November 12, 2018

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On behalf of the joint membership of the American Thoracic Society (ATS) and the American College of Chest Physicians (CHEST), we appreciate the opportunity to comment on Anthems draft policy: Fractional Exhaled Nitric Oxide and Exhaled Breath Condensate Measurements for Respiratory Disorders. ATS and CHEST believe there are several problems with the draft Anthem coverage policy that should be addressed.

CHEST is a global leader in advancing best patient outcomes through innovative chest medicine education, clinical research, and team-based care with more than 19,000 members representing 100+ countries around the world. We join the American Thoracic Society in strongly opposing Anthem's decision to consider fractional exhaled nitric oxide (FENO) as an experimental procedure. FENO is an important test commonly used in clinical practice for evaluation and management, with clear evidence-based indications. There is a large body of published data supporting its role in asthma and allergic diseases as detailed in the response from the ATS, with which we fully agree."

The ATS is a medical professional society with over 16,000 members dedicated to the prevention, diagnosis, treatment cure and research of pulmonary disease, critical care and sleep disordered breathing. ATS members are thought leaders in the development of new technology to diagnose, manage and cure respiratory illness, including asthma and other reactive airway diseases. As such, we are keenly interested in Anthem's draft coverage policy: Fractional Exhaled Nitric Oxide and Exhaled Breath Condensate Measurements for Respiratory Disorders.

Further, the ATS has published a clinical practice guideline on the appropriate clinical application of FENO for patient care, titled: **An Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications (2011).** We believe the ATS guidelines continue to provide useful guidance to clinicians and insurers on the appropriate use of FENO for patient care. There are several key points we would like to make.

ATS does not accept industry support for any of its clinical practice guidelines. The ATS notes with concern the follow text found on page 4 of 13 in the draft Anthem coverage document:

> In an industry-supported clinical practice guideline on the interpretation of FENO for clinical applications (Dweik et al, 2011), the American Thoracic Society (ATS) states the following recommendations for individuals with asthma:

The ATS would like to correct the record. The ATS **does not** accept industry money for the development of any clinical practice guideline (or any official position document) developed by the ATS. In 2000, the ATS adopted a policy to ban industry funding for the development of all ATS documents, including clinical practice guidelines. Consistent with that policy, the ATS document: **An Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications** did **not** receive any industry funding. We are perplexed as to how Anthem staff received the impression that our guideline was industry supported. We are further concerned that Anthem staff, under the false impression that our statement was industry funded, may have dismissed our guideline recommendations, and that distribution of this inaccurate information damages the reputation of the ATS.

To correct these damaging errors, we strongly urge a) Anthem to explicitly correct the record in the next iteration of the draft document, b) for Anthem staff involved in the review process to be more familiar with the Institute of Medicine (now the National Academy of Medicine) Standards for Trustworthy Guidelines that prevent societies like ATS from accepting industry money when developing clinical practice guidelines and c) to the extent that Anthem's staff was biased in its review of the ATS guideline by the false impression of potential industry influence, Anthem staff should re-review the ATS guideline without concerns of industry bias.

FENO is not investigational. FENO is useful and clinically appropriate for use in the management of patients with asthma and other reactive airway diseases. As clearly stated in the 2011 ATS clinical practice guideline, FENO is not experimental. The ATS FENO guideline makes the following recommendations:

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

- We recommend accounting for age as a factor affecting FENO in children younger than 12 years of age (strong recommendation, high quality of evidence).
- We recommend that low FENO less than 25 ppb (, 20 ppb in children) be used to indicate that eosinophilic inflammation and responsiveness to corticosteroids are less likely (strong recommendation, moderate quality of evidence).
- We recommend that FENO greater than 50 ppb (. 35 ppb in children) be used to indicate that eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids are likely (strong recommendation, moderate quality of evidence).
- We recommend that FENO values between 25 ppb and 50 ppb (20–35 ppb in children) should be interpreted cautiously and with reference to the clinical context. (strong recommendation, low quality of evidence).
- We recommend accounting for persistent and/or high allergen exposure as a factor associated with higher levels of FENO (strong recommendation, moderate quality of evidence).
- We recommend the use of FENO in monitoring airway inflammation in patients with asthma (strong recommendation, low quality of evidence).
- We suggest using the following values to determine a significant increase in FENO: greater than 20% for values over 50 ppb or more than 10 ppb for values lower than 50 ppb from one visit to the next (weak recommendation, low quality of evidence).
- We suggest using a reduction of at least 20% in FENO for values over 50 ppb or more than 10 ppb for values lower than 50 ppb as the cut point to indicate a significant response to anti-inflammatory therapy (weak recommendation, low quality of evidence).

Each recommendation was presented with a strength of recommendation and quality of evidence rating, as required by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach for clinical practice guidelines. None of the recommendations explicitly state or imply that FENO is investigational. In fact, our guideline specifically outlines how FENO can and should be used in clinical practice. We are perplexed as to how Anthem staff could mis-read the clear intent of the ATS clinical practice guideline.

FENO is widely used in clinical practice. As shown in the below data table, in the Medicare population alone, FENO is widely used by U.S. physicians to manage patient with asthma and other reactive airway diseases. American Medical Association (AMA) Relative Value Scale Update Committee (RUC) data shows that in 2017, FENO (CPT 95012 – ***Nitric oxide expired gas determination***) was billed over 111,000 times by physician treating Medicare beneficiaries. These data do not include Medicaid or private payer billing frequency, which would show even higher FENO utilization.

CPT	2011	2012	2013	2014	2015	2016	2017e
95012	11,025	21,941	38,928	47,446	57,026	79,350	111,353

(source: AMA RUC data files)

In light of the Medicare frequency data alone, it is counter factual for Anthem to conclude that FENO is investigational.

Additional research published since the 2011 further support the clinical application of FENO for asthma and other reactive airway diseases.

1. Assessment of active airway inflammation, especially eosinophilic**.** The studies below have shown a relationship between eosinophilic airway inflammation and increased FENO levels in both children and adults with asthma of different severities before and after steroids as well as in sputum, bronchoalveolar lavage fluid, and bronchial biopsies. These studies support that FENO reflects enhanced eosinophilic infiltration in asthmatic patients' bronchial mucosa during an allergic exacerbation.

- **J Asthma Allergy. 2018 Apr 10;11:73-79. Both fractional exhaled nitric oxide and sputum eosinophil were associated with uncontrolled asthma. Gao J1 et al.**
- **Phenotypes in asthma: useful guides for therapy, distinct biological processes or both? Am J Respir Crit Care Med 2004; 170:579-580. Wenzel, S.**
- **Noninvasive assessment of airway inflammation in children: induced sputum, exhaled nitric oxide, and breath condensate. Eur Respir J 2000; 16:1008-1015. Gibson PG.**
- **The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. Clin Exp Allergy 2005; 35:1175-1179. Berry MA, et al.**

2. In children 5 years of age and older, FENO algorithms help in monitoring the response to anti-inflammatory meds, long-term controller meds, dose titration of controller meds, weaning from controller meds, and assessing treatment adherence.

- **The Clinical Utility of Fractional Exhaled Nitric Oxide (FENO) in Asthma Management [Internet]. Agency for Healthcare Research and Quality (US); 2017 Dec. Report No.:17(18)-EJC030-EF. Want Z, et al.**

3. In patients without an asthma diagnosis, but with symptoms suggestive of such, a FENO of >50 ppb in adults and >35 ppb in children suggests significant eosinophilic inflammation and the expectation of responsiveness to ICS. In subjects without an asthma diagnosis, FENO less than 25 ppb (<20 ppb children) suggests eosinophilic inflammation and responsiveness to ICS are unlikely. In this situation one should execute a more thorough differential diagnosis.

In patients with a diagnosis of asthma, the presence of symptoms with FENO >50 ppb in adults (>35 ppb children) may indicate: inadequate ICS dosing, high allergen exposure, and/or risk of exacerbation.

- **An Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications. Am J Resp Crit Care Med 2011. Vol 184:602-615. Dweik R, et al.**

4. Even when nonallergic asthmatic patients do not show sputum eosinophilia, FENO is highly predictive of ICS response at a cut-off point of 33 ppb.

- **Effects of steroid therapy on inflammatory cell subtypes in asthma. Thorax 2010; 65:384-390. Cowan DC, et al.**

5. Assessment of non-adherence in patients with ongoing asthma.

- **High exhaled nitric oxide levels correlate with nonadherence in acute asthmatic children. Ann Allergy Asthma Immunol. 2017 Apr;118 (4) 521-523. Tsai YG, et al.**

- **High exhaled nitric oxide levels correlate with nonadherence in acute asthmatic children. Tsai YG, Sun HL, Chien JW, Chen CY, Lin CH, Lin CY. Ann Allergy Asthma Immunol. 2017 Apr;118(4):521-523.**

- **The utility of fractional exhaled nitric oxide suppression in the identification of nonadherence in difficult asthma.**
  McNicholl DM, Stevenson M, McGarvey LP, Heaney LG.
  Am J Respir Crit Care Med. 2012 Dec 1;186(11):1102-8.

6. Provides insight into whether step-down dosing is a correct decision.
In diagnosed asthma with no symptoms, FENO values of <25 ppb in adults and < 20 in children suggest ICS dosing can be reduced or discontinued.

- **Allergy Asthma Proc 36:e1-e8, 2015. FENO as biomarker for asthma phenotyping and management. Ricciardolo FL, et al.**

7. Can help in the differential diagnosis of problematic cough: cough variant asthma versus other causes.

- **Respirology. 2008 May;13(3):359-364. Exhaled nitric oxide levels in patients with atopic cough and cough variant asthma Fujimura M, et al.**

8. Can help in the selection of which patients with exercise-induced bronchoconstriction may benefit from ICS use.

- **Nitric Oxide. 2012 Aug 15; 27(2):82087. Fractional exhaled nitric oxide (FENO) may predict exercise induced bronchoconstriction (EIB) in schoolchildren with atopic asthma. Grzelewski T, et al.**
- **Nitric Oxide. 2018 Jun 1:76:45-62. Exhaled NO as a predictor of exercise-induced asthma in cold air. Drebler M, et al.**

9. Gives insight into the prognosis of continuing a treatment program that does not control FENO.
The ATS Guidelines (above) suggest that a FENO less than 25 ppb in adults (<20 in children) is a strong indicator of an unlikely ICS response, whereas an FENO > 50 ppb in adults (>35 ppb in children) is a strong indicator of a likely response to ICS. (43) From the clinical perspective, this enables a clinician to elect to continue or discontinue ICS treatment and monitor the impact on FENO of the change. If the incorrect decision is made, a low FENO will likely rise. This suggests the diagnosis of asthma should be considered if sufficiently elevated in specific age groups with suggestive symptoms. FENO can be useful in differentiating asthma from other diseases with high sensitivity and specificity at pre-specified cut-off levels and opens the door to an improved diagnostic approach.

- **Am J Respir Crit Care Med. 2004; 169:473-478. Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests. Smith AD, et al.**

10. Alerts the clinician to possible exposure to an agent that triggers increased FENO in a patient who presents for evaluation but has no asthma symptoms.

- There is plenty of evidence in the references cited above and below to support this statement as it is well known allergen exposure increases exhaled nitric oxide in patients with asthma.

11. In patients with a diagnosis of asthma and symptoms, an FENO >50 ppb in adults (>35 ppb children) may indicate otherwise unanticipated high allergen exposure**.**

- **An Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications. Am J Respir Crit Care Med. 2011, 184: 602-615. Dweik RA, et al.**

12. FENO may be an early way to detect airway inflammation before symptoms and spirometric changes take place.

- **Association between fraction of exhaled nitric oxide and spirometry data and clinical control of asthma in children and adolescents. Rev Paul Pediatr 2018 Jan 15,36(1):8. Salviano LDDS.**

13. FENO enables physicians to significantly modify their treatment decisions: diagnosis, monitoring of controller medication effectiveness, ICS dosing, assessing adherence. This enable one to make more rational step-up or step-down ICS dosing decisions**.**

- **Measurement of fractional exhaled nitric oxide in real-world clinical practice alters asthma treatment decisions. Ann Allergy Asthma Immunol 2018 Apr, 120(4):414-418. Hanania Na, et al.**

14. An increase in FENO after specific inhalation challenges with occupational allergens is highly predictive of occupational asthma**.**

- **An increase of fractional exhaled nitric oxide after specific inhalation challenge is highly predictive of occupational asthma. Int Arch Occup Environ Health. 2018 Oct;91(7):799-809. Engel J, et al.**

15. FENO is cost-effective in the management of uncontrolled asthma given its ability to improve diagnostic accuracy, monitor treatment response, optimize inhaled corticosteroid dosing, and identify patient nonadherence.

- **Managed Care. 2018 Jul;27(7):34-41. A Review of the Utility and Cost Effectiveness of Monitoring Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management. Arnold RJ, et al.**

Attached, please find a copy of the ATS 2011 guidelines**: An Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications (2011).** For additional literature on the clinical application of FENO, please find the attached list of peer reviewed articles that further describe FENO's appropriate use and limitations.

In conclusion, the ATS and CHEST recommend Anthem revise its draft policy document to explicitly cover the appropriate use of FENO for the monitoring and management of patients with asthma.

In addition, the ATS and CHEST feels that Expired Breath Condensate (EBC) analysis should remain experimental. If you have questions or need additional information, please contact Mr. Gary Ewart in the ATS Washington D.C. office. Mr. Ewart can be reached at (gewart@thoracic.org) or at (202) 296-9970.

Sincerely,

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ATS Co-Chair
Joint ATS/ CHEST Clinical Practice Committee

Kevin Kotvitz, MD
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LIST of FENO REFERENCES:

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Exhaled nitric oxide in relation to asthma control: A real-life survey. Ricciardolo FL, Sorbello V, Bellezza Fontana R, Schiavetti I, Ciprandi G. Allergol Immunopathol (Madr). 2016 May-Jun;44(3):197-205. doi: 10.1016/j.aller.2015.05.012. Epub 2015 Nov 14.

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Review of exhaled nitric oxide in chronic obstructive pulmonary disease. Gelb AF, Barnes PJ, George SC, Ricciardolo FL, DiMaria G, Zamel N. J Breath Res. 2012 Dec;6(4):047101. doi: 10.1088/1752-7155/6/4/047101. Epub 2012 Jun 7. Review.

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