both trials, the treatment effect estimates for dupilumab versus placebo for the outcome of severe exacerbations favored dupilumab across the 3 subgroups of baseline FeNO even when a statistically significant, quantitative interaction was reported. Therefore, it is unclear if baseline FeNO can identify a group for whom there is no benefit from dupilumab. Evaluation of subgroups in 1 trial of mepolizumab reported annualized rates of exacerbations by baseline eosinophil and FeNO measures showing elevated values for both indices was associated with a more pronounced effect compared to placebo. However, statistical comparisons between subgroups were not performed and outcomes stratified by baseline FeNO only were not reported, precluding insight into the utility of using FeNO alone to predict response to treatment.

In an analysis of the EXTRA trial, omalizumab treatment resulted in numerically similar mean exacerbation rates in patients with high and low baseline FeNO, though the relative reduction was greater in the high FeNO subgroup. Data from the analysis was limited by a large early discontinuation rate (20.8%) in the original trial as well as the absence of statistical comparisons between subgroups. Additionally, a 48-week multicenter prospective observational study with over 700 participants found that asthma exacerbations were reduced with omalizumab over a 12-month treatment period irrespective of baseline FeNO.

Eosinophilic Asthma

(2018) Goa et al. completed a review on the association between fractional exhaled nitric oxide, sputum induction and peripheral blood eosinophil in uncontrolled asthma his study evaluated 75 uncontrolled asthmatic patients (symptom control and future risk of adverse outcomes). All patients underwent the following on the same day: FeNO, spirometry, BHR or bronchodilator reversibility, sputum induction and blood collection. Eosinophilic airway inflammation was defined as sputum eosinophils ≥ 2.5% or FeNO levels ≥ 32 parts per billion (ppb). The results noted a significant positive relationship was between percentage of sputum eosinophils and FeNO ($r = 0.4556$; $p < 0.0001$) and percentage of blood eosinophils ($r = 0.3647$; $p = 0.0013$), and a significant negative correlation was between percentage of sputum neutrophils and FeNO ($r = - 0.3653$; $p = 0.0013$). No relationship between FeNO and percentage of blood eosinophils ($p = 0.5801$). ROC curve analysis identified FeNO was predictive of sputum eosinophilia [area under the curve (AUC) 0.707, $p = 0.004$] at a cutoff point of 35.5 ppb (sensitivity = 67.3%, specificity = 73.9%). Percentage of blood eosinophils was also highly predictive with an AUC of 0.73 ($p = 0.002$) at a cut-off point of 1.5%, sensitivity and specificity were 61.5 and 78.3%, respectively. Although the sputum neutrophil percentage was correlated with FeNO, ROC curve of these parameters did not show useful values (AUC = 0.297, $p = 0.003$; AUC = 0.295, $p = 0.021$). In conclusion, blood eosinophils and FeNO can accurately predict eosinophilic airway inflammation in uncontrolled asthmatic patients. FeNO is poor surrogates for sputum neutrophils and blood eosinophils. The FeNO level and blood eosinophils, which determine an optimal cutoff for sputum eosinophilia, need more studies.

(2018) Pesky et al. complete a meta-analysis to synthesize the evidence from updated Cochrane systematic reviews, for tailoring asthma medication based on eosinophilic inflammatory markers (sputum analysis and FeNO) for improving asthma-related outcomes in children and adults. The 16 included studies of FeNO-based management (seven in adults) and 6 of sputum-based management (five in adults) were clinically heterogeneous. On follow-up, participants randomized to the sputum eosinophils strategy (compared with controls) were significantly less likely to have exacerbations (62 vs 82/100 participants with ≥1 exacerbation: OR 0.36, 95% CI 0.21 to 0.62). For the FeNO strategy, the respective numbers were adults OR 0.60 (95% CI 0.43 to 0.84) and children 0.58 (95% CI 0.45 to 0.75). However, there were no significant group differences for either strategy on daily inhaled corticosteroids dose (at end of study), asthma control or lung function. In conclusion, adjusting treatment based on airway eosinophilic markers reduced the likelihood of asthma exacerbations but had no significant impact on asthma control or lung function.

(2015) Korevaar et al. completed a systematic review and meta-analysis assessing the diagnostic accuracy of minimally invasive markers for detection of airway eosinophilia in asthma. The diagnostic accuracy of markers against a reference standard of induced sputum, bronchoalveolar lavage, or endobronchial biopsy in patients with asthma or

suspected asthma. They included 32 studies: 24 in adults and eight in children. Of these, 26 (81%) showed risk of bias in at least one domain. In adults, three markers had extensively been investigated: fraction of exhaled nitric oxide (FeNO) (17 studies; 3216 patients; summary area under the receiver operator curve [AUC] 0·75 [95% CI 0·72-0·78]); blood eosinophils (14 studies; 2405 patients; 0·78 [0·74-0·82]); total IgE (seven studies; 942 patients; 0·65 [0·61-0·69]). In children, only FeNO (six studies; 349 patients; summary AUC 0·81 [0·72-0·89]) and blood eosinophils (three studies; 192 patients; 0·78 [0·71-0·85]) had been investigated in more than one 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 (0·57-0·75) and 0·76 (0·65-0·85) for FeNO; 0·71 (0·65-0·76) and 0·77 (0·70-0·83) for blood eosinophils; and 0·64 (0·42-0·81) and 0·71 (0·42-0·89) for IgE. In conclusion, FeNO, blood eosinophils, and IgE have 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.

Section Summary: **Eosinophilic Asthma**
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 remain to be defined. The largest clinical trials and systematic reviews did not find sufficient evidence to support routine use of FeNO to guide asthma therapy.

Fractional Exhaled Nitric Oxide in Respiratory Disorders Other Than Asthma
The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients with suspected or confirmed respiratory disorders other than asthma. A precise explication of the population of interest depends on the position of the FeNO test in the diagnostic or management pathway.

Interventions
The test being considered is measurement of FeNO.

Comparators
The following practice is currently being used to diagnose and treat respiratory disorders other than asthma: standard clinical diagnosis and management. The appropriate comparator depends on the position of the FeNO in the diagnostic or management pathway.

Outcomes
The general outcomes of interest are test validity, symptoms, change in disease status, morbid events, and functional outcomes. Specific outcomes of interest would be diagnostic accuracy, rates of exacerbations, symptoms, hospitalizations, use of medications, and quality of life.

COVID-19

(2021) Li et al. noted in the COVID-19 outbreak year 2020, a consensus was reached on the fact that SARS-CoV-2 spreads through aerosols. However, finding an efficient method to detect viruses in aerosols to monitor the risk of similar infections and enact effective control remains a great challenge. These researchers built a swirling aerosol collection (SAC) device to collect viral particles in exhaled breath and subsequently detect SARS-CoV-2 using RT-PCR. Laboratory tests of the SAC device using aerosolized SARS-CoV-2 pseudo-virus indicated that the SAC device can produce a positive result in only 10 s, with a collection distance to the source of 10 cm in a biosafety chamber, when the release rate of the pseudo-virus source was 1,000,000 copies/hour. Subsequent clinical trials of the device reported 3 positives and 14 negatives out of 27 patients in agreement with pharyngeal swabs, and 10 patients obtained opposite results, while no positive results were found in a healthy control group (n = 12). Based on standard curve calibration, several thousand viruses/min were observed in the tested exhalations. Furthermore, referring to the average tidal volume data of adults, it was estimated that an exhaled SARS-CoV-2 concentration of approximately 1 copy/ml is detectable for COVID-19 patients. The authors concluded that the findings of this validated the concept that detection of SARS-CoV-2 in the breath of COVID-19 patients is feasible, implying potential applications for rapid screening of infectious individuals and automatic early epidemic prevention of respiratory pathogens in public environments. The authors stated there were several drawbacks in this study, including the fact that only 3 of 27 subjects tested positive for SARS-CoV-2 by breath analysis. Notably, patients were in a late course of the disease. This result was maintained even after 9 of the 24 subjects underwent a 2nd analysis. Viral load has been shown to be high in COVID-19 patients during the 1st week of symptoms and decrease during the 2nd week. Since most of the patients were asymptomatic at the time of sampling and had shown a long course of disease (23 to 70 days) prior to sampling, a low viral load was the most likely reason for their negative test results. To increase the positive rate for the SAC device, pre-clinical tests using pseudo-viruses have shown that the suitable product of virus source concentration and sampling time is larger than the threshold 100,000 s·copies/ml, or the product of virus concentration in aerosols and sampling time was larger than the threshold 1.5 s·copies/ml. In principle, through very sophisticated clinical trials for patients, i.e., longer, and higher frequency exhalation tests, it is feasible to determine whether the exhalation results are truly negative. Actually, clinical tests with a relatively long time, such as half an hour for patients, would not be necessary and practical for this study. Moreover, it is not possible to test additional patients in China at this time due to a shortage of patients with COVID-19. Nevertheless, improvements to the new method and systematic studies of influenza viruses are still in progress, and additional researchers are getting involved to push the method forward.

(2021) Ryan et al. noted that false negatives from nasopharyngeal swabs (NPS) using reverse transcriptase PCR (RT-PCR) in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are high; EBC contains lower respiratory droplets that may improve

detection. These researchers carried out EBC RT-PCR for SARS-CoV-2 genes (E, S, N, ORF1ab) on NPS-positive (n = 16) and NPS-negative/clinically positive COVID-19 patients (n = 15) using 2 commercial assays. EBC detected SARS-CoV-2 in 93.5 % (29/31) using the 4 genes. Pre-SARS-CoV-2 era controls (n = 14) were negative. EBC was positive in NPS negative/clinically positive patients in 66.6 % (10/15) using the identical E and S (E/S) gene assay used for NPS, 73.3 % (11/15) using the N/ORF1ab assay and 14/15 (93.3 %) combined. The authors concluded that the findings of this study provided promising results that EBC RT-PCR is an effective, non-invasive method of identifying SARS-CoV-2 from lower respiratory tract samples and should be considered to aid diagnosis of COVID-19 in patients with a high suspicion of infection but negative NPS The authors stated this study had several drawbacks. Power calculations indicated a need for 155 samples to detect a statistically significant difference between NPS and EBC RT-PCR using the same E/S assay with an 80 % power and alpha value of 0.05. However, increased sample size was not possible due to decreased admissions in response to public health measures. EBC RT-PCR failed to identify SARS-CoV-2 in 5/16 (31 %) NPS-positive cases using the identical E/S assay, suggesting EBC should be used as an adjunct rather than a replacement for NPS RT-PCR. Owing to strict laboratory access restrictions and some patients being initially too unwell to provide samples, EBC collection occurred a median of 2 days (range of 0 to 19) after NPS testing, potentially introducing bias favoring EBC detection; 3 out of 9 (33.3 %) patients had no evidence of antibodies to COVID-19 despite having positive EBC RT-PCR. However, median time to serology was 34 days (range of 34 to 51), and currently few data are available to confirm continued antibody response 35 days post-infection, especially in milder cases.

(2021) Sawano et al. noted that current diagnostic testing for COVID-19 is based on detection of SARS-CoV-2 in NPS samples by RT-PCR; however, this test is associated with increased risks of viral dissemination and environmental contamination and showed relatively low sensitivity, attributable to technical deficiencies in the sampling method . Given that COVID-19 is transmitted via exhaled aerosols and droplets, and that EBC is an established modality for sampling exhaled aerosols, detection of SARS-CoV-2 in EBC offers a promising diagnostic approach. However, current knowledge on the detection and load of the virus in EBC collected from COVID-19 patients remains limited and inconsistent. These researchers quantified the viral load in EBC collected from COVID-19 patients and examined the feasibility of SARS-CoV-2 detection from EBC as a diagnostic test for the infection. EBC samples were collected from 48 COVID-19 patients using a collection device, and viral loads were quantified by RT-PCR targeting the E gene. Changes in detection rates and viral loads relative to patient characteristics and days since disease onset were statistically evaluated. Need for mechanical ventilation was significantly associated with higher viral load ($p < 0.05$). Need for oxygen administration or mechanical ventilation, less than 3 days since onset, and presence of cough or fever were significantly associated with higher detection rates ($p < 0.05$). Among spontaneously breathing patients, viral load in EBC attenuated exponentially over time. The detection rate was 86 % at 2 days since onset and deteriorated thereafter. In mechanically ventilated patients, detection rate and viral load

were high regardless of days since onset. The authors concluded that the findings of this study supported the feasibility of using RT-PCR to detect SARS-CoV-2 from EBC for COVID-19 patients within 2 days of symptom onset. Moreover, these researchers stated that future investigation by RT-PCR assay targeting the 4 genes is expected to extend the feasibility of EBC-PCR testing up to 10 days after onset or even later. The authors stated the main drawback of this trial entailed the relatively low detection rate (31.2 %) of viral RNA from EBC samples, and the small sample size (15 samples) of viral RNA load in EBC as a consequence. The small sample size precluded the use of multi-variate analysis methods to clarify exact associations between viral RNA load in EBC and patient characteristics at the time of EBC collection. A previous study by Ryan et al (2021) reported that detection rates of viral RNA in EBC collected from patients with positive results from NPS RT-PCR tests were 68.3 % by RT-PCR assay targeting 2 genes (E and S genes) and 93.5 % by an assay targeting all 4 genes (E, S, N and ORF1ab genes). That study enrolled spontaneously breathing hospitalized patients, and median time from disease onset to EBC collection was 13 days, longer than in the present study. Given the proportionality between detection rates and number of targeted genes, the low overall detection rate in the present study could be attributed to the fact that the RT-PCR assay targeted a single gene (E gene). In this context, future investigations by RT-PCR assay targeting 4 genes are expected to achieve higher detection rates and to extend the feasibility of EBC-PCR testing beyond 10 days after disease onset, or even later. Investigations are also expected to clarify the exact associations between viral RNA load in EBC and patient characteristics at the time of EBC collection by employing multi-variate analysis. On the other hand, possible over-estimation of the viral RNA load, which was derived from amplification of fragmented viral RNA, should be taken into consideration when interpreting RT-PCR assay results. Another drawback of this study was that it did not enroll spontaneously breathing patients, who received COVID-19-specific treatment (dexamethasone, remdesivir) prior to EBC collection. As a result, the study was unable to clarify the effect of the treatment on the viral RNA load in EBC and its attenuation over time. This drawback was attributable to the study protocol of collecting EBC as soon as possible after admission, and to the national guideline of recommending treatment only for patients with moderate-to-severe disease. This issue warrants further investigation including sequential EBC collection from increased number of the spontaneously breathing patients.

Fractional Exhaled Nitric Oxide for Diagnosing Other Respiratory Disorders: Chronic Obstructive Pulmonary Disease

(2021) Vincken et al. performed a single-center, prospective pilot study to assess the relationship between FeNO and blood eosinophil counts in 136 patients with stable COPD. In this study, there was a significant correlation between FeNO and blood eosinophils in patients who had experienced at least 2 COPD exacerbations within the previous year (ρ=.48, p=.02). In this population, FeNO was a significant predictor of blood eosinophil counts greater than 300 cells/mcL (area under the curve, 74%, p=.04), with a specificity of 70% and a sensitivity of 71% at a FeNO threshold of 14.7 ppb.

(2020) Tang et al. evaluated the association between blood eosinophils and FeNO in a cross-sectional study that evaluated 247 patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD). Blood eosinophil counts correlated positively with FeNO values (ρ=.383, p=.004). A cutoff value of 22.5 ppb for FeNO was determined to perform best in a ROC analysis to predict blood eosinophilia with a sensitivity of 77.3% and a specificity of 60.0%.

(2017) Gao et al. reported on results of a cross-sectional study evaluating the association between FeNO and sputum eosinophilia in 163 patients with COPD exacerbations. Sputum eosinophils correlated with both FeNO levels (ρ=0.221, p<.01) and blood eosinophilic percentage (ρ=0.399, p<.001). Fractional expired NO and blood eosinophilic percentage did not correlate significantly. At a cutoff point of 17.5 ppb, the sensitivity and specificity rates of FeNO compared with sputum eosinophilia were 65% and 56%, respectively (precision not reported).

(2014) Chou et al. reported on the use of FeNO measurements in predicting sputum eosinophilia in patients with COPD. The study included 90 subjects with COPD with no known history of asthma or allergic diseases. Compared with patients without sputum eosinophilia, those with sputum eosinophilia had higher FeNO levels (29 ppb vs 18 ppb; p=.01). In ROC analysis, an FeNO cutoff of 23.5 ppb had the highest sensitivity (62.1%) and specificity (70.5%) for predicting sputum eosinophilia. After adjusting for age, sex, smoking status, serum IgE, and allergy test results, an FeNO value greater than 23.5 ppb was significantly associated with the presence of sputum eosinophilia (adjusted OR, 4.329; 95% CI, 1.306 to 14.356; p=.017). The authors hypothesized that individuals with COPD with sputum eosinophilia might respond well to ICS or OCS.

Fractional Exhaled Nitric Oxide for Diagnosing Other Respiratory Disorders: Interstitial Lung Disease

(2017) Oishi et al. evaluated whether there were differences in FeNO levels in different types of acute-onset interstitial lung disease. The median FeNO level in patients with acute eosinophilic pneumonia (48.1 ppb) was significantly higher than in patients with cryptogenic organizing pneumonia (17.4 ppb), hypersensitivity pneumonia (20.5 ppb), or sarcoidosis (12.0 ppb; p<.001). At a cutoff of 23.4 ppb, the area under the ROC curve was 0.90.

Fractional Exhaled Nitric Oxide for Diagnosing Other Respiratory Disorders: Primary Ciliary Dyskinesia

Boon et al (2014) evaluated the role of nasal NO and FeNO in the diagnosis of primary ciliary dyskinesia (PCD).60, The study included 226 individuals: 38 individuals with PCD, 49 healthy controls, and 139 individuals with other respiratory diseases. A definitive diagnosis of PCD was made by structural and functional evaluation of the cilia on a nasal or bronchial biopsy. The highest sensitivity (89.5%) and specificity (87.3%) were obtained with nasal NO measured during plateau against resistance. Using an FeNO cutoff of 10 ppb, with lower values predictive of PCD, the sensitivity for PCD diagnosis

was 89.5%, but specificity was low at 58.3%. Diagnostic accuracy would likely be even lower if assessed in the more relevant population of patients with suspected PCD**.**

Fractional Exhaled Nitric Oxide for Diagnosing Other Respiratory Disorders: Pulmonary Fibrosis

(2013) Guilleminault et al retrospectively evaluated whether FeNO could differentiate causes of pulmonary fibrosis. The study included 61 patients divided into 4 groups based on pulmonary fibrosis etiology: idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, connective tissue disease-associated interstitial lung disease, and drug-induced pneumonia. The median FeNO level was higher in patients with hypersensitivity pneumonitis (51 ppb) than in patients in the other groups (median range, 19 to 25 ppb; p=.008). Optimum sensitivity (76.9%) and specificity (85.4%) were established at a cutoff of 41 ppb.

Section Summary: Fractional Exhaled Nitric Oxide for Respiratory Disorders Other Than Asthma

Measurement of FeNO is being investigated for various lung disorders other than asthma. These studies are primarily exploratory and establish differences in median FeNO levels for related conditions. Some studies have evaluated the optimum cutoff for sensitivity and specificity. However, the median FeNO level and cutoffs varied by the study of the same condition (e.g., hypersensitivity pneumonia). Prospective studies with standard protocols and predefined cutoffs are needed to determine diagnostic accuracy. Also, evidence of clinical utility is lacking. No controlled studies compared health outcomes in patients with COPD or other respiratory diseases whose treatment was managed with and without FeNO measurement.

Fractional Exhaled Nitric Oxide for Predicting Response to Medication Therapy in Other Respiratory Conditions

(2009) Dummer et al. completed a double-blind crossover trial by evaluated the ability of FeNO test results to predict corticosteroid response in COPD. The trial included 65 patients with COPD who were 45 years or older, were previous smokers with at least a 10-pack a year history, had persistent symptoms of chronic airflow obstruction, had a postbronchodilator FEV1/forced vital capacity of less than 70%, and an FEV1 of 30% to 80% of predicted. Patients with asthma or other comorbidities were excluded, as were those taking regular corticosteroids and those who had used OCS for exacerbations more than twice during the past 6 months. Treatments, given in random order, were prednisone 30 mg/day or placebo for 3 weeks; there was a 4-week washout period before each treatment. Patients who withdrew during the first treatment period were excluded from the analysis. Those who withdrew between treatments or during the second treatment were assigned a net change of 0 for the second treatment period. Fifty-five patients completed the study. Two of the 3 primary outcomes (6-minute walk distance, FEV1) increased significantly from baseline with prednisone compared with placebo. There was a nonsignificant decrease in the third primary outcome, score on the St. George's Respiratory Questionnaire. Baseline FeNO did not correlate significantly with change in 6-minute walk distance (r=0.10, p=.45) or St. George's Respiratory Questionnaire score

(r=0.12, p=.36) but was significantly related to change in FEV1 (r=0.32, p=.01). At the optimal FeNO cutoff of 50 ppb, as determined by ROC analysis, there was a 29% sensitivity and 96% specificity for predicting a 0.2-liter increase in FEV1. (A 0.2-liter change was considered the minimal clinically important difference.) The authors concluded that FeNO is a weak predictor of short-term response to OCS treatment in patients with stable, moderately severe COPD and that a normal test result could help clinicians avoid unnecessary prescriptions; only about 20% of patients responded to corticosteroid treatments. Study limitations included short-term measurement of response to treatment, and not basing management decisions on FeNO test results.

(2008) Kunisaki et al. completed a prospective study of 60 patients with severe COPD and reported that patients considered responders to ICS had higher FeNO values (46.5 ppb) than nonresponders (25 ppb; p=.028). However, an optimal FeNO cutpoint to discriminate between responders and nonresponders could not be determined.

(2003) Prieto et al. completed a prospective uncontrolled study by assessing the utility of FeNO measurement for predicting response to ICS in patients with chronic cough. The study included 43 patients with cough of at least 8 weeks in duration who were nonsmokers without a history of another lung disease. Patients were evaluated at baseline and 4 weeks after treatment with inhaled fluticasone propionate 100 µg twice daily. Nineteen (44%) patients had a positive response to treatment, defined as at least a 50% reduction in mean daily cough symptom scores. The ROC analysis showed that using 20 ppb as the FeNO cutoff, the sensitivity was 53% and the specificity was 63%. The authors concluded that FeNO was not an adequate predictor of treatment response.

Section Summary: Fractional Exhaled Nitric Oxide for Other Respiratory Disorders Other Than Asthma

Measurement of FeNO is being investigated for various lung disorders other than asthma. These studies are primarily exploratory and establish differences in median FeNO levels for related conditions. Some studies have evaluated the optimum cutoff for sensitivity and specificity. However, the median FeNO level and cutoffs varied by the study of the same condition (e.g., hypersensitivity pneumonia). Prospective studies with standard protocols and predefined cutoffs are needed to determine diagnostic accuracy. Also, evidence of clinical utility is lacking. No controlled studies compared health outcomes in patients with COPD, COVID-19, or other respiratory diseases whose treatment was managed with and without FeNO measurement.

Summary of Evidence

For individuals who have suspected asthma who receive measurement of fractional exhaled nitric oxide (FeNO) for diagnosis, the evidence includes multiple retrospective and prospective studies of diagnostic accuracy, along with systematic reviews of those studies. Relevant outcomes are test validity, symptoms, change in disease status, morbid events, and functional outcomes. There are multiple reports on the sensitivity and specificity of FeNO in asthma diagnosis; however, most studies are in the setting of patients with asthma symptoms without previous testing (or with unclear previous

testing), which is unlikely to be how the test is used in a U.S. setting. The available evidence is limited by variability in FeNO cutoff levels used to diagnose asthma, lack of data on performance characteristics in challenging diagnostic settings, and lack of data on the incremental value of adding FeNO to existing diagnostic algorithms from studies with concurrent controls. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have asthma who receive medication management directed by FeNO, the evidence includes diagnostic accuracy studies, multiple randomized controlled trials (RCTs), and systematic reviews of those trials. Relevant outcomes are symptoms, change in disease status, morbid events, and functional outcomes. The available RCTs evaluating the use of FeNO tests to guide step-up/step-down therapy in patients have not consistently found improvement in health outcomes. Two Cochrane reviews from 2016, 1 on adults and the other on children, found that FeNO-guided asthma management to guide step-up/step-down therapy reduced the number of individuals who had more than 1 exacerbation in children but not in adults compared with guidelines-driven therapy. However, it had no impact on day-to-day symptoms or hospitalizations. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have asthma, which is managed by inhaled corticosteroids, several studies have evaluated the association between FeNO and response to inhaled corticosteroid (ICS). Inhaled corticosteroid use is in the guidelines-recommended management pathway for all patients with persistent asthma; however, there are no RCTs examining the efficacy and safety of withholding ICS in patients with low FeNO. Therefore, RCTs are needed to evaluate the utility for FeNO to be used to determine patients who should not receive ICS.

For individuals who have severe asthma who receive measurement of FeNO to select treatment, the evidence includes diagnostic accuracy studies and subgroup analyses of RCTs and observational studies. Relevant outcomes are test validity, symptoms, change in disease status, morbid events, and functional outcomes. For the use of FeNO to identify eosinophilic asthma for the purpose of selecting patients for therapy with anti-interleukin (IL)-5 therapy or an anti-IL-4 and -13 monoclonal antibody, subgroup analyses of RCTs are available. The evidence that points toward an interaction between baseline FeNO and treatment for the outcome of response suggests that there may be a quantitative but not necessarily a qualitative interaction between baseline FeNO and anti-IL-4 treatment (dupilumab), i.e., it is unclear if baseline FeNO can identify a group for whom there is no benefit from dupilumab. Similarly, a subgroup analysis for mepolizumab suggested a more pronounced effect compared to placebo in those with elevated levels of both blood eosinophils and FeNO. However, outcomes were not reported stratified based on FeNO alone, precluding insight into the utility of using FeNO to predict response to treatment. For use of FeNO to predict response to therapy for patients with other severe asthma phenotypes, such as the allergic subtype, where anti-immunoglobulin E therapy is used, a subgroup analysis of an RCT is available. Subgroup

analysis of omalizumab showed an association with more favorable outcomes in patients with high FeNO levels, but as with dupilumab, a qualitative interaction has not been established. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected or confirmed respiratory disorders other than asthma who receive measurement of FeNO, the evidence includes crossover trials, pilot studies, and observational studies. Relevant outcomes are test validity, symptoms, change in disease status, morbid events, and functional outcomes. The available evidence assessing the use of FeNO for respiratory disorders other than asthma is limited by heterogeneity in the conditions evaluated and uncertainty about how the test fits in defined clinical management pathways. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected or confirmed respiratory disorders who receive measurement of EBC, the evidence includes observational studies reporting on the association between various EBC components and disease severity. Relevant outcomes are test validity, symptoms, change in disease status, morbid events, and functional outcomes. There is considerable variability in the particular EBC components measured and criteria for standardized measurements. Also, there is limited evidence on the use of EBC for determining asthma severity, diagnosing other respiratory conditions, or guiding treatment decisions for asthma or other respiratory conditions. The available published evidence does not support conclusions on the utility of EBC for any indication. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements
American Academy of Pediatrics (AAP)
(2017) In the AAP clinical report for Clinical Tools to Assess Asthma Control in Children for Initial consultation it noted:

- Airway obstruction and AHR can be assessed by measuring prebronchodilator and postbronchodilator FEV_1. Some specialists may consider evaluation of airway inflammation by using FENO to be useful. (*Accessed February 2022*)

American Thoracic Society (ATS)
(2021) The American Thoracic Society published a guideline on the use of fractional exhaled nitric oxide to guide the treatment of Asthma which stated:

- Should patients with asthma in whom treatment is being contemplated undergo FENO testing?
    - In patients with asthma in whom treatment is being considered, we suggest the use of FENO testing in addition to usual care over usual care alone (conditional recommendation, low confidence in estimates of effect).
        - Future research opportunities. There are several limitations identified in this report and other contemporary systematic reviews regarding the use of FENO testing that should be further evaluated. Larger pragmatic

randomized controlled trials that are powered on the basis of the available evidence should be conducted to more clearly delineate the benefit of FENO-based care in patients with asthma in whom treatment is being considered. There is similarly a need for larger trials that evaluate the use of FENO testing to monitor therapy with serial measurements once the FENO level is established, and there is a need to better delineate the potential diagnostic accuracy of FENO testing as a tool to establish the diagnosis of asthma. Timing of the initial assessment of FENO is also uncertain because there are anticipated differences between the values when individuals with asthma are medication naive and the values when establishing the initial FENO value while individuals are on a stable dose of therapy, as was the case in the majority of trials identified in this report. Another area that requires further investigation is specific subgroups with asthma and the need to adequately power future clinical studies and trials specifically for analyses of these subgroups. Pertinent subgroups include individuals with T2-predominant asthma as well as individuals with allergic sensitization, in whom the value may be greater; however, the value added to other currently used tests such as those measuring peripheral blood eosinophils and allergen-specific IgE needs further delineation. Studies should also further evaluate subgroups in which FENO based care may be less helpful, as there are lower anticipated levels in subgroups such as individuals with obesity-associated asthma and cigarette smokers. There were also notable differences between children and adults in the studies evaluated for this guideline, indicating that larger studies are needed to further define the benefits within these different populations. (*Accessed February 2022*)

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

The American Thoracic Society guideline recommendations on the management of patients with asthma includes the following recommendations:

- "We recommend the use of FENO in the diagnosis of eosinophilic airway inflammation" (SOR: Strong, QOE: Moderate)
- "We recommend the use of FENO in determining the likelihood of steroid responsiveness in individuals with chronic respiratory symptoms possibly due to airway inflammation" (SOR: Strong, QOE Low)
- "We recommend accounting for age as a factor affecting FENO in children younger than 12 years of age" (SOR: Strong, QOE: High)

- "We recommend that low FENO less than 25 ppb (<20 ppb in children) be used to indicate that eosinophilic inflammation and responsiveness to corticosteroids are less likely" (SOR: Strong, QOE: Moderate)
- "We recommend that FENO greater than 50 ppb (>35 ppb in children) be used to indicate that eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids are likely" (SOR: Strong, QOE: Moderate)
- "We recommend that FENO values between 25 ppb and 50 ppb (20-35 ppb in children) should be interpreted cautiously and with reference to the clinical context" (SOR: Strong, QOE: Low)
- "We recommend accounting for persistent and/or high allergen exposure as a factor associated with higher levels of FENO" (SOR: Strong, QOE: Moderate)
- "We recommend the use of FENO in monitoring airway inflammation in patients with asthma" (SOR: Strong, QOE Low)

(*Accessed February 2022*)

American Thoracic Society (ATS)/European Respiratory Society (ERS)
(2020) The European Respiratory Society and American Thoracic Society published a joint guideline on the management of severe asthma.

The guideline addresses whether measurement of a specific biomarker should be used to guide initiation of treatment with an anti- interleukin (IL)-5 therapy or anti-immunoglobulin E (IgE) therapy for adults and children with severe asthma.

- For anti-IL-5 therapies, the guideline states that most studies focused on blood eosinophils and no data were available for FeNO.
- For adult and adolescent patients with severe asthma being considered for omalizumab, the guideline suggested "using a FeNO cut-off ≥19.5 ppb to identify adolescents (>12 years) and adults with severe allergic asthma more likely to benefit from anti-IgE treatment (conditional recommendation, low quality of evidence)."

(*Accessed February 2022*)

Global Initiative for Asthma (GINA)
(2021) The Global Initiative for Asthma (GINA) published a report on the management and prevention of asthma which states the following:

- The fractional concentration of exhaled nitric oxide (FeNO) is modestly associated with levels of sputum and blood eosinophils. FeNO has not been established as useful for ruling in or ruling out a diagnosis of asthma…FeNO is higher in asthma that is characterized by Type 2 airway inflammation, but it is also elevated 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). FeNO is lower in smokers and during bronchoconstriction and the early phases of allergic response; it may be increased or decreased during viral respiratory infections.
- Treatment guided by fractional concentration of exhaled nitric oxide (FeNO): In several studies of FeNO-guided treatment, problems with the design of the

intervention and/or control algorithms make comparisons and conclusions difficult. Results of FeNO measurement at a single point in time should be interpreted with caution (see In children and young adults with asthma, FeNO-guided treatment was associated with a significant reduction in the number of patients with 21 exacerbation (OR 0.67 195% Cl 0.51—0.90]) and in exacerbation rate (mean difference -0.271-0.49 to -0.061 per year) compared with guidelines-based treatment'" (Evidence A); similar differences were seen in comparisons between FeNO-guided treatment and non-guidelines- based algorithms. However, in non-smoking adults with asthma, no significant reduction in risk of exacerbations and in exacerbation rates was observed when compared to guideline-base treatment; a difference was only seen in studies with other (non-typical) comparator approaches. No significant differences were seen in symptoms or ICS dose with FeNO-guided treatment compared with other strategies.

- Sputum-guided treatment is recommended for adult patients with moderate or severe asthma who are managed in (or can be referred to) centers experienced in this technique (Evidence A). In children, FeNO-guided treatment significantly reduces exacerbation rates compared with guidelines-based treatment (Evidence A). However, 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.
- In studies mainly limited to non-smoking patients, FeNO > 50 parts per billion (ppb) has been associated with a good short-term response to ICS. However, these studies did not examine the longer-term risk of exacerbations. Such evidence therefore does not mean that is safe with regard to exacerbations to withhold ICS in patients with low initial FeNO. More recently, in two 12-month studies in mild asthma, severe exacerbations were reduced with as-needed ICS- formoterol versus as-needed SABA and versus maintenance ICS, independent of baseline inflammatory characteristics including FeNO. Consequently, in patients with a diagnosis or suspected diagnosis of asthma, measurement of FeNO can support the decision to start ICS but cannot be used to decide against treatment with ICS. Based on past and current evidence, GINA recommends treatment with daily low dose ICS or as-needed low dose ICS-formoterol for all patients with mild asthma, to reduce the risk of serious exacerbations.
- FeNO was significantly reduced with both as-needed budesonide-formoterol and maintenance ICS, and there was no significant difference in treatment effect with as-needed budesonide-formoterol by baseline eosinophils or baseline FeNO.
- If treatment is stepped down too far or too quickly, exacerbation risk may increase even if symptoms remain reasonably controlled (Evidence B) To date, higher baseline FeNO has not been found to be predictive of exacerbation following step-down of ICS dose. A meta-analysis of several step-down studies, most with small numbers, suggested that greater reduction in ICS dose may be able to be achieved in patients with baseline FeNO < 50PpB, but the findings point to the need for further research.

- The possibility of refractory Type 2 inflammation should be considered if any of the following are found while the patient is taking high dose ICS or daily OCS:
    - Blood eosinophils $\geq$ 150/ ul and/or
    - FeNO $\geq$ 20 ppb and/or
    - Sputum eosinophils >2% and/or
    - Asthma is clinically allergen-driven
        - The above criteria are suggested for *initial assessment;* those for blood eosinophils and FeNO are based on lowest levels associated with response to some biologics. They are not the criteria for eligibility for Type 2-targeted biologic therapy, which may differ. Consider repeating blood eosinophils and FeNO up to 3 times (e.g. when asthma worsens, before giving OCS), before assuming asthma is non-Type 2. One study of patients with uncontrolled asthma taking medium-high dose ICS-LABA found that 65% had a shift in their blood eosinophil category over 48- 56 weeks.
- Assess adherence objectively by monitoring of prescribing or dispensing records, blood prednisone levels or electronic inhaler monitoring, In one, study suppression of high FeNO after 5 days of directly observed therapy was an indicatory of past poor adherence.
- Measurement of fractional concentration of exhaled nitric oxide (FeNO) is not widely available for most children in this age group and currently remains primarily a research tool. FeNO can be measured in young children with tidal breathing, and normal reference values have been published for children aged 1-5 years. In pre-school children with recurrent coughing and wheezing, an elevated FeNO recorded 4 weeks from any URTI predicted physician-diagnosed asthma at school age, and increased the odds for wheezing, asthma and ICS use by school age, independent of clinical history and presence of specific IgE

(*Accessed February 2022*)

National Heart Lung and Blood Institute

In 2007, the National Heart Lung and Blood Institute's expert panel guidelines on the diagnosis and management of asthma stated:

- "Use of minimally invasive markers (‘biomarkers') to monitor asthma control and guide treatment decisions for therapy is of increasing interest. Some markers, such as spirometry measures, are currently and widely used in clinical care; others, such as sputum eosinophils and FeNO, may also be useful, but they require further evaluation in both children and adults before they can be recommended as clinical tools for routine asthma management (Evidence D)."
- "The Expert Panel recommends some minimally invasive markers for monitoring asthma control, such as spirometry and airway hyper-responsiveness, that are appropriately used, currently and widely, in asthma care (Evidence B). Other markers, such as sputum eosinophils and FeNO, are increasingly used in clinical research and will require further evaluation in adults and children before they can be recommended as a clinical tool for routine asthma management (Evidence D)."

A focused update to the 2007 guidelines was published in 2020.

- The focused update included several updated recommendations on the role of FeNO in asthma diagnosis and management. For asthma diagnosis, the expert panel "conditionally recommends the addition of FeNO measurement as an adjunct to the evaluation process" in individuals 5 years of age or older "for whom the diagnosis of asthma is uncertain using history, clinical findings, clinical course, and spirometry, including bronchodilator responsiveness testing, or in whom spirometry cannot be performed" (conditional recommendation, moderate certainty of evidence). The guidelines mention that FeNO levels greater than 50 parts per billion (ppb) or greater than 35 ppb in children aged 5 to 12 years are consistent with elevated type 2 inflammation and support an asthma diagnosis.
- With regard to the role of FeNO testing in asthma management, the expert panel "conditionally recommends the addition of FeNO measurement as part of an ongoing asthma monitoring and management strategy that includes frequent assessments" in "individuals ages 5 years and older with persistent allergic asthma, for whom there is uncertainty in choosing, monitoring, or adjusting anti-inflammatory therapies based on history, clinical findings, and spirometry" (conditional recommendation, low certainty of evidence). Of note, this recommendation does not apply to individuals taking biologic agents, with the exception of omalizumab. The expert panel "recommends against the use of FeNO measurements in isolation to assess asthma control, predict future exacerbations, or assess exacerbation severity" in individuals 5 years of age or older, stating that "FeNO should only be used as part of an ongoing monitoring and management strategy" (strong recommendation, low certainty of evidence). The expert panel also recommended "against FeNO measurement to predict the future development of asthma" in children aged 0 to 4 years with recurrent wheezing (strong recommendation, low certainty of evidence).

(*Accessed February 2022*)

National Institute for Health and Clinical Excellence (NICE):
(2017; Updated March 2021) NICE issued a guideline on asthma: diagnosis, monitoring and chronic asthma management

- Initial treatment and objective tests for acute symptoms at presentation:
  - Treat people immediately if they are acutely unwell at presentation, and perform objective tests for asthma (for example, fractional exhaled nitric oxide [FeNO], spirometry and peak flow variability) if the equipment is available and testing will not compromise treatment of the acute episode.

- Fractional Exhaled Nitric Oxide
  - Offer a FeNO test to adults (aged 17 and over) if a diagnosis of asthma is being considered. Regard a FeNO level of 40 parts per billion (ppb) or more as a positive test.
  - Consider a FeNO test in children and young people (aged 5 to 16) if there is diagnostic uncertainty after initial assessment and they have either:
    - normal spirometry or

        - obstructive spirometry with a negative bronchodilator reversibility (BDR) test.

    Regard a FeNO level of 35 ppb or more as a positive test

- Peak expiratory flow variability
    - Monitor peak flow variability for 2 to 4 weeks in adults (aged 17 and over) if there is diagnostic uncertainty after initial assessment and a FeNO test and they have either:
        - normal spirometry or
        - obstructive spirometry, reversible airways obstruction (positive BDR) but a FeNO level of 39 ppb or less.

    - Monitor peak flow variability for 2 to 4 weeks in children and young people (aged 5 to 16) if there is diagnostic uncertainty after initial assessment and a FeNO test and they have either:
        - normal spirometry or
        - obstructive spirometry, irreversible airways obstruction (negative BDR) and a FeNO level of 35 ppb or more.

    Regard a value of more than 20% variability as a positive test.

- Diagnosis in children and young people aged 5 to 16
- Consider alternative diagnoses and referral for specialist assessment in children and young people (aged 5 to 16) if they have symptoms suggestive of asthma but normal spirometry, a FeNO level of 34 ppb or less and negative peak flow variability.

- Diagnosis in adults aged 17 and over
    - Diagnose asthma in adults (aged 17 and over) if they have symptoms suggestive of asthma and:
        - a FeNO level of 40 ppb or more with either positive bronchodilator reversibility or positive peak flow variability or bronchial hyperreactivity or
        - a FeNO level between 25 ppb and 39 ppb and a positive bronchial challenge test or
        - • positive bronchodilator reversibility and positive peak flow variability irrespective of FeNO level

    - Suspect asthma in adults (aged 17 and over) with symptoms suggestive of asthma, obstructive spirometry and:
        - negative bronchodilator reversibility, and either a FeNO level of 40 ppb or more, or a FeNO level between 25 ppb and 39 ppb and positive peak flow variability or
        - positive bronchodilator reversibility, a FeNO level between 25 ppb and 39 ppb and negative peak flow variability.

    Do not rule out other diagnoses if symptom control continues to remain poor after treatment. Review the diagnosis after 6 to 10 weeks by repeating spirometry and objective measures of asthma control and reviewing symptoms.

    - Consider alternative diagnoses, or referral for a second opinion, in adults (aged 17 and over) with symptoms suggestive of asthma and:
        - a FeNO level below 40 ppb, normal spirometry and positive peak flow variability or
        - a FeNO level of 40 ppb or more but normal spirometry, negative peak flow variability, and negative bronchial challenge test or
        - obstructive spirometry with bronchodilator reversibility, but a FeNO level below 25 ppb, and negative peak flow variability or
        - positive peak flow variability but normal spirometry, a FeNO level below 40 ppb, and a negative bronchial challenge test or
        - obstructive spirometry with negative bronchodilator reversibility, a FeNO level below 25 ppb, and negative peak flow variability (if measured).
- Consider FeNO measurement as an option to support asthma management in people who are symptomatic despite using inhaled corticosteroids.

Be aware that a person's current smoking status can lower FeNO levels both acutely and cumulatively. However, a high level remains useful in supporting a diagnosis of asthma.

- Putting the Guideline into Practice:
    - NICE is recommending objective testing with spirometry and FeNO for most people with suspected asthma. This is a significant enhancement to current practice, which will take the NHS some time to implement, with additional infrastructure and training needed in primary care.
    - Testing for airway inflammation is increasingly used as a diagnostic strategy in clinical practice. This includes measuring fractional exhaled nitric oxide (FeNO).

The table below includes a diagnostic summary for asthma:

Test	Population	Positive Result
Fractional exhaled nitric oxide (FeNO)	Adults	40 ppb or more
FeNO	Children and young individuals	35 ppb or more
Obstructive spirometry	Adults, young people and children	Forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio less than 70% (or below the lower limit of normal if this value is available)
Bronchodilator reversibility (BDR) test	Adults	Improvement in FEV1 of 12% or more and increase in volume of 200 ml or more
BDR test	Children and young individuals	Improvement in FEV1 of 12% or more

Peak flow variability	Adults, young individuals and children	Variability over 20%
Direct bronchial challenge test with histamine or methacholine	Adults	Provocative concentration of methacholine causing a 20% fall in FEV1 (PC20) of 8 mg/ml or less
Direct bronchial challenge test with histamine or methacholine	Children and young individuals	N/A

(*Accessed February 2022*)

Regulatory Status

Until recently, most asthma management strategies did not depend on the recognition or diagnosis of a particular subtype. However, medications recently have been approved by the Food and Drug Administration (FDA) for the treatment of *severe asthma with an eosinophilic phenotype*. The measurements of NO and EBC are also being investigated in the diagnosis pathway to determine eosinophilic status.

The following list includes devices/systems have been cleared for marketing by the FDA. *Please note this is not an all-inclusive list*:

Device	Manufacturer	510(K) Approval	Description
Fenom Pro™ Nitric Oxide Test	Spirosure, Inc.,	2019	A class II medical device to measure the decrease in FeNO concentration in asthma patients that often occurs after treatment with anti-inflammatory pharmacological therapy as an indication of therapeutic effect in patients with elevated FeNO levels. FeNO measurements are to be used as an adjunct to establish clinical assessments. Fenom Pro™ is suitable for children, approximately 7-17 years, and adults 18 years and older. Testing using the Fenom Pro™ should only be done in a point-of-care healthcare setting under professional supervision. Fenom Pro™ should not be used in critical care, emergency care or in anesthesiology.

INSIGHT™ eNO System	Apieron	2008	The device was considered to be substantially equivalent to the predicate device, Aerocrine NIOX System. The intended use is to quantitatively measure exhaled nitric oxide in expired breath as a maker of inflammation for persons with asthma. The system can be used by trained operators in a physician's office laboratory setting, and should not be used in critical care, emergency care, or in anesthesiology. It is suitable for use in children ages 8 to 17 years of age, and in adults 18 years of age and older.
NIOX Breath Nitric Oxide Test System®	Aerocrine; acquired by Circassia	2003	Measurements of the fractional nitric oxide (NO) concentration in expired breath (FE-NO)] provide the physician with means of evaluating an asthma patient's response to anti-inflammatory therapy, as an adjunct to established clinical and laboratory assessments in asthma. NIOX should only be used by trained physicians, nurses and laboratory technicians. NIOX cannot be used with infants or by children approximately under the age of 4, as measurement requires patient cooperation. NIOX should not be used in critical care, emergency care or in anesthesiology."
NIOX MINO®	Aerocrine; acquired by Circassia	2008	The main differences between this new device and the NIOX are that the NIOX MINO is hand-held and portable and that it is not suitable for children under age 7 years.
Niox® Vero	Aerocrine; acquired by Circassia	2014	The is a portable gas analyzer intended to help physicians diagnose and assess asthma severity. Niox measures a patient's fraction of exhaled nitric oxide (FeNO) and is intended as a point-of-care test used to complement clinical examination and as a supplement or alternative to conventional spirometry asthma testing. differs from prior devices in terms of its battery and display format.

The RTube™ Exhaled Breath Condensate collection system (Respiratory Research) and the ECoScreen EBC collection system (CareFusion) are registered with the FDA as class

I devices that collect expired gas. Respiratory Research has a proprietary gas-standardized pH assay, which, when performed by the company, is considered a laboratory-developed test.

PRIOR APPROVAL

Not applicable.

POLICY

Exhaled Breath Condensate
Measurement of exhaled breath condensate is considered **investigational** in the diagnosis and management of all respiratory disorders including but not limited to the following:

- Asthma
- Chronic cough
- Chronic obstructive pulmonary disease (COPD)
- SARS-COV-2 (COVID-19)

Exhaled Nitric Oxide
Measurement of exhaled nitric oxide is considered **investigational** in the diagnosis and management of all respiratory disorders including but not limited to the following:

- Asthma and eosinophilic subtypes
- Chronic cough
- Chronic obstructive pulmonary disease (COPD)

The recent studies do prove that there is treatment change with the addition of FeNO measurements but fail to examine the effect of the treatment changes on outcomes. There is still no validated standardized cutoff of FeNO to use for diagnosing asthma. As a result, it is not possible to determine the true sensitivity and specificity of the test for diagnosing asthma or any other disorder. Further investigation is recommended because a negative result does not exclude asthma. Inhaled steroids are a mainstay of treatment of asthma and have been associated with a variety of health outcome benefits. The change in management must be examined to determine net benefits on health outcomes. Recent systematic review concluded FeNO guided management showed no statistically significant benefit in terms of severe exacerbations or ICS use but showed a statistically significant reduction in exacerbations of any severity. However, further research is warranted to clearly define which management protocols (including cut-off points) offer best efficacy and which patient groups would benefit the most. Additionally, ongoing research should provide guidance on whether characterization of asthma phenotypes by assessment of biomarkers improve asthma management. The evidence is insufficient to determine the effect of exhaled nitric oxide and exhaled breath condensate tests on health outcomes.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 95012 Nitric oxide expired gas determination
- 83987 pH; exhaled breath condensate

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POLICY HISTORY

Date	Reason	Action
February 2022	Annual Review	Policy Revised
February 2021	Annual Review	Policy Revised
February 2020	Annual Review	Policy Revised
February 2019	Annual Review	Policy Revised
February 2018	Annual Review	Policy Renewed
February 2017	Annual Review	Policy Renewed
February 2016	Annual Review	Policy Revised
March 2015	Annual Review	Policy Revised
April 2014	Annual Review	Policy Renewed
May 2013	Annual Review	Policy Renewed
May 2012		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
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