Clinical Benefits of FeNO Monitoring in Asthma

RYAN BURTON, MS, RPFT
Disclosures

Employee of Circassia Pharmaceuticals, Inc.
Objectives

• Nitric Oxide
• Inflammation in Asthma
• Phenotyping Personalized Medicine
• Aids in the diagnosis of Th2 allergic inflammation
• Instrument for optimizing the dose of inhaled corticosteroids (ICS)
• Non-Adherence to medication (ICS) / Improper Medication Technique
• Outcomes Data
• Helps to Identify Asthmatics Who Are Possible Candidates for Treatment with a Biologic
• Clinical Utility of FeNO testing / Guideline Support
• Cost Effectiveness / Current Reimbursement Coverage
• Case Study
Fractional Exhaled Nitric Oxide — (FeNO)
What is Nitric Oxide (NO)?

• NO is present in virtually all mammalian organ systems, including the human lung

• Present in the exhaled breath of all humans

• NO is recognized to play key roles in virtually all aspects of lung biology and has been implicated in the pathophysiology of lung diseases, including asthma

• The functions and effects of NO in the lung/airways reflect its key roles as a vasodilator, bronchodilator, neurotransmitter, and inflammatory mediator
  • Neonatal respiratory distress syndrome
  • Health/Fitness supplements

2011 ATS FeNO Guidelines on Interpretation
Nitric Oxide (NO) Production

• NO endogenous regulatory molecule
• Synthesis regulated by family of enzymes—NO synthases (NOS)
• Inducible NOS-derived NO is predominantly produced in bronchial wall epithelial cells
• Exhaled NO levels increase during Th2 (allergic) inflammation—often correlate with eosinophilic inflammation

Asthma Inflammation and Pathophysiology

Environmental factors

Airway inflammation

B lymphocyte
IL-3, IL-4, IL-13, IL-9

T lymphocyte
IL-3, IL-5
GM-CSF

Th2/Th1 cytokines (e.g., IL-13, TNF-α)

Environmental factors and inflammatory products

MUCUS

Acute inflammation

Bronchospasm

Acute inflammation

Persistent inflammation

Remodeling

Airway effects

Mast cell

Eosinophil

Neutrophil

Dendritic cell

B lymphocyte

T lymphocyte

IgE

IL-3, IL-4, IL-13, IL-9

TNF-α

Environmental microenvironment

Airway microenvironment

Initiation

Amplification

Propagation

Blood vessels

Smooth muscle

Myo (fibroblasts)

Acute inflammation and development of remodeling

Inflammation

Antigens

Epithelial cells

Phagocytes

Dendritic cells

Macrophages

Asthma

Adapted from Barnes et al. Pharmacological Reviews. 1998; Vol. 50 (4)
Fractional Exhaled Nitric Oxide — (FeNO)

ASTHMA AND INFLAMMATION
Misdiagnosis of Asthma Is Common

- Asthma symptoms are nonspecific and can be misleading\(^1\)
- Asthma is a clinical diagnosis; no single definitive test exists\(^1-3\)
- Objective information should be used\(^3\)
  - Lung function is difficult to assess, and is often normal in patients with asthma, even in some patients with severe asthma\(^4,5\)

> When objectively assessed, approximately 1/3 of patients diagnosed with asthma do not have asthma\(^3\)

*Data from a study with patients who had been diagnosed with asthma in the previous 5 years and had no evidence of current asthma and were prospectively assessed (symptoms, lung function, and bronchial provocation tests) while not using medications.

71% of misdiagnosed patients are on therapy\(^2\)

Pharmaceuticals represent the single-largest expenditure in asthma care\(^2\)

Asthma: A Syndrome of Variable Inflammation, Airflow Obstruction, and Symptoms

FeNO: A Monitoring Tool to Assist in Implementation of the Asthma Guidelines

**Diagnosis vs Classification of Asthma**

- **Reversible Airflow Obstruction**
- **Presence of Th2 Inflammation**
- **Symptoms**
- **Presence of Risk For Exacerbations**

**Monitoring to Reduce Exacerbations**

- **Titrate Dose of ICS to Control Inflammation**
- **Identify Severe Exacerbation Prone Phenotype**
- **Risk for Loss of Lung Function**
- **Identify Nonadherence**

FeNO, fractional exhaled nitric oxide.

FeNO: A Monitoring Tool To Assist In Implementation of the Asthma Guidelines


**Diagnosis vs Classification of Asthma**

- Reversible Airflow Obstruction
- Presence of Th2 Inflammation
- Symptoms
- Presence of Risk for Exacerbations

**Monitoring to Reduce Exacerbations**

- Titrate Dose of ICS to Control Inflammation
- Identify Severe Exacerbation Prone Phenotype
- Risk for Loss of Lung Function
- Identify Nonadherence

FeNO, fractional exhaled nitric oxide.
FeNO: A Monitoring Tool to Assist in Implementation of the Asthma Guidelines

FeNO, fractional exhaled nitric oxide.

Asthma: Inflammation is at the Core

INFLAMMATION

Airway Hyperresponsiveness  
Airway Obstruction

CLINICAL SYMPTOMS

Increased levels of NO production help identify allergic airway inflammation.

1 National Asthma Education and Prevention Program 2007
Guideline Recommendations for Stepwise Treatment of Asthma

**Intermittent Asthma**

**Step 1**
- Preferred: SABA PRN

**Step 2**
- Preferred: Low-dose ICS
- Alternative: Cromolyn, LTRA, nedocromil, or theophylline

**Step 3**
- Preferred: Medium-dose ICS + LABA OR Medium-dose ICS
- Alternative: Low-dose ICS + either LTRA, theophylline, or zileuton

**Step 4**
- Preferred: High-dose ICS + LABA AND Consider omalizumab for patients who have allergies
- Alternative: Medium-dose ICS + either LTRA, theophylline, or zileuton

**Step 5**
- Preferred: High-dose ICS + LABA + oral corticosteroid AND Consider omalizumab for patients who have allergies

**Step 6**
- Preferred: High-dose ICS + LABA + oral corticosteroid

**Persistent Asthma: Daily Medication**
- Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.

**Steps 2-4**: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).

Quick-relief Medication for All Patients • SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed • Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment

Step up if needed (first check adherence, environmental control, and comorbid conditions)

Step down if possible (and asthma is well controlled for at least 3 months)

Assess Control
Asthma Guidelines Approach

Accurate Diagnosis:
- Thorough History
- Spirometry/Reversibility Testing

Classify Severity:
- Impairment (Symptoms/Lung Function)
- Risk (Exacerbations)

Initiate Therapy Based on Severity Assessment

Ongoing Monitoring for Control:
- Symptoms/Spirometry

Fractional Exhaled Nitric Oxide — (FeNO)
Asthma Phenotypes: Not All Asthma is Th2 Inflammation!

80% of Pediatric Asthma is Allergic Driven
Mahr et al. Allergy Asthma Proc 34. 2013

50-60% of Adult Asthma is Allergic Driven
Fractional Exhaled Nitric Oxide — (FeNO)

AIDS IN THE DIAGNOSIS OF TH2 ALLERGIC INFLAMMATION
Aids in the Diagnosis of Asthma and Identifies Patients with Th-2 Mediated Allergic/Eosinophilic Airway Inflammation

• Typically asthma patients are diagnosed using traditional clinical methodology including symptoms, family history, and spirometry. ¹

• However, a large study recently published in JAMA pointed out that the traditional ways of diagnosing asthma are associated with a significant rate of misdiagnosis. ²

• Incorporating objective diagnostic measures can improve the accuracy of diagnosis. ³

• Spirometry is an objective and sensitive measure of airway obstruction and air flow, however it is not a measure of airway inflammation. ³

• Since the majority of patients with asthma have Th-2 mediated allergic/eosinophilic airway inflammation, incorporating biomarkers into the patient’s clinical evaluation improves the accuracy of diagnosis. ⁴

Elevated FeNO Distinguishes Asthma From Other Allergic Conditions

![Box plot showing FeNO levels for different conditions.](Figure from Cordeiro et al. With permission. AR, allergic rhinitis; NAR, nonallergic rhinitis; Cordeiro et al. Allergy Asthma Proc. 2011;32(2):119-126.)
Diagnostic Accuracy of FeNO, Blood Eosinophils, Total IgE And Their Combinations To Identify Sputum Eosinophils

ROC Characteristics for FeNO, Blood Eosinophils, IgE and combinations

Fractional Exhaled Nitric Oxide — (FeNO)

INSTRUMENT FOR OPTIMIZING THE DOSE OF INHALED CORTICOSTEROIDS (ICS)
Significantly Better Than FEV\textsubscript{1–}

FeNO Measurement Predicts ICS Responsiveness

In patients with nonspecific symptoms, a FeNO value of > 47 ppb is highly indicative of corticosteroid responsiveness.

FeNO measurement was significantly better than FEV\textsubscript{1}, bronchodilator for predicting response to inhaled fluticasone propionate (P < 0.01).

52 patients referred by their family practitioners to the hospital with persistent, previously undiagnosed respiratory symptoms.

FeNO Levels Indicate Poor Response to ICS in Patients With Non Eosinophilic Asthma


Noneosinophilic asthma (n=11)  
Eosinophilic asthma (n=12)

Mean methacholine PC_{20}, mg/mL

- Placebo
- Mometasone 400 µg/d

Noneosinophilic asthma

- Placebo: 0, 1, 1.5, 2
- Mometasone 400 µg/d: 0, 1, 1.5, 2

P=0.72

Eosinophilic asthma

- Placebo: 0, 1, 1.5, 2
- Mometasone 400 µg/d: 0, 1, 1.5, 2

P=0.01

Mean FeNO, ppb

- Placebo
- Mometasone 400 µg/d

Noneosinophilic asthma

- Placebo: 0, 8
- Mometasone 400 µg/d: 0, 8

P=0.14

Eosinophilic asthma

- Placebo: 0, 8
- Mometasone 400 µg/d: 0, 8

P=0.003

Week
Exhaled NO Identifies Steroid Responsiveness

FeNO measurements provide the physician with means of evaluating asthma patients’ response to anti-inflammatory therapy, as an adjunct to the established clinical and laboratory assessments in asthma. Not all patients with asthma will have an elevated FeNO level. FeNO levels should be interpreted in the clinical context.

Fractional Exhaled Nitric Oxide — (FeNO)

NON-ADHERENCE/TECHNIQUE TO MEDICATION (ICS)
Lack of Improvement in Medication Adherence in Asthma

- Adherence improvement strategies have included patient education, motivational interviewing, adherence feedback, provider communication skill training, and use of mobile communication technology.
- Collectively, most interventions had a positive but modest impact on adherence that was not sustainable long term.
- A sample of 9 studies conducted between 1996 and 2015 using objective measures of adherence indicate no overall change in adherence rates over 2 decades.
Asthma Patients do not Use Medication Inhalers Correctly

- High prevalence (90%) of inhaler technique errors (>1 error) across all devices.
- More than 20% of the patients demonstrated at least 4 errors when using their controller inhalers.

<table>
<thead>
<tr>
<th>TABLE II. The 12 most common DPI Diskus errors recorded in the iHARP study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Did not slide cover fully open</td>
</tr>
<tr>
<td>2. Dose lost after preparation because of holding downward</td>
</tr>
<tr>
<td>3. Shook inhaler device after dose preparation</td>
</tr>
<tr>
<td>4. Did not breathe out to empty lungs</td>
</tr>
<tr>
<td>5. Exhaled into the inhaler before inhalation</td>
</tr>
<tr>
<td>6. Did not put Diskus in mouth and seal lips around mouthpiece</td>
</tr>
<tr>
<td>7. Did not have head tilted such that chin is slightly upward</td>
</tr>
<tr>
<td>8. Insufficient inhalation effort (inhalation is not fast, forceful from the start, and as long as possible)</td>
</tr>
<tr>
<td>9. Did not inhale through mouth</td>
</tr>
<tr>
<td>10. No breath-hold follow inhalation (or holds breath for &lt;3 s)</td>
</tr>
<tr>
<td>11. Patient had expired inhaler or empty inhaler</td>
</tr>
<tr>
<td>12. After inhalation did not replace cover</td>
</tr>
</tbody>
</table>

Braido, JACI IP 2016
FeNO Measurement Detects ICS Nonadherence

- Randomized study in 54 patients ages 6-16
- Patients all had mild-moderate asthma and are currently not taking an ICS
- 4-week run-in period with ICS treatment of budesonide bid, followed by a 4-week wash-out period, and then an 8-week randomization to either budesonide or placebo.

Percent of Correct, Acceptable, Poor Inhaler Tests

Correct or acceptable inhaler technique over course of 40 years has remained below 50%
FeNO but Not FEV\textsubscript{1} Was Associated with ICS Non-Adherence

- Patients followed for 2.5yrs; total of 53 visits
- Mean FeNO levels were significantly reduced in patients with good ICS adherence
- FEV\textsubscript{1} levels were not substantially different among adherence groups
- Adherence determined by calculating number of doses taken per day/doses prescribed x 100. Good, moderate, and poor adherence defined as >75% adherence, 50% to 75% adherence, or <50% adherence to prescribed medication, respectively.

Fractional Exhaled Nitric Oxide — (FeNO)
Cochrane: FeNO-based Management Reduces Exacerbation Rates

<table>
<thead>
<tr>
<th>Population</th>
<th>Meta-Analysis Design</th>
<th>Odds Ratio for Reducing Exacerbations Using FeNO vs. Symptoms-based Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult¹</td>
<td>7 Studies, 1700 Randomized Subjects, 1546 Completed Study</td>
<td>OR 0.60 (95% CI 0.43-0.84); NNTB in one year = 12 (95% CI 8-32)</td>
</tr>
<tr>
<td>Pediatric²</td>
<td>9 Studies, 1426 Randomized Subjects, 1370 Completed Study</td>
<td>OR 0.63 (95% CI 0.49-0.83)</td>
</tr>
</tbody>
</table>

- Conclusions: Tailoring asthma medications based on FeNO levels (compared with primarily on clinical symptoms) decreases the frequency of asthma exacerbations.
- The rate of exacerbations (number of exacerbations per 52 weeks) was significantly reduced by at least 40% by incorporating FeNO into asthma management.
- Number needed to treat to benefit (NNTB) over 52 weeks was clinically relevant and very low (12 in adults, 9 in children)

Syk et al. 2013

- ACQ, SABA, ICS use recorded at every visit
- 181 total patients (93 FeNO, 88 Control) recruited from 17 primary care sites in Sweden, mild-to-moderate asthma
- Average age: 40.9 y FeNO, 41.1 y Control
- Baseline FEV₁ (% predicted): 84.3 ±14.1 FeNO, 83.7 ±12.5; Baseline ICS dose 400 μg/d

ACQ, Asthma Control Questionnaire; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; mAQLQ, mini Asthma Quality of Life Questionnaire; SABA, short-acting β₂-agonist. 1. Syk et al. J Allergy Clin Immunol Pract. 2013;1:639-648.
Real World Experience with Use of FeNO-LaForce Study

- Treatment decision-making study to evaluate the impact of FeNO testing on asthma management (physician assessment of inflammation, dosing and cost savings)
- Treatment decisions were altered (step up, step down, add-on) in 36% of subjects when FeNO was used in conjunction with standard clinical assessment, ACT, and spirometry

LaForce et al Annals Allergy Asthma Immun 2014
Measurement of FeNO in Real-World Clinical Practice

- Measurement of FeNO enabled clinicians to assess underlying airway inflammation, leading to a significant revision of their treatment plans compared with real-world clinical assessment of asthma alone.
- Clinical assessment was concordant with FeNO measurement in only 56% of cases, matching FeNO more frequently in patients with low inflammation (64%) vs high inflammation (34%).
- After FeNO measurement, clinicians modified their treatment plan in 31% and altered prescriptions for inhaled corticosteroids in 90% of cases.

---

**Table 1**

<table>
<thead>
<tr>
<th>Level of inflammation</th>
<th>Clinical assessment, n/N (%)</th>
<th>FeNO assessment, n/N (%)</th>
<th>Agreement, n/N (%)</th>
<th>Clinical underestimation vs FeNO, n/N (%)</th>
<th>Clinical overestimation vs FeNO, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>4,247/7,901 (53.8)</td>
<td>5,083/7,901 (64.3)</td>
<td>3,271/5,083 (54.4)</td>
<td>N/A</td>
<td>1,812/5,083 (35.6)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2,749/7,901 (34.8)</td>
<td>1,802/7,901 (22.8)</td>
<td>845/1,802 (46.9)</td>
<td>732/1,802 (40.6)</td>
<td>225/1,802 (12.5)</td>
</tr>
<tr>
<td>High</td>
<td>905/7,901 (11.5)</td>
<td>1,016/7,901 (12.9)</td>
<td>341/1,016 (33.6)</td>
<td>675/1,016 (66.4)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Abbreviations: FeNO, fractionated exhaled nitric oxide; N/A, not applicable.

*Agreement indicates the proportion of patients within the inflammation category defined by FeNO assessment who also were assessed clinically as belonging to that category. For the overall group, agreement between FeNO and clinical assessment was 4,457 of 7,901 (55.4%).*
Measurement of FeNO in Real-World Clinical Practice

Table 2
Changes Made to Corticosteroids (Inhaled Corticosterid, Inhaled Corticosteroid + Long-Acting β-Agonist, or Oral Corticosterid) Based on FeNO Measurements

<table>
<thead>
<tr>
<th>Change in corticosteroids</th>
<th>Study population (N=7,901), n (%)</th>
<th>FeNO subgroup, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (n=5,083)</td>
<td>Intermediate (n=1,802)</td>
</tr>
<tr>
<td>Start</td>
<td>1,163 (14.7)</td>
<td>179 (3.5)</td>
</tr>
<tr>
<td>Increase dose</td>
<td>503 (6.4)</td>
<td>59 (1.1)</td>
</tr>
<tr>
<td>Stop</td>
<td>230 (2.9)</td>
<td>182 (3.6)</td>
</tr>
<tr>
<td>Decrease dose</td>
<td>284 (3.6)</td>
<td>248 (4.9)</td>
</tr>
</tbody>
</table>

Abbreviation: FeNO, fractionated exhaled nitric oxide.

Figure 1. Changes in corticosteroids based on fractionated exhaled nitric oxide (FeNO) measurement for the overall survey population and individual inflammation subgroups.
Fractional Exhaled Nitric Oxide — (FeNO)

HELP TO IDENTIFY ASTHMATICS WHO ARE POSSIBLE CANDIDATES FOR TREATMENT WITH A BIOLOGIC
Severe Asthma vs Difficult to Control Asthma

**Severe refractory asthma** is characterized by difficulty to achieve disease control despite high dose inhaled steroids plus long acting beta agonists (LABAs) or oral corticosteroids (OCS).

**Difficult to control asthma** can be attributed to factors other than asthma itself such as: Non adherence, Poor inhaler technique, Comorbidities

- 5 - 10% of 26 million Americans suffering from asthma experience severe disease
- Approximately 1/2 of direct asthma costs related to care of patients with severe disease ($56 billion total, $28 billion for severe asthma)
- Patients with uncontrolled severe asthma incur up to 3x cost compared to controlled severe asthma ($21 billion)
- Pharmaceuticals represent the single largest expenditure for asthma care

Asthma Remains a Serious Health Risk in the United States

Cost

Patients with severe uncontrolled asthma estimated to incur nearly 40% of all asthma-related costs

- All asthma patients
- Patients with severe asthma
- Patients with uncontrolled severe asthma

Estimated annual direct cost

- $56 Billion
- $28 Billion
- $21 Billion

Despite guidelines, patients continue to experience exacerbations and a lack of asthma control

Only 5% to 10% of all asthma patients in the United States have severe asthma; however, they incur 50% of all direct asthma-related costs

Recommended Treatment Options for Severe Asthma

- **IgE (allergic)**
  - **Preferred**: 3-month trial of anti-IgE (omalizumab) → determine responsiveness
  - **Alternatives**: newer targeted biologics, or BT

- **Eosinophilic**
  - **Preferred**: Either biologic type with observation → switch if non-responsive
  - **Alternatives**: BT or new biologics**†** (currently in development)

- **Non-eosinophilic/Non-IgE (allergic)**
  - **Preferred**: BT
  - **Alternatives**: theophylline or biologics in development**†**

**BT** = Bronchial Thermoplasty
# Currently Available Biologic Agents for Asthma

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Indication</th>
<th>Approx Annual Cost (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab Xolair™ (2003)</td>
<td>Per serum IgE and body weight Average dose 2-4 vials SQ/q2 or 4 weeks</td>
<td>Moderate-severe allergic asthma not controlled by ICS in adults and children Boxed warning for anaphylaxis</td>
<td>$23,000-$45,792*</td>
</tr>
<tr>
<td>Mepolizumab Nucala™ (2015)</td>
<td>100mg SQ q4 weeks</td>
<td>Severe asthma aged 12 years and older with an eosinophilic phenotype</td>
<td>$30,300</td>
</tr>
<tr>
<td>Reslizumab Cinqair™ (2016)</td>
<td>3mg/kg IV q4 weeks (approx. 2 vials/month)</td>
<td>Severe asthma aged 12 years and older with eosinophilic phenotype Boxed warning for anaphylaxis</td>
<td>$40,320*</td>
</tr>
<tr>
<td>Benralizumab Fasenra™ (2017)</td>
<td>30mg SQ q4weeks x 3 months then q8weeks</td>
<td>Severe asthma aged 12 years and older with an eosinophilic phenotype</td>
<td>$38,000 (less after 1st year)</td>
</tr>
<tr>
<td>Dupilumab (expected 2018)</td>
<td>200-300mg SQ q2-4weeks</td>
<td>Not FDA approved. Phase III completed. Currently approved for atopic dermatitis.</td>
<td>$29,000-$40,000</td>
</tr>
</tbody>
</table>

* Additional costs for IV infusion/post infusion anaphylaxis monitoring
Helps to Identify Asthmatics Who Are Possible Candidates for Treatment with a Biologic

- A small minority of asthma patients cannot achieve control of their disease with traditional therapies and are considered for treatment with biologic therapy. ¹
- Decision making in these patients is difficult; FeNO helps to confirm ICS failures, non-adherence/compliance and identifies patients that have persistent airway inflammation despite optimization on current therapy.
- Baseline measurement of FeNO identifies patients with persistent inflammation and who will benefit most from a biologic such as omalizumab. ²
- FeNO identifies patients likely (and unlikely) to respond to Xolair® (omalizumab)²

Dupilumab Phase III: Liberty Asthma QUEST Study

Reduction of Risk of Severe Exacerbations at Week 52 by Baseline Blood Eosinophils and FeNO

Fractional Exhaled Nitric Oxide — (FeNO)

CLINICAL UTILITY OF FENO TESTING / GUIDELINE SUPPORT
Clinical Interpretation of FeNO Measurements (2011 ATS)

• Use of cut points rather than reference values
• Account for age as a factor in children <12 years old
• Clinical context in which FeNO is obtained should be taken into account and reported*
• When monitoring patients, clinically significant increase determined as
  • >20% significant change for levels >50 ppb
  • >10 ppb significant change for levels <50 ppb
• Decrease of >20% in an elevated FeNO level, which often occurs 2 to 6 weeks after initiation of anti-inflammatory therapy, supports that treatment was successful for reduction of inflammation

*Includes date, time of day, age, sex, ethnicity, height, weight, smoking status, reasons for test, prior diagnosis if known, whether patient was using ICS or oral steroids at time of testing, and number of measurements made. Dweik et al. Am J Respir Crit Care Med. 2011;184(5):602-615.
Interpretation and Clinical utility of FeNO score

**HIGH**
>50 ppb adults
>35 ppb children

- **New patient:** Start ICS
- **Existing asthma patient:** Check adherence and technique, consider increasing ICS

**INTERMEDIATE**
25-50 ppb adults
20-35 ppb children

- **New patient:** Consider ICS trial with follow-up if rest of clinical evaluation is consistent with asthma (symptoms, history, PFTs)
- **Existing asthma patient:** Check adherence and technique, consider increasing dose

**LOW**
<25 ppb adults
<20 ppb children

- **New patient:** Consider other diagnoses
- **Existing asthma patient:** Consider decreasing/discontinuing ICS and monitoring

---

Additional Factors Affecting FeNO Levels

- Airway infection (viral)
- Allergic rhinitis
- Atopy
- Nitrate-rich diet
- Acute Bronchodilator
- Spirometric maneuvers that cause bronchospasm
- Smoking
- Acute Bronchoconstriction
- Alcohol consumption
- Exercise

Effects generally not clinically significant

# Effect of Drug Therapy on FeNO Levels

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Effect on FeNO</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Marked Decrease</td>
<td>Less IL4/IL13 release&lt;br&gt;Less STAT 6 Activation in epithelium&lt;br&gt;Less iNOS Expression in epithelium</td>
</tr>
<tr>
<td>LTRA</td>
<td>Slight Decrease</td>
<td>Reduces eos&lt;br&gt;Slight less IL13 release</td>
</tr>
<tr>
<td>Anti-IgE</td>
<td>Decrease</td>
<td>Blocks Th2/mast cell activation&lt;br&gt;Less IL4/IL13 release</td>
</tr>
<tr>
<td>Anti IL4/IL13</td>
<td>Decrease</td>
<td>Reduces STAT 6 Activation in epithelium</td>
</tr>
<tr>
<td>Anti IL5</td>
<td>No Effect</td>
<td></td>
</tr>
<tr>
<td>Anti TNF-x</td>
<td>No Effect</td>
<td></td>
</tr>
<tr>
<td>Methylxanthines (theophylline, caffeine, etc)</td>
<td>No Effect</td>
<td></td>
</tr>
</tbody>
</table>
New Evidence to Support FeNO Monitoring in Asthma

• Cochrane 2018 Review¹
• UK NICE Guidelines: released 11/29/2017 ²
• NIH AHRQ Evidence Summary: released 12/21/2017 ³
• Cost Effectiveness
  • FeNO monitoring impacting treatment decisions⁴
  • FeNO cost model in asthma management⁵
  • Cost savings associated with FeNO use in a Medicare population⁶
  • FeNO cost model in identifying omalizumab responders⁷
  • Cost effectiveness review of FeNO monitoring in asthma management⁸

ATS, AAAAI and ACAAI Support the Use of FeNO Testing

American Thoracic Society (ATS)

American Academy of Allergy Asthma & Immunology (AAAAI)

American College of Allergy, Asthma & Immunology (ACAAI)


Guideline Support

Agency for Healthcare Research and Quality (AHRQ)

• The Agency for Healthcare Research and Quality (AHRQ) is the lead Federal agency charged with improving the safety and quality of America's health care system.
• AHRQ develops the knowledge, tools, and data needed to improve the health care system and help Americans, health care professionals, and policymakers make informed health decisions.

Key Findings
1. Depending on the FeNO cutoff (<20, 20-30, 30-40, >40 part per billion (ppb)) 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.
2. FeNO results can predict which patients will respond to inhaled corticosteroid therapy.
3. Using FeNO to manage long-term control medications including dose titration, weaning, and monitoring of adherence, reduces the frequency of exacerbations. https://www.ahrq.gov/
Guideline Support

National Institute for Health and Care Excellence (NICE)

• Fractional Exhaled Nitric Oxide (FeNO) can be used as a surrogate marker of eosinophilic airway inflammation with specific sensitivity/specificity for predicting asthma1,2

• 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.
  • A FeNO level between 25 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 and 39 ppb and positive peak flow variability, or positive bronchodilator reversibility, a FeNO level between 25 and 39 ppb and negative peak flow variability.

1. NICE guideline (NG80): Asthma: diagnosis, monitoring and chronic asthma management. Published November 2017. https://www.nice.org.uk/guidance/ng80
Guideline Support

National Institute for Health and Care Excellence (NICE)

• In Children and young people aged 5-16

• Diagnose asthma in children and young people (aged 5 to 16) if they have symptoms suggestive of asthma and:
  • A FeNO level of 35 ppb or more and positive peak flow variability or obstructive spirometry and positive bronchodilator reversibility.

• Suspect asthma in children and young people (aged 5 to 16) if they have symptoms suggestive of asthma and:
  • A FeNO level of 35 ppb or more with normal spirometry and negative peak flow variability.
  • A FeNO level of 35 ppb or more with obstructive spirometry but negative bronchodilator reversibility and no variability in peak flow readings.
  • Normal spirometry, a FeNO level of 34 ppb or less and positive peak flow variability.

1. NICE guideline [NG80]: Asthma: diagnosis, monitoring and chronic asthma management. Published November 2017. https://www.nice.org.uk/guidance/ng80
Fractional Exhaled Nitric Oxide — (FeNO)

COST EFFECTIVENESS/CURRENT REIMBURSEMENT COVERAGE
Why Would the Use of FeNO be Cost Effective?

- High Prevalence of asthma
- Misdiagnosis is common
- Poor control of asthma drives costs
- Asthma disease management strategies are effective but long term success is difficult
- FeNO monitoring is a low cost strategy; easily implemented, at the point of care
- FeNO reduces costs related to diagnosis, drug utilization and costs of exacerbations
- FeNO adds value and reduces costs across all severities of asthma

# 2017 / 2018 – Plans with New Positive Coverage

<table>
<thead>
<tr>
<th>2017</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tufts Health Plan</td>
<td>Highmark</td>
</tr>
<tr>
<td>Kaiser Permanente</td>
<td>Regence (Cambia)</td>
</tr>
<tr>
<td>Oklahoma HealthCare Authority</td>
<td>Independence Blue Cross</td>
</tr>
<tr>
<td>UPMC</td>
<td>BCBS of South Carolina</td>
</tr>
<tr>
<td>Group Health Cooperative</td>
<td>Aetna</td>
</tr>
<tr>
<td>Quartz</td>
<td></td>
</tr>
<tr>
<td>Passport Health Plan</td>
<td></td>
</tr>
<tr>
<td>Vantage Health Plan</td>
<td></td>
</tr>
</tbody>
</table>
Fractional Exhaled Nitric Oxide — (FeNO)

CASE STUDY
Case Study

Case: 34-year-old with possible asthma

Cassandra, a 34-year-old female, presents with suspected asthma and variable symptoms of cough, wheeze, and shortness of breath

• Is this asthma? If so, how would you characterize it?

• What other information do you need to make a decision about treatment?

*The case study presented is for educational purposes only and does not represent a real patient case.*
Case: 34-year-old with confirmed asthma

- Cassandra confirmed to have asthma based on history, elevated FeNO (80 ppb), and documented response to medium dose ICS
- History of two exacerbations requiring prednisone in the past year
- ACT 23
- Spirometry normal

Is Cassandra controlled?
How would you assess her risk for future exacerbations?
What other information do you need to make decisions about therapy?

*The case study presented is for educational purposes only and does not represent a real patient case.*
Summary

• Aids in the Diagnosis of Asthma and Identifies Patients with T2 Allergic Inflammatory Phenotype

• Instrument for Optimizing the Dose of Inhaled Corticosteroids (ICS)

• Uncovers Non Adherence to ICS

• Reduces the Likelihood of Exacerbations in Patients at Risk for Future Events

• Helps to Identify Asthmatics Who Are Possible Candidates for Treatment with a Biologic
FeNO Value

Simple

A + B = C

- Respiratory vital sign
- Quick and accurate objective test
- Numbers resonate with patients
- Easy for provider to administer / easy for the patient to perform

Informative

- Guides direction in treatment
- Seasonal or clinical trending

Drives Action

- Potential change in disease management – provides insight
- Provides information to physicians when patients are referred
- Patients may need to return for “inflammometry”¹ check