Exhaled Breath Tests

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INSTRUCTIONS FOR USE: Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

SCOPE: Providence Health Plan, Providence Health Assurance, and Providence Plan Partners as applicable (referred to individually as “Company” and collectively as “Companies”).

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☐ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

Notice to Medicaid Policy Readers: For comprehensive rules and guidelines pertaining to this policy, readers are advised to consult the Oregon Health Authority. It is essential to ensure full understanding and compliance with the state's regulations and directives. Please refer to OHA's prioritized list for the following coverage guidelines:

Exhaled Breath Tests: Are considered new and emerging medical technologies that are considered investigational, and therefore are not covered, because the current scientific evidence is not yet sufficient to establish the impact of these technologies on health outcomes

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

Exhaled Breath Tests for Gastrointestinal Conditions

I. Hydrogen breath testing is considered **not medically necessary** for the diagnosis or management of any condition, including but not limited to the following:

   A. Irritable bowel syndrome
   B. Small intestine bacterial overgrowth (SIBO)
   C. Lactose malabsorption
   D. Fructose intolerance
   E. Oro-cecal gastrointestinal transit

II. Methane breath testing is considered **not medically necessary** for the diagnosis or management of any gastrointestinal condition, including carbohydrate or other malabsorption syndromes.

III. Gastric emptying breath testing is considered **not medically necessary** for the diagnosis or management of any gastrointestinal condition, including but not limited to gastroparesis.

IV. Carbon Dioxide (CO_2) breath testing is considered **not medically necessary** for the diagnosis or management of any gastrointestinal condition or carbohydrate or other malabsorption syndromes, including but not limited to the following:

A. Lactose malabsorption
B. Bile acid malabsorption
C. Fat malabsorption

Exhaled Breath Tests for Respiratory Conditions

V. The following exhaled breath tests are considered **not medically necessary** for the diagnosis or management of any respiratory condition, including but not limited to asthma, chronic obstructive pulmonary disease (COPD) and chronic cough:

A. Nitric oxide analysis of expired breath (also known as fractional exhaled nitric oxide or FeNO)
B. Exhaled breath condensate (EBC), including assaying for all markers (e.g. pH, hydrogen peroxide).

Other Exhaled Breath Tests

VI. Carbon monoxide (CO) expired gas analysis (also known as end tidal CO or ETCO) is considered **not medically necessary** for the diagnosis or management of any condition, including but not limited to the following:

A. Respiratory conditions, including but not limited to asthma and COPD
B. Hemolytic disease
C. Conditions with abnormal bilirubin production

Link to Evidence Summary

POLICY CROSS REFERENCES

None

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

BACKGROUND

Exhaled breath tests measuring specific markers are currently being investigated as noninvasive techniques to aid in the diagnosis of respiratory disorders such as asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, pulmonary hypertension and are also suggested in the management of asthma. Other exhaled breath tests are proposed as diagnostic tools for gastrointestinal (GI) conditions including gastroparesis, lactose malabsorption, irritable bowel syndrome

and others. Examples of specific tests, the markers they measure, and conditions they are being proposed for are described below.

Exhaled Breath Tests for Gastrointestinal Conditions

Hydrogen Breath Test (HBT)

Hydrogen breath tests (HBTs) may be used to identify carbohydrate malabsorption, which is suspected in patients with symptoms suggestive of functional bowel disorders, including irritable bowel syndrome (IBS) and small intestinal bacterial overgrowth (SIBO). In these patients, HBTs are proposed as a tool to identify the underlying cause of the symptoms and thereby also potential treatments.[1]

HBTs are thought to detect carbohydrate malabsorption by assessing changes in hydrogen expiration following the administration of lactose, fructose, or other carbohydrates. In general, these tests involve the patient ingesting a carbohydrate substrate and then exhaling into a mouthpiece or tube connected to a breath testing device to obtain the breath sample. Samples are taken at baseline and then at timed intervals and then analyzed for hydrogen content.[1] HBT is purportedly used in conjunction with other tests for diagnosing IBS; however, there remains no definitive diagnostic test for IBS.

HBTs have also been investigated as a tool to identify SIBO by administering the HBT after ingestion of glucose, lactulose, or other compounds. The use of HBT to detect SIBO is based on the concept that when SIBO is present, fermentation by bacteria in the small intestine produces a large amount of H2, the magnitude and pattern of which may be used to distinguish SIBO-positive patients from SIBO-negative patients.[2] The HBT has been proposed as an alternative to the current diagnostic test, bacteriological analysis of jejunal or duodenal aspirate via endoscopy.

Along with hydrogen, HBTs have been investigated for detection of additional substrates, such as methane and carbon dioxide (CO_2), which remain in the gut in patients with functional bowel disorders. CO_2. These two substrates may be measured at the same time as hydrogen during the breath test, as all three substrates are produced by intestinal bacteria, diffuse into the bloodstream, and are then excreted in exhaled breath. Quantifying methane and CO_2 in conjunction with hydrogen is thought to increase the accuracy of the HBT. Since these gases are produced exclusively by microbial fermentation in the gut, they may potentially provide a surrogate measure indicating whether the substrate is remaining in the gut or is metabolized.[1]

Gastric Emptying Breath Test (GEBT)

Gastric emptying breath tests (GEBT) or gastric breath tests (GBTs) have been proposed as noninvasive tests to detect delays in gastric emptying. Historically, a number of GBTs were studied which labelled various substrates with 13C or 14C, including C-octanoic acid (or octanoate) for the purpose of evaluating various disorders including functional dyspepsia and diabetes. Most recently, a GEBT which consists of 13C-labelled spirulina (Cairn Diagnostics, formerly Advanced Breath Diagnostics) has been developed that is proposed as a noninvasive diagnostic test for gastroparesis.

This GEBT involves an initial baseline breath test after which the patient then consumes a proprietary test meal of Spirulina algae, containing nonradioactive 13C that can be measured by a gas isotope ratio mass spectrometry (GIRMS), which is an FDA-approved analytical system for conducting GEBT breath

analyses.[3] The spectrometer is used to analyze breath samples taken at intervals after the meal is consumed in order to detect how quickly the stomach empties solids by measuring the amount of the nonradioactive material in the patient's breath.

Currently, standard, gastric emptying tests are performed using scintigraphy. Alternative approaches to scintigraphy have been proposed, including upper gastrointestinal endoscopy, barium swallow, ultrasound, and wireless motility capsule testing. Unlike the GEBT, scintigraphy and other alternative tests are typically performed by specially trained healthcare providers and may require special precautions for handling of radiation-emitting compounds.

Exhaled Breath Tests for Respiratory Conditions

Fractional Exhaled Nitric Oxide (FeNO)

The measurement of nitric oxide (NO) concentration in expired breath has been proposed as test to diagnose several pulmonary conditions, including asthma. The test has been most frequently studied in the context of asthma, as an adjunct to and a replacement for established clinical and laboratory diagnostic tests for asthma, which currently include spirometry for lung function and asthma symptom scores. In addition, the test is also being evaluated as a tool to assess asthma control in order to guide management of asthma.

This test is based on the premise that NO, which is normally produced by the respiratory tract mucosa, is a mediator of airway inflammation that is substantially increased in the breath of asthma patients compared to healthy subjects. Therefore, an elevated level of NO in exhaled air, referred to as fractional exhaled NO (FeNO), has been proposed as a surrogate indicator or marker of airway inflammation.[4]

The FeNO test measures NO molecules exhaled in breath using a handheld electrochemical sensor or a large, stationary chemiluminescence gas analyzer. The test involves the patient exhaling through a mouthpiece that is connected to the analyzer and a flow control system in the device maintains exhalation at 50 milliliters (mL) per second, regardless of how forcefully a patient exhales. A visual display guides the patient to maintain an appropriate range of pressure while exhaling.[4]

Exhaled Breath Condensate (EBC)

Exhaled breath condensate (EBC) tests may be used to measure airway acidity or pH levels and has been proposed as a surrogate biomarker of the increased airway inflammation observed in patients with asthma and other respiratory conditions. In these patients, respiratory airway droplets and volatile gases trapped in expired air during its condensation are thought to be the cause of airway acidity.[5] Although breath pH is the most commonly studied marker using the EBC test, additional markers are currently being investigated for evaluating inflammatory lung disorders, including but not limited to hydrogen peroxide, oxides of nitrogen, prostaglandins, interleukins (IL-4 and IL-5) and others.

The EBC pH test involves the patient wearing a nose clip and breathing quietly for 10 to 15 minutes through a mouthpiece attached via a two-way non-rebreathing valve to a cooled condensing system. A standard pH meter measures the pH of the collected condensate. The EBC test, which can be performed at home or in an outpatient setting, is intended as an adjunct to standard testing.[5]

Carbon Monoxide (CO) Expired Gas Analysis

Exhaled carbon monoxide (CO) concentration can be quantitated in end-tidal breath CO (ETCO), and has been described as a candidate marker for airway inflammation in lung diseases like cystic fibrosis (CF) and asthma. The measurement of ETCO in the breath is thought to detect the rate of hemolysis and/or assist in the tracking of hemolytic conditions and well as conditions with abnormal bilirubin production.[6] Administration of the test involves placement of a catheter into a patient's nostril and sampling of patient's breath with background air check for base levels.

REGULATORY STATUS

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

Exhaled Breath Tests for Gastrointestinal Conditions

Hydrogen breath tests (HBTs) are regulated as class I devices that have been cleared via the U.S. Food and Drug Administration (FDA) 510(k) process under the product code NRH (system, breath management). These devices are designed to measure constituents of exhaled breath as an aid in the diagnosis of sugar/nutrient malabsorption and other conditions. Individual components, such as gas collecting vessels, gas calibration, and gas chromatography may have been approved separately.

Examples of systems for HBTs cleared by the FDA include:

- In 2004, the Micro H_2 breath monitoring device with Hydra software utility was approved for use for screening and diagnosis of lactose malabsorption. The device consists of a hand-held hydrogen breath monitor (cleared as K963376), a personal computer and software that acquires and logs successive breath measurement data from the hydrogen monitor and provides data analysis and organization functions.[7]

At the time of this review, there was only one gastric emptying breath test (GEBT) that had received approval from the FDA. This system was cleared for use through the FDA Premarket Approval process in 2015. This device, to be used with the GEBT test meal, is intended for use in the measurement of the rate of gastric emptying of solids and as an aid in the diagnosis of delayed gastric emptying in adults who are symptomatic for gastroparesis.[8]

Exhaled Breath Tests for Respiratory Conditions

The FDA regulates devices used to measure exhaled nitric oxide (NO) as class II devices. To date, all of the approved FeNO systems are intended to provide quantitative measurement of the fraction of

exhaled nitric oxide (NO) in expired human breath (FeNO). Examples of systems for measurement of exhaled NO cleared by the FDA 510(k) process include:

- In March 2008, the NIOX MINO® Airway Inflammation Monitor approved as a substantial equivalent to the previously cleared the NIOX. The NIOX MINO is intended to measure the decrease in FENO concentration in asthma in children aged 7-17 years and adults over 18 years.[9]

- November 2014 the NIOX VERO was approved for the same indications as its predecessors. This device differs from prior NIOX devices in terms of its battery and display format.[10]

- In 2008, The Apieron INSIGHT™ eNO System was approved as substantially equivalent to the predicate device, the Aerocrine NIOX System. The Apieron INSIGHT™ system is intended to measure the decrease in FENO concentration in asthma in children aged 8-17 years and adults over 18 years.[11]

There are various systems for the collection of EBC listed with the FDA as Class I exempt devices, which do not require a 510(k) premarket notification application and subsequent FDA clearance before marketing the device in the United States. Some of the devices that collect expired gas include:

- RTube™ Exhaled Breath Condensate collection system (Respiratory Research, Inc)

- The ECoScreen/ECoCheck collection system (CareFusion Germany 234 GmbH)

Carbon Monoxide (CO) Expired Gas Analysis

At the time of this review, there was only one end tidal carbon monoxide (ETCO) monitor that had received approval from the FDA. This system was cleared for use through the FDA 510(k) premarket notification process in 2015 as a class II device. This device is indicated for the monitoring of carbon monoxide from endogenous sources (including hemolysis) and exogenous sources (including CO poisoning and smoke inhalation) in exhaled breath.[12]

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of exhaled breath tests for the diagnosis and management of a variety of respiratory and gastrointestinal indications. Below is a summary of the available evidence identified through November 2023. The evidence review below is focused on the clinical validity and clinical utility of exhaled breath tests.

To assess clinical validity studies should compare test results to an appropriate reference standard, if available. For example, in the case of HBTs, results must be compared with results from duodenal biopsy or genotype for lactase deficiency.

To assess clinical utility, clinical or patient-relevant outcomes in patients who underwent an exhaled breath test should be compared to outcomes of patients who did not undergo testing. For example, for HBTs, outcomes of patients who underwent an HBT and had a positive result must be compared to outcomes of patients who underwent an HBT and had a negative result. The clinical utility of testing is established if test results are used to alter or direct patient management which then result in improved overall outcomes.

Hydrogen Breath Test (HBT)

Evaluation of Carbohydrate Malabsorption

In 2020 (archived 2022), Hayes published a review that evaluated the use of the HBTs in patients with functional bowel disorders (FBDs) and suspected carbohydrate malabsorption, including six studies that examined HBTs for the detection of lactose malabsorption (leading to lactase deficiency) and two studies that examined fructose malabsorption in patients with irritable bowel syndrome (IBS) or FBDs.[1] Only one randomized study was included in the review and all but one study included only adult patients. In terms of clinical validity, the review found that, based on a small number of studies, lactose HBTs had variable but moderate-to-high sensitivity (77%-100%) and negative predictive value (NPV) (67%-100%). However, the low specificity (53%-100%) and positive predicted value (PPV) (62%-100%) suggests that HBTs have a high rate of false-positive rates. This suggests that lactase HBTs may have potential as a "rule out" test for lactase deficiency, but not as a "rule in" test to diagnose lactase deficiency. In terms of the clinical utility of HBTs, the review stated that there was inconsistent evidence that the use of HBTs improved outcomes in patients with IBS or FBD symptoms, since patients tested for lactase and fructose deficiency benefited from dietary interventions regardless of the results of the HBT. Of note, there were no studies reporting the clinical validity of HBTs administered with fructose and no clinical studies at all on sucrose malabsorption. All studies included were determined to be of low quality, were all limited by their study design, and were considered to have high selection bias. As a result, the review rated the use of HBTs to evaluate lactose malabsorption as a "C" in adult patients, a "D2" in pediatric patients, and HBTs testing for fructose or sucrose malabsorption as "D2".

No additional studies were identified that reported on the clinical validity or clinical utility of HBTs for carbohydrate malabsorption since the publication of the Hayes review described above.

Diagnosis of Small Intestinal Bacterial Overgrowth (SIBO)

In 2020 (archived 2022), Hayes published a review that evaluated the use of the HBT for the diagnosis of small intestinal bacterial overgrowth (SIBO) in FBDs, including eight nonrandomized studies on adult patients.[2] Four of the studies included patients diagnosed with IBS and the remaining four studies included patients with unexplained bowel symptoms. In terms of clinical validity, the review found that, based on four number of studies, glucose HBTs had moderate-to-high specificity (80%-100%) and negative predictive value (NPV) (78%-97%). However, the low sensitivity (27%-64%) and the variable positive predicted value (PPV) (42%-100%) suggested that HBTs are not effective in correctly identifying the presence of SIBO in these patient populations. Test performance measures when lactulose was used

as the HBT substrate were worse than when glucose was used. Regarding the two studies included in the review that reported on clinical utility of HBT, it was found that only one small case-control study (n=94 patients) reported symptom improvement after treatment based on lactulose HBT test results. The other clinical utility study had widely varying treatment regimens, including 9 different drugs, with additional combinations of the drugs, all of which render the findings difficult to interpret. Both of these studies were deemed of poor quality. Limitations of the evidence-base for HBT for SIBO includes heterogeneity in terms substrate used, normal/abnormal cut-off values, and differences in diagnostic accuracy depending on substrate and the cutoff value.

No additional studies were identified that reported on the clinical validity or clinical utility of HBTs for SIBO since the publication of the Hayes review described above.

Gastric Emptying Breath Test (GEBT)

Only two small studies were identified that evaluated the clinical validity of GEBTs. In 2003, Zahn et al. published a small case series that measured gastric emptying by 13C-octanoic acid breath test versus scintigraphy in 24 diabetic patients.[13] All patients underwent a GEBT using 13C-octanoic acid and scintigraphy with 50 MBq 99mTechnetium-Nanocoll. The sensitivity of the 13C-octanoic acid breath test was reported as 100% and the specificity was 73%.

In 2008, Szarka et al. published an initial small industry-sponsored validation study on the use of the 13C-Spirulina GEBT, including 38 healthy volunteers and 129 patients with clinically suspected delayed GE.[14] All subjects underwent GEBT as well as standard scintigraphy with 0.5 mCi ^{99m}Tc to evaluate the use of GEBT. The authors reported that individual GEBT samples at 45, 150 and 180 minutes has a specificity of 80% when predicting whether GE was delayed, normal or accelerated. Only combined sensitivities were reported: 45 and 180 min samples combined were 93% sensitive to identify accelerated GE, and 150 and 180 min combined were 89% sensitive for delayed GE. The authors concluded by indicating that further studies were needed to determine if this test could be used in clinical practice.

No studies were identified that reported on whether the use of the GEBTs improved health outcomes of patients with gastroparesis or any other condition.

Fractional Exhaled Nitric Oxide (FeNO)

Diagnosis of Asthma

- In 2016 (archived 2021), Hayes published a review of evidence regarding the use of FeNO as a single measure for the diagnosis if asthma in patients with or without symptoms, including 13 nonrandomized studies in which FeNO was compared to other standard diagnostic techniques such as lung function, airway reversibility, immunoglobulin E, and sputum cytology.[4] The review included studies published up to September of 2016. Of note, this review included the recent high quality systematic review by Karrasch et al. and the health technology assessment by Harnan et al. conducted as part of the development of National Institute for Health and Care

Excellence (NICE) guidance update.[15,16] The review rated FeNO a "D1", indicating the published evidence shows that the use of FeNO testing to diagnose asthma does not improve health outcomes or patient management. Limitations of the current evidence-base include variability of sensitivity and specificity of FeNO results across study results due to heterogeneous FeNO cutoff values used (range: 13 to 60 ppb), patient age, and prevalence of eosinophilic asthma in study participants. In addition, studies varied in the reference standard tested used as a comparator. The review concluded the quality of evidence to support the use of FeNO to diagnose asthma was low, reflecting the lack of consistency across study findings, populations and testing protocols, and the poor reporting and lack of precision in patient and outcome data.

No studies were identified after the Hayes review described above that reported on the clinical validity or utility of FeNO testing to diagnose asthma.

- Additional systematic reviews report that FeNO may be a moderately accurate measure for the diagnosis of asthma, yet conclude that additional studies are needed to better establish validity and overcome limitations in trials conducted to date.[17-20]

Diagnosis of Respiratory Disorders other than Asthma

FeNO testing has been reported in several small case series as a potential tool for diagnosing other respiratory conditions including chronic obstructive pulmonary disease (COPD), different types of acute-onset interstitial lung disease, pulmonary fibrosis, primary ciliary dyskinesia.[21-24] However, most of these studies evaluated associations between FeNO and presence of disease, with very few studies reporting on test performance measures or clinical validity. Of those that did report on the diagnostic value of the FeNo test, specificities ranged from 58%-85%, while sensitivities ranged from 77%-89%, depending on the condition.

Management of Asthma

In 2016 (archived 2021), Hayes published a review of evidence regarding the use of FeNO in guiding asthma therapy in adults and children, including 17 randomized controlled trials (RCTs) published up to September 2016.[25] Twelve studies evaluated the use of FeNO as an adjunct to standard measures of asthma control and five RCTs evaluated the use of FeNO as a replacement measure. Study design and results were highly varied with inconsistencies among how FeNO results would alter current asthma medication regimens. There were a number of issues that complicated data interpretation, including differences in the asthma severity of included cohorts and variations in treatment protocols. The overall quality of evidence was rated low due to the following: "lack of a statistical correction for multiple comparisons, which increased the risk that the studies may have found a statistically significant result in error; inadequate reporting of any statistically significant baseline differences in some studies; poor adherence to medication in a number of studies; loss to follow-up; and a fairly short follow-up period in many studies." In addition, there was, "significant inconsistency in the direction of findings across studies, as well as the inconsistency in study protocol seen across the body of literature, making applicability to general practice difficult to interpret." The review assigned a "C" rating for the use of

FeNO to guide asthma therapy in adult and pediatric patients as the impact of FeNO on health outcomes has not been demonstrated and due to the limitations stated above.

A 2016 Cochrane systematic review evaluated the use of FeNO to inform asthma interventions compared to asthma therapy conducted without FeNO results in adults (N=1700 patients).[26] Seven studies met inclusion criteria and differed in methodological design, with varying definitions of asthma exacerbations, FeNo cutoff levels (15 to 35 ppb), and methods for adjusting therapy based on FeNO results. In addition, the durations of the studies ranged from 4-12 months and the mean age of participants ranged from 28 to 54 years. The studies ranged from very low to moderate quality and three studies were determined to have a high risk of bias due to inadequate blinding. The reviewers reported that the meta-analysis suggested 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." Similar limitations and conclusions were drawn by a second 2016 Cochrane review that evaluated the use of FeNO to guide treatment for children with asthma (N= 9 studies, 1426 patients).[27]

No studies were identified after the Hayes and Cochrane reviews described above that reported on the clinical validity or utility of FeNO testing to manage asthma.

Management of Respiratory Disorders other than Asthma

In 2008, Kunisaki et al. published the results of a small prospective study that evaluated the ability of FeNO to independently predict spirometric responses to inhaled corticosteroids (ICS) in patients with severe COPD, including 60 nonsmoking patients. [28] After four weeks on ICS, the authors reported that patients who were considered responders to ICS had higher FeNO values (46.5 ppb) than nonresponders (25 ppb; p=0.028). However, an optimal FeNO cutpoint to discriminate between responders and nonresponders could not be determined, and therefore optimal sensitivity and specificity could not be determined. For example, evaluating ≥60 ppb as a cut-point yielded a specificity of 94%, sensitivity of 50%, positive predictive value of 63% and negative predictive value of 88%.

In 2009, Drummer et al. published the results of a double-blind crossover trial that evaluated the ability of FeNO test results to predict oral corticosteroid response in COPD, including 65 patients with COPD who were 45 years or older, were previous smokers, and had persistent symptoms of chronic airflow obstruction.[29] The 65 patients were randomized to either 30 mg/d of prednisone or placebo for three weeks, but only 55 patients completed the study. The investigators reported that two of the three primary outcomes (6-minute walk distance [6MWD] and spirometry [FEV1]) increased significantly from baseline with prednisone compared with placebo (net increase of 13 m in 6MWD; p = 0.02 and net increase of 0.06 L in postbronchodilator FEV1; p= 0.02). There was a nonsignificant decrease in the third primary outcome, score on the St. George's Respiratory Questionnaire (SGRQ). At the optimal FeNO cutoff of 50 ppb, as determined by ROC analysis, there was 29% sensitivity and 96% specificity for predicting a 0.2-liter increase in FEV1. The investigators concluded that FeNO is only a weak predictor of short-term response to oral corticosteroid treatment in patients with severe COPD and its potential usefulness was limited to predicting increase in FEV1. Limitations of the study included short-term

measurement of response to treatment, and the fact that actual management decisions were not based on FeNO test results. In addition, the results of this study having limited applicability to a broader COPD population (e.g. those that smoke or are on inhaled corticosteroids.

Earlier prospective and retrospective studies have reported on the association between FeNO and response to ICS in COPD and other non-asthma respiratory diagnoses. A 2008 prospective study in 60 patients with severe COPD reported that patients who were considered responders to ICS had higher FeNO values (46.5 ppb) than nonresponders (25 ppb; p=0.028).47 However, an optimal FeNO cutpoint to discriminate between responders and nonresponders could not be determined.

Exhaled Breath Condensate (EBC) pH

In 2011 (archived 2014), Hayes published a review of exhaled breath condensate pH testing for asthma diagnosis and management, including three nonrandomized studies reporting on clinical validity, two of which included adult patients and one cross-sectional study that included only young children.[5] Only one small study included healthy control subjects for comparison. All included studies were heterogeneous in terms of study design (cross-sectional, case series and cohort), patient population in terms of age and smoking status, and outcomes assessed (including asthma diagnosis and degree of airway inflammation). No studies were identified that evaluated the role of EBC pH tests in treatment decision making or clinical management of patients with asthma. The included studies reported that using EBC pH was inferior to the current clinical reference standard for diagnosing asthma and the study on children found that EBC pH did not differ between children with and without symptoms suggestive of asthma. Therefore, the review concluded that there was "no consistent association between EBC pH and lung function, airway hyperresponsiveness, and airway inflammation", and that there was "insufficient evidence to support the use of EBC pH testing as a diagnostic or monitoring tool for asthma."

There have been several systematic reviews published after the 2011 Hayes review on the use of EBC for the evaluation and management of pediatric and adult asthma, with the most recent review published by Peele et al. in 2017.[30-32] However, these reviews have focused on reporting the association between various components and the presence or severity of disease. These reviews did not report any measures of clinical validity or clinical utility. Most of the studies included in these reviews were cross-sectional, there was wide variation in the definitions used to identify children and adults with asthma, and the collection devices and assays for EBC components varied between studies, with a large number of studies reporting the use of homemade condensing devices. Overall, the association of any given marker was variable between studies, even within similar study populations. This also includes the two most commonly studied markers, NO and pH. The reviews concluded that more consistent EBC collection and interpretation techniques are needed, as well as studies that evaluate the ability of EBC biomarkers to predict future asthma exacerbations and tailor asthma treatment.

Carbon Monoxide (CO) Expired Gas Analysis

A number of small case series have assessed the use of ETCO in predicting a variety of diseases including respiratory distress syndrome (RDS), predict chronic lung disease, hyperbilirubinemia, bronchopulmonary dysplasia (BPD), sickle cell anemia, cystic fibrosis and others.[33-38] These case series

ranged from 14-78 patients. While some studies reported associations between ETCO and the condition in question, others did not. Overall, test performance values, when reported, were promising, typically reporting sensitivities, and specificities between 80-90% and negative predictive values between 90-100%.[33,34] However, in the one study identified which evaluated ETCO for predicting hyperbilirubinemia, the positive predictive value of the test was 40%.[36] These studies are limited by their noncomparative study design, lack of follow-up data, small sample size and heterogeneity in terms of ETCO cut-off values used to calculated measures of clinical validity.

CLINICAL PRACTICE GUIDELINES

Gastrointestinal Conditions

American College of Gastroenterology

In 2020, the American College of Gastroenterology published clinical practice guidelines for the testing and treatment of small intestinal bacterial overgrowth (SIBO).[39] On the basis of a non-systematic review of "very low level" evidence, authors "conditionally recommended" breath testing for the diagnosis of SIBO.[39]

North American Consensus Group on Hydrogen and Methane-Based Breath Testing

In 2017, the North American Consensus Group on Hydrogen and Methane-Based Breath Testing recommended the use of breath tests for the diagnosis of small intestinal bacterial overgrowth.[40] Investigators stated, however, that "there is significant heterogeneity in test performance/preparation, the indications for breath testing and the interpretation of results." This recommendation was also limited by its lack of a systematic review of evidence, and a lack of detail about their evidence review methodology.

National Collaborating Centre for Nursing and Supportive Care (NCC-NSC) and National Institute for Health and Care Excellence (NICE)

In collaboration with the NICE, the NCC-NSC published guidelines for the diagnosis and management of irritable bowel syndrome in adults.[41,42] The updated 2017 guidelines recommended against the use of hydrogen breath testing for lactose intolerance and bacterial overgrowth as a means of diagnosing people who meet standard IBS diagnostic criteria. The guideline stated that an abnormal hydrogen breath test result does not provide a definitive diagnosis of either condition.

American College of Gastroenterology (ACG)

In 2013, the ACG published an evidence-based clinical guideline that recommended against the use of gastric emptying breath testing for diagnosis of gastroparesis, stating that the test requires further validation before it can be considered as an alternative to the gold standard of scintigraphy.[43] This recommendation was based on a moderate level of evidence.

Respiratory Conditions

Global Initiative for Asthma (GINA)

In 2021, GINA published guidance addressing asthma management and prevention.[44] Based on a systematic review of evidence, GINA stated that "FeNO has not been established as useful for ruling in or out a diagnosis of asthma."[44]

National Institute for Health and Care Excellence (NICE)

In 2021, NICE published guidance on the diagnosis and monitoring of asthma in adults, children and young people.[45] This guideline included a review of studies published up to 10/1/2014. Regarding the use of FeNO testing for diagnosis, the guideline reviewed cross sectional studies, cohort studies, case series and large case-control studies but did not include any randomized controlled studies, including five studies on adults and two studies on children/adolescents. Regarding the use of FeNO testing for asthma management, only RCTs were included.

For acute symptoms at presentation: FeNO was listed as one of several examples of tests that may be considered if the equipment is available and testing will not compromise treatment of the acute episode.

The guideline recommended the following:

Diagnosis:

- "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."

However, the guidelines noted that FeNO test results may be affected in patients who have been treated with inhaled corticosteroids or who currently smoke.

Management

- The guideline indicted that FeNO measurement may be an option to support asthma management in select patients despite using inhaled corticosteroids in specific circumstances. In addition, the routine use of FENO was NOT recommended by NICE for monitoring asthma management.

This guideline had several limitations. First, the review only included studies published prior to 10/1/2014, thereby precluding a significant number of studies published subsequently that were used as the basis of more recent recommendations by Hayes and Cochrane systematic reviews. Of note, two large (n=553 and 923 patients) prospective studies of fair quality published in 2015 were not included in the NICE review of the evidence for the use of FeNO for diagnosis. These studies, which were larger than the studies included in the NICE evidence review, reported optimal FeNO levels similar to the NICE studies, but low sensitivities (60%) and specificities (61-63%) (single study). In addition, six systematic

reviews and meta-analyses published in 2015 and 2016 were also omitted from the guideline. Despite having similar result, systematic reviews all reached differing conclusions regarding the diagnostic accuracy of FENO, indicating that considerable heterogeneity regarding FeNO testing still exists in the literature.

Second, only studies that reported sensitivity, specificity, positive and negative predictive values were included and only studies with a FeNO cut-off threshold for diagnosis between 20-50ppb. This excludes a large number of studies that used thresholds above 50ppb, which may have provided further insight into optimizing diagnostic FeNO values and/or allowed for better test performance values.

Third, the guideline only included two studies when assessing the diagnostic accuracy of children using FeNO who reported conflicting sensitivity values. One study was deemed to be of poor quality and one of fair quality. Within the five studies included on adult populations, test performance values were not consistently high.

Lastly, the studies used as the basis for the NICE diagnostic recommendations were limited by study design, patient heterogeneity, and large ranges for clinical validity measures between published studies. For the use of FeNO for asthma diagnosis, sensitivity ranged from 22-78%, specificity from 56-100%, positive predictive value from 43-100%, and negative predictive value from 48-100%. Studies used as the basis for the weak recommendation for FENO use for asthma management all suffer from at least one of the following limitations: high or very high risk of bias, serious imprecision as indicated by wide confidence intervals, and/or reporting of only indirect outcomes.

American Thoracic Society (ATS) / European Respiratory Society (ERS)

In 2020, ATS/ERS published evidence-based joint guidelines on the definition, evaluation, and treatment of severe asthma. The guideline offers a conditional recommendation based on low quality of evidence to use FeNO cutoff to Identify adolescents and adults with severe allergic asthma more likely to benefit from anti-IgE treatment.[46]

No clinical practice guidelines were identified for the remaining tests addressed in this policy for any indication.

EVIDENCE SUMMARY

To date, the body of evidence regarding the use of exhaled breath tests suffer from a number of limitations. There is a paucity of evidence related to all breath tests, all markers measured and all conditions evaluated. Overall, study heterogeneity and variation in the cutoff value used for interpretation of marker measurements indicates that these tests are not reliable for routine clinical use. Uniform protocols and test algorithms, which establish cutoff levels for the various markers and test interpretation parameters, are needed to evaluate the clinical validity and utility of exhaled breath testing as diagnostic and treatment management tools for any condition. In addition, the few evidence-based clinical practice guidelines identified that addressed specific exhaled breath tests in this policy recommended against the use of exhaled breath tests, including hydrogen breath testing for lactose intolerance and bacterial overgrowth, gastric emptying breath testing for gastroparesis, and FeNO testing to guide therapy for severe asthma.

BILLING GUIDELINES AND CODING

The following code is not specific to exhaled breath testing and is therefore NOT appropriate: 82542.

CODES*		
CPT	83987	pH; exhaled breath condensate
	91065	Breath hydrogen or methane test (eg, for detection of lactase deficiency, fructose intolerance, bacterial overgrowth, or oro-cecal gastrointestinal transit)
	95012	Nitric oxide expired gas determination
	0106U	Gastric emptying, serial collection of 7 timed breath specimens, non-radioisotope carbon-13 (13C) spirulina substrate, analysis of each specimen by gas isotope ra83987tio mass spectrometry, reported as rate of 13CO2 excretion
	84999	Unlisted chemistry procedure
	91299	Unlisted diagnostic gastroenterology procedure
	94799	Unlisted pulmonary service or procedure

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

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POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
2/2024	Annual update. No changes to criteria.