Measuring Exhaled Nitric Oxide in Asthma: Pro

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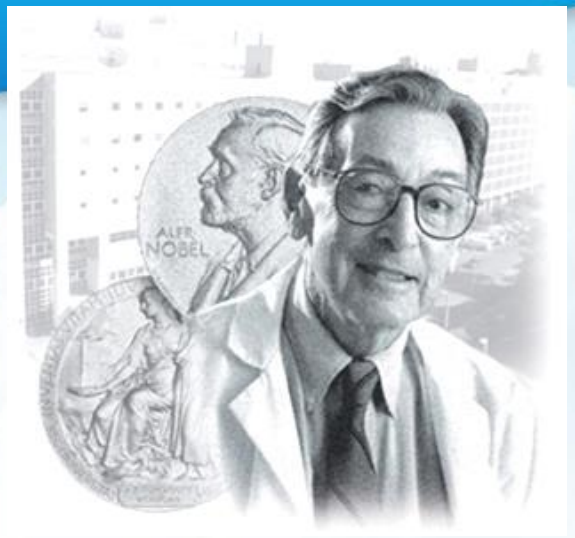
What is Nitric Oxide (NO)?



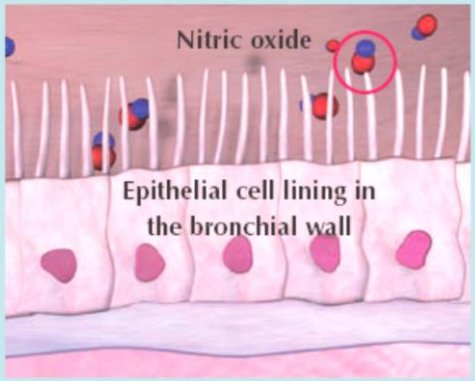
Drs. Robert F. Furchgott, Louis Ignarro & Ferid Murad 1998 Nobel Prize in Physiology or Medicine

- NO
  - A biological mediator in human
  - Highly reactive molecule/ free radical and has oxidant property
  - Signaling molecule
- Role of Nitric Oxide (NO)
  - Vasodilator
  - Bronchodilator
  - Neurotransmitter
  - Inflammatory mediator
- Production
  - Produced from L-arginine by NO synthase (NOS)
  - Inducible NOS (iNOS), neuronal NOS (nNOS), endothelial NOS (eNOS)

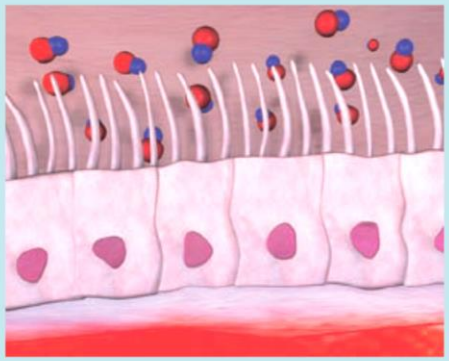
Reid DW, et al. Respirology 2003;8:479-86

Production of NO

- Upregulation of iNOS in the respiratory epithelium via TNF-α, IFN-γ, IL-4, IL-13, and IL-1β produces greater NO concentrations.



Normal epithelial cells. Minimal release of NO.

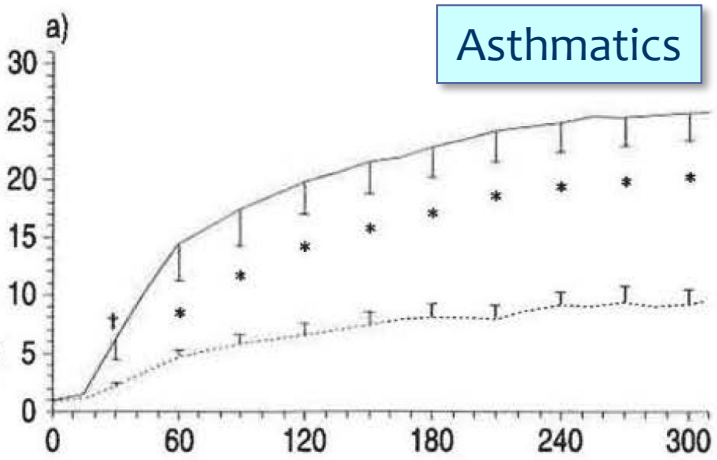


Activated epithelial cells during inflammation demonstrate increased production of NO.

- NO is measured in exhaled breath
  - fractional concentration of exhaled NO (FENO)

Exhaled NO in Asthmatics

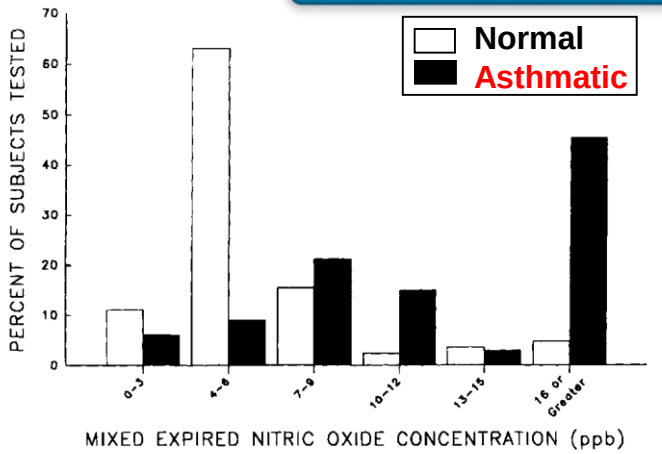
- 8 asthma patients
- 12 control



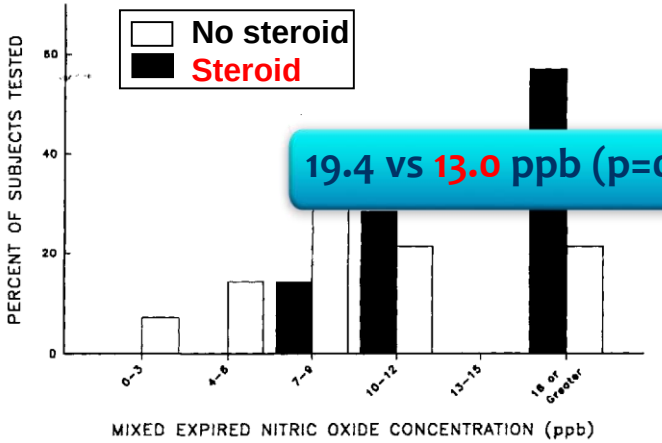
Alving K, et al. Eur Respir J 1993;6:1368-1370

- 43 asthma patients
- 90 normal subjects

6.2 vs 13.9 ppb (p <0.001)



19.4 vs 13.0 ppb (p=0.02)



Massaro AF, et al. AJRCCM 1995;152:800-3

1 What is NO?

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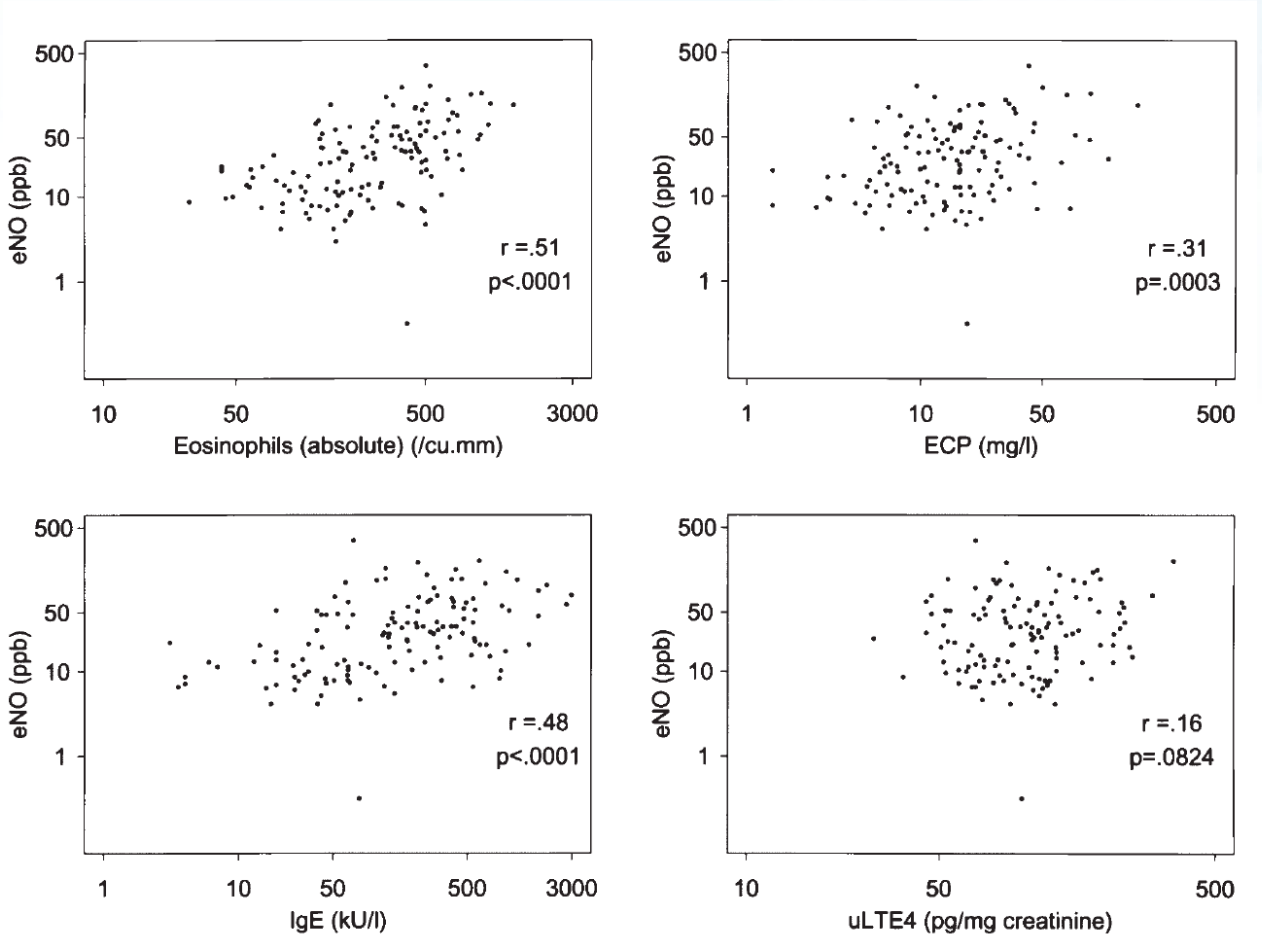
3 FENO in Asthma Guidelines

FENO and Blood Eosinophils

- 144 asthmatic patients



Strunk RC, et al. J Allergy Clin Immunol 2003;112:883-92

FENO and Sputum Eosinophils

- The largest study (n=566)

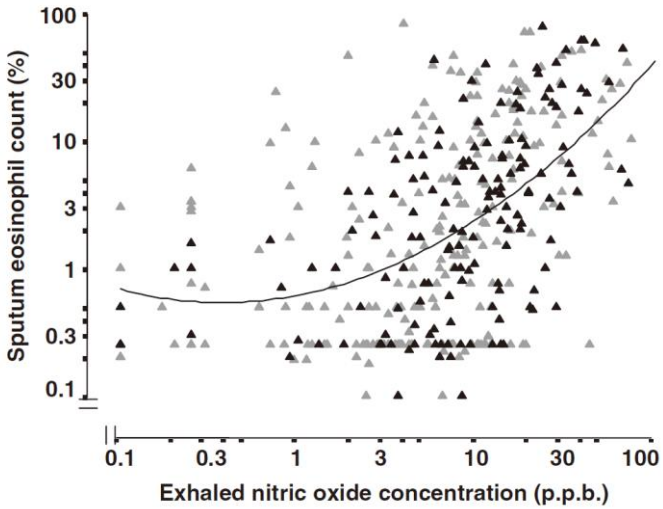


Table 3. Table of analysis of ROC curves of exhaled nitric oxide (NO) concentration at different flows to determine a sputum eosinophil count of >3% and correlation co-efficients for the association between exhaled NO concentration and sputum eosinophil counts at different flows

								Correlations	
Flow (mL/s)	Number	AUC	95% CI	*P*	Value (ppb)	Sensitivity	Specificity	Coefficient	*P*
10	60	0.68	0.54, 0.83	0.02	112	70	70	0.32	0.013
30	60	0.75	0.61, 0.88	0.002	53	74	72	0.37	0.004
50	60	0.77	0.63, 0.9	0.001	36	78	72	0.39	0.002
100	60	0.76	0.63, 0.89	0.001	22	78	72	0.39	0.002
200	60	0.73	0.59, 0.87	0.004	13	74	72	0.30	0.018
250	405	0.77	0.73, 0.82	<0.001	8.3	71	72	0.47	<0.001
CbrMax*	60	0.76	0.63, 0.89	0.001	87†	83	69	0.43	0.001

Berry MA, et al. Clin Exp Allergy 2005;35:1175-79

FENO and Eosinophils in BAL Fluid

- 71 subjects (29 asthma, 42 control)

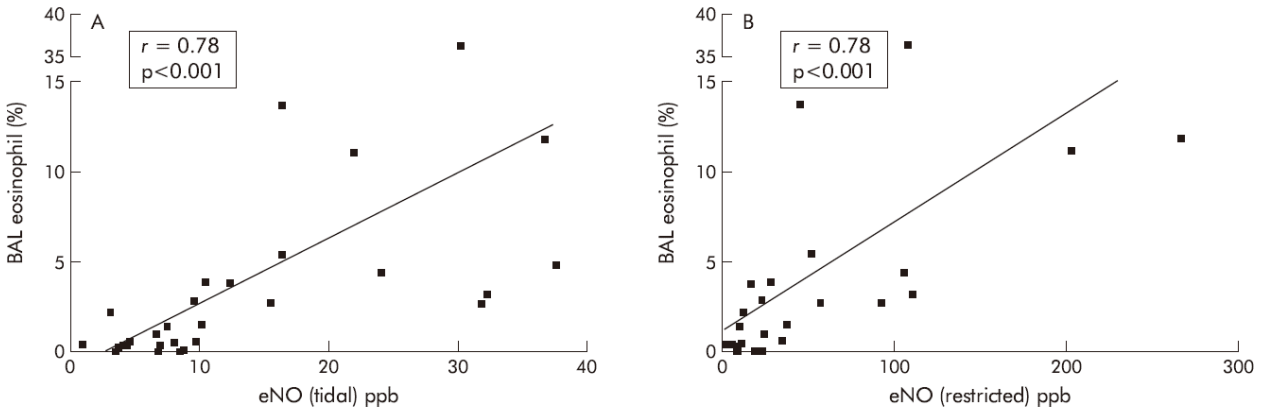


Figure 2 Spearman's correlations (*r*) between exhaled NO levels of asthmatic subjects measured by (A) tidal breathing and (B) restricted breath analysis and percentage BAL fluid eosinophils.

Table 2 Comparison of the sensitivity, specificity, and likelihood ratio of a positive test for the prediction of airways inflammation with the corresponding cut off values for eNO (measured by tidal breathing (TB) or restricted breath analysis (RB)) and blood eosinophil count

	AUC (SE)	Cut off value	Sensitivity (%)	Specificity (%)	Positive likelihood ratio
eNO (TB)	0.80 (0.07)	8.9 ppb	76	83	4.5
eNO (RB)	0.87 (0.05)	16.9 ppb	81	80	4.1
Blood eosinophils	0.74 (0.1)	5.6%	69	87	5.3

AUC = area under curve; eNO = exhaled nitric oxide; TB = tidal breathing; RB = restricted breath.

Warke TJ, et al. Thorax 2002;57:383-7

FENO and Biopsy Eosinophils

- 31 children with difficult asthma
- FENO obtained in 21 asthmatics

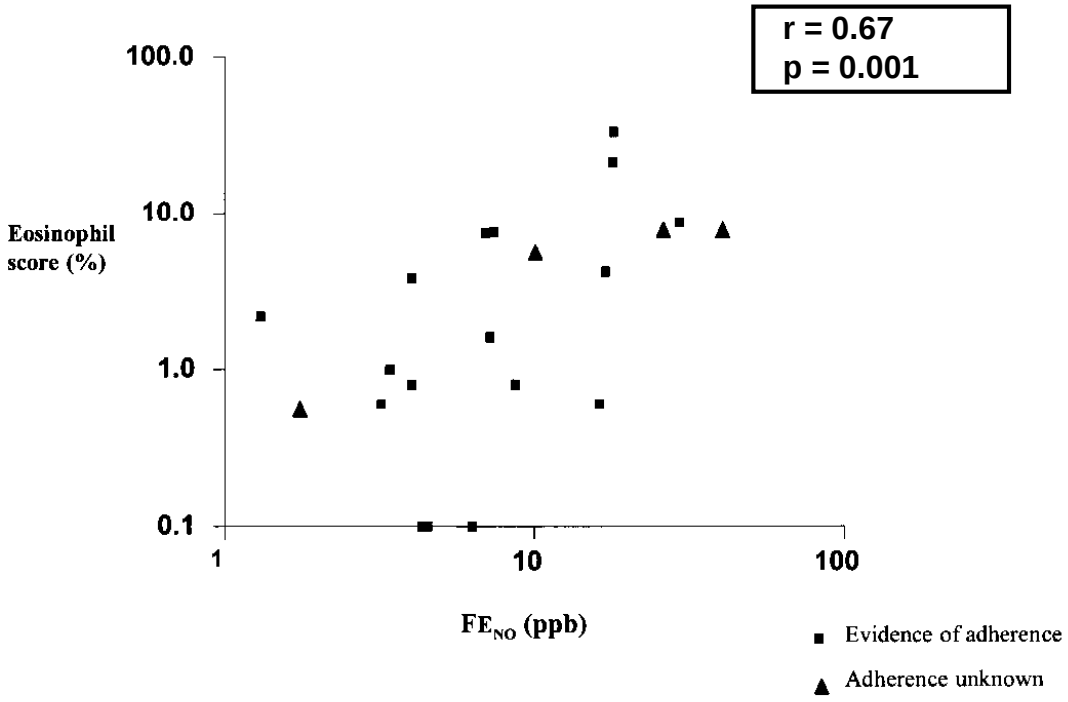


Figure 3. Correlation between FE_{NO} and eosinophil score.

Payne DN, et al. Am J Respir Crit Care Med 2001;164:1376-81

Markers for Airway Eosinophilia in Asthma

- Diagnostic accuracy for detection of airway eosinophilia

: meta-analysis of 32 studies (24 in adults and 8 in children)

	Studies in adults*			
	Studies assessing marker (n)	AUCs included (n)	Patients (n)	AUC† (pooled 95% CI)
FeNO	17	19	3216	0·75 (0·72–0·78)
Blood eosinophils	14	14	2405	0·78 (0·74–0·82)
Serum IgE	7	7	942	0·65 (0·61–0·69)
Serum periostin	2	3	204	0·65 (0·49–0·81)
Serum ECP	2	2	174	0·72 (0·64–0·81)
EBC pH	2	2	96	0·76 (0·63–0·90)

Korevaar DA, et al. Lancet Respir Med 2015;3:290-300

Markers for Airway Eosinophilia in Asthma

	Sputum eosinophils ≥3%				Sputum eosinophils ≥2%			
	Studies (n)	Patients (n)	Sensitivity (95% CI)	Specificity (95% CI)	Studies (n)	Patients (n)	Sensitivity (95% CI)	Specificity (95% CI)
FeNO (ppb)	12	1720	0·66 (0·57–0·75)	0·76 (0·65–0·85)	9	1667	0·65 (0·55–0·74)	0·75 (0·62–0·84)
Blood eosinophils (per µL)	12	1967	0·71 (0·65–0·76)	0·77 (0·70–0·83)	6	1180	0·66 (0·56–0·75)	0·83 (0·62–0·94)
Blood eosinophils (%)	5	920	0·76 (0·52–0·90)	0·74 (0·67–0·80)	2	171	..	..
Serum IgE (IU/mL)	6	699	0·64 (0·42–0·81)	0·71 (0·42–0·89)	4	754	0·63 (0·36–0·84)	0·59 (0·37–0·79)

FeNO=fraction of exhaled nitric oxide. ppb=parts per billion.

Table 2: **Summary estimates of sensitivity and specificity for detecting sputum eosinophilia in adults**

FENO, blood eosinophils, and IgE have moderate diagnostic accuracy for detection of airway eosinophilia in asthma.

Korevaar DA, et al. Lancet Respir Med 2015;3:290-300

FENO and AHR

- 85 subjects (40 asthma patients)

Table 2 Optimal cut off values for eNO and bronchial provocation tests for the diagnosis of asthma

	Best cut off value	Sensitivity % (95% CI)	Specificity % (95% CI)
eNO	>7 ppb	82.5 (67.2 to 92.7)	88.9 (76.0 to 96.3)
Exercise	⩾10% fall	57.9 (38.5 to 70.7)	100 (91.8 to 100)
MCH	⩽3 mg/ml	87.5 (73.2 to 95.8)	86.7 (73.2 to 95.0)
AMP	⩽150 mg/ml	89.5 (75.2 to 97.1)	95.6 (84.9 to 99.5)

eNO, exhaled nitric oxide; MCH, methacholine; AMP, adenosine 5′-monophosphate.

Measurement of exhaled NO can be used as a diagnostic test of asthma and is as good as bronchial provocation test.

Berkman N, et al. Thorax 2005;60:383-388

Diagnosis of Asthma

- 47 subjects (17 asthma, 30 control)

TABLE 3. SENSITIVITY, SPECIFICITY, AND POSITIVE AND NEGATIVE PREDICTIVE VALUES FOR EACH OF THE DIAGNOSTIC TESTS FOR ASTHMA

	Asthma ($n = 17$)		Nonasthma ($n = 30$)		Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
	Yes	No	Yes	No				
Bronchodilator reversibility > 12%	7	10	0	30	—	—	—	—
Bronchial hyperresponsiveness	17	0	29*	1	100	97	94	100
Peak flow variation > 20%	0	17	0	29*	0	100	NA	70
Peak flow steroid response > 20%	0	17	0	29*	24	100	100	69
FEV$_1$ < 80% predicted	5	12	0	30	29	100	100	71
FEV$_1$ < 90% predicted	6	11	2	28	35	93	75	72
FEV$_1$/FVC ratio < 70%	6	11	0	30	35	100	100	73
FEV$_1$/FVC ratio < 80%	8	9	6	24	47	80	57	73
FEV$_1$ improvement with steroid > 15%	2	15	0	29*	12	100	100	66
Sputum eosinophils > 3%	12	2*	3	23*	86	88	80	92
F_{ENO50} > 20 ppb	14	2†	6	22†	88	79	70	92

FENO measurements and induced sputum eosinophilia are superior to conventional tests

TABLE 4. MATRIX OF COMPARISONS FOR AREAS UNDER THE CURVE FOR RECEIVER–OPERATOR CHARACTERISTIC CURVES FOR EACH OF THE DIAGNOSTIC TESTS

	AUC	Peak Flow Variation	Peak Flow Steroid Response	FEV$_1$/FVC Ratio	FEV$_1$ (*% Predicted*)	FEV$_1$ Steroid Response	Eosinophils
Peak flow variation	0.626						
Peak flow steroid response	0.640	0.117 (p = 0.453)					
FEV$_1$/FVC ratio	0.678	0.429 (p = 0.334)	0.303 (p = 0.381)				
FEV$_1$ (% predicted)	0.804	**1.753 (p = 0.040)**	1.548 (p = 0.061)	1.324 (p = 0.093)			
FEV$_1$ steroid response	0.554	−0.537 (p = 0.296)	−0.754 (p = 0.225)	−0.926 (p = 0.177)	**−2.118 (p = 0.017)**		
Eosinophils	**0.861**	**2.201 (p = 0.014)**	**2.279 (p = 0.011)**	1.565 (p = 0.059)	0.626 (p = 0.266)	**2.557 (p = 0.005)**	
F_{ENO50}	0.864	**2.086 (p = 0.018)**	**2.332 (p = 0.010)**	1.734 (p = 0.041)	0.786 (p = 0.216)	**2.643 (p = 0.004)**	0.036 (p = 0.486)

Smith AD, et al. Am J Respir Crit Care Med 2004;169:473-8

Diagnosis of Asthma

- Meta-analysis of 4,691 participants (19 publications)

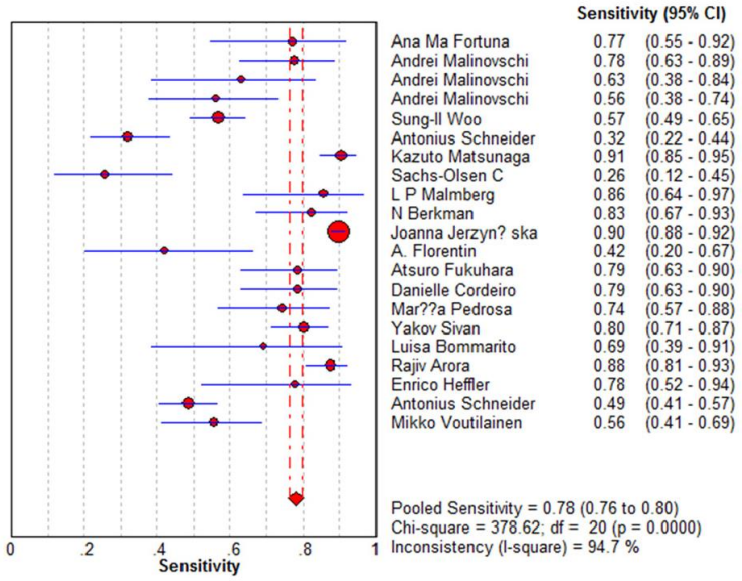


Figure 1. Forest plot of estimates of sensitivity for eNO in the diagnosis of asthma. Point estimates of sensitivity from each study are shown as solid circles, the size of which reflects the total number of cases and controls.

Sensitivity: 0.78 (95% CI 0.76-0.80)

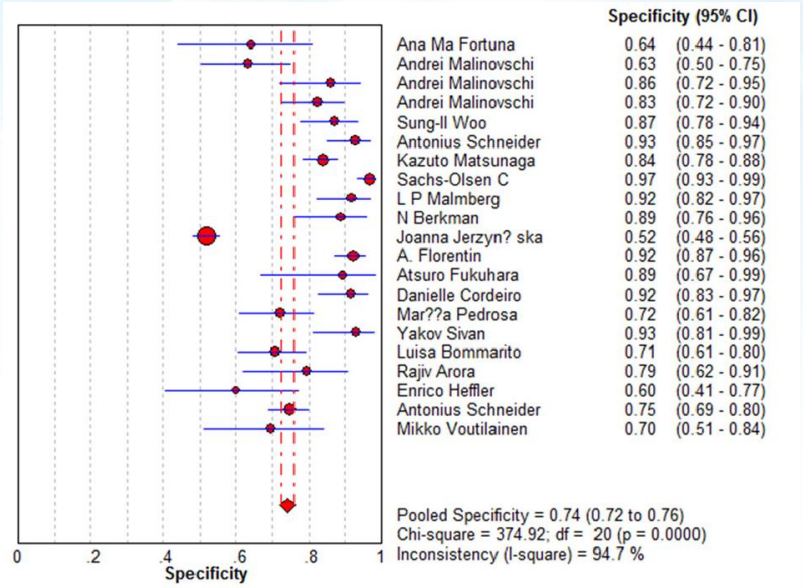


Figure 2. Forest plot of estimates of specificity for eNO in the diagnosis of asthma. Point estimates of specificity from each study are shown as solid circles, the size of which reflects the total number of cases and controls.

Specificity: 0.74 (95% CI 0.72-0.76)

Diagnostic odds ratio: 11.37 (95% CI 7.54-17.13)

Li Z, et al. Int J Clin Exp Med 2015;8:8516-8524

Diagnosis of Asthma

- Meta-analysis of 3,983 subjects (25 studies)

Table 2. Pooled diagnostic accuracy of FeNO.

Group (No. of studies/ No. of patients)	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratio + (95%CI)	Likelihood ratio – (95%CI)	DOR (95%CI)	AUROC
The entire population (25/3983)	72% (70–74%)	78% (76–80%)	4.34 (3.39–5.55)	0.29 (0.22–0.37)	15.92 (10.70–23.68)	0.88
Patients using corticosteroids (6/950)	53% (48–58%)	78% (74– 81%)	2.45 (2.05–2.92)	0.59 (0.53–0.67)	4.47 (3.39–5.90)	0.76
Steroid-naïve patients(19/3033)	77% (75–79%)	78% (76–80%)	5.12 (3.67–7.13)	0.24 (0.18–0.31)	21.40 (15.38–29.76)	0.89
Non-smoking patients (14/2134)	77% (74–79%)	83% (81–85%)	4.65 (4.03–5.36)	0.26 (0.22–0.29)	19.84 (15.63–25.19)	0.89
Smoking patients (3/228)	50% (38–62%)	84% (77–89%)	3.16 (2.08–4.81)	0.58 (0.45–0.75)	5.41 (2.97–9.86)	0.91
Chronic cough patients (5/873)	85% (81–89%)	85% (82–88%)	5.58 (4.75–7.22)	0.17 (0.13–0.22)	35.36 (23.90–52.29)	0.92
Allergic rhinitis patients (2/167)	50% (39–61%)	70% (59–80%)	2.09 (0.70–6.28)	0.69 (0.54–0.88)	2.99 (0.85–10.45)	NA

DOR, diagnostic odds ratio; AUROC, area under the curve for the receiver-operating characteristic.

FENO is accurate for the diagnosis of asthma in steroid-naïve or non-smoking patients, particularly chronic cough patients

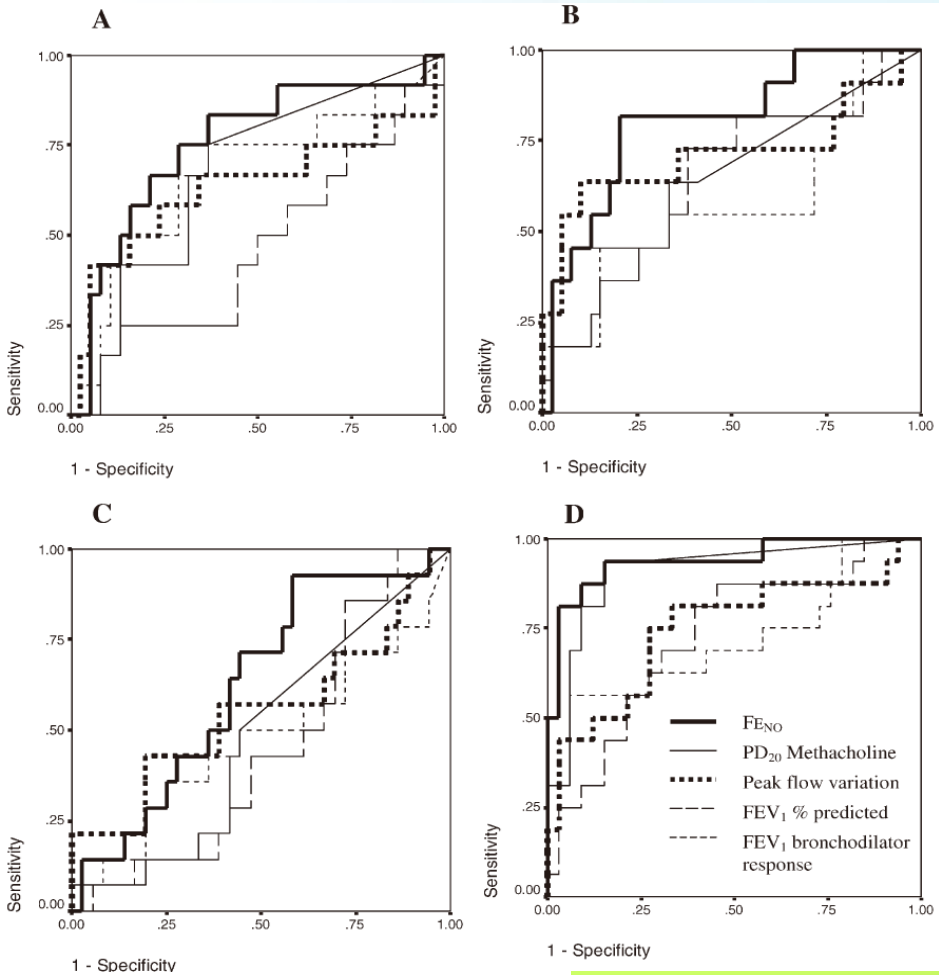
Guo Z, et al. J Asthma 2016;53:404-12

Strategy	Description*	Parameter*	Range of predictive values* (Note that a single value indicates data from a single study)				Comments**
Strategies for demonstrating airway obstruction							
Spirometry	Regard a FEV_1/FVC ratio of less than 70% as a positive test for obstructive airway disease.	Obstructive spirometry in adults Obstructive spirometry in children (5-18 yrs)	23–47% 52%	31–100% 73%	45–100% 75%	18–73% 49%	In the four larger studies (adults and children), the NPV was between 18% and 54% which means that more than half of patients being investigated who have normal spirometry will have asthma (ie false negatives).
Strategies for demonstrating variability in airway obstruction							
Broncho-dilator reversibility	In adults, regard an improvement in FEV_1 of ≥12% and ≥200 ml as a positive test. In children regard an improvement in FEV_1 of ≥12% as a positive test.	Bronchodilator reversibility in adults Bronchodilator reversibility in schoolchildren (using a threshold of 9% change in FEV_1)[70]	17–69% 50%	55–81% 86%	53–82%	22–68%	In these secondary care populations, about 1 in 3 people with a positive reversibility test will not have asthma (the cohorts all included people with COPD); and at least 1 in 3 people with a negative bronchodilator reversibility test will have asthma.
Challenge tests	Regard a PC_{20} value of 8 mg/ml or less as a positive test.	Methacholine challenge in adults. Methacholine challenge in children[30,42,71]	51–100% 47–86%	39–100% 36–97%	60–100% 20%	46–100% 94%	Challenge tests are a good indicator for those with a definitive diagnosis of asthma already (based upon clinical judgment, signs and symptoms and response to anti-asthma therapy)
Strategies for detecting eosinophilic inflammation or atopy							
FeNO	Adults: Regard a FeNO level of 40 ppb or more as a positive test Children 5–16yrs: regard a FeNO level of 35 ppb or more as a positive test.	FeNO in adults FeNO in schoolchildren	43–88% 57%	60–92% 87%	54–95% 90%	65–93% 49%	These studies are all in secondary care populations. Approximately 1 in 5 adults with a positive FeNO test will not have asthma (ie false positives) and 1 in 5 adults with a negative FeNO test will have asthma (ie false negatives).
Blood eosinophils	Suggested thresholds for blood eosinophils: Adults >4.15% Children ≥4%[64]	Blood eosinophils in adults Blood eosinophils in children	15–36% 55–62%	39–100% 67–84%	39–100% 56–69%	27–65% 73%	Elevated blood eosinophil level is poorly predictive. The threshold varies in these studies from 4.0 to 6.3%.
IgE		Any allergen-specific IgE >0.35 kU/l in adults Total IgE in adults >100 kU/l	54–93% 57%	67–73% 78%	5–14% 5%	95–99% 99%	A normal IgE substantially reduces the probability of asthma in adults with a false negative rate of less than 1 in 10, although a positive result is poorly predictive.
Skin prick testing		Any positive test (wheal ≥3 mm) in adults Any positive test (wheal ≥3 mm) in children	61–62% 44–79%	63–69% 56–92%	14–81% 65–92%	39–96% 36–79%	

British Guideline for Asthma- September 2016

FENO as a Predictor of Steroid Response

- 52 patients with undiagnosed respiratory symptoms



ROC curves for each tests as predictors of steroid response (AUC)

	A. FEV1	B. Peak flow	C. Symptom	D. PC20 AMP
FENO	0.76	0.81	0.64	0.91
FEV1%	0.47	0.68	0.45	0.68
BDR	0.66	0.57	0.46	0.71
PD20	0.63	0.65	0.45	0.84
Peak flow	0.63	0.58	0.45	0.72

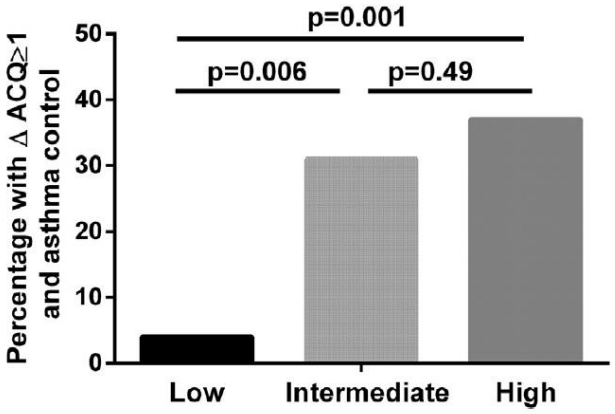
Smith AD, et al. Am J Respir Crit Care Med 2005;172:453-9

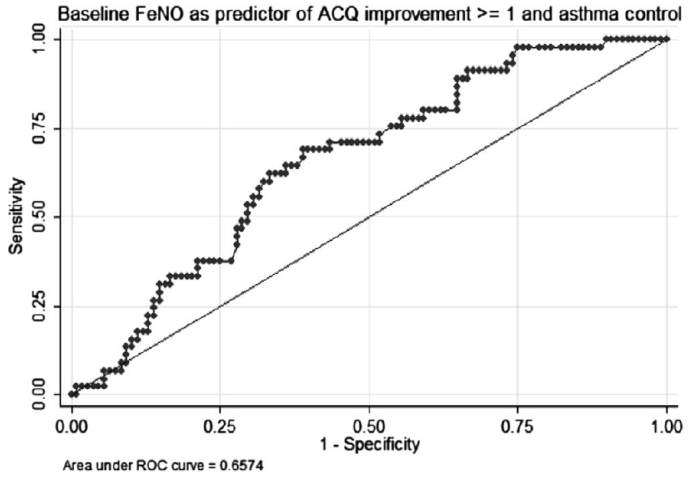
FeNO as a Predictor of ICS response

- 153 steroid-naïve subjects with asthma

Table 2
Factors associated with achieving asthma improvement and/or control ($n = 146$). Results presented as adjusted odds ratios (aOR) and 95% confidence interval (CI) from multiple logistic regression analyses where all variables listed in the first column were predictors and achieving asthma improvement and/or control was outcome. An association is significant if the CI does not include 1.

	Achieving improvement of ACQ with 0.5 ($n = 123$)	Achieving improvement of ACQ with 1 ($n = 100$)	Achieving improvement of ACQ with 1 and asthma control (ACQ $\leqslant$ 0.75) ($n = 45$)
Displaying intermediate FeNO vs low FeNO	1.53 (0.33, 7.12)	7.63 (1.65, 35.3)	9.46 (1.11, 80.8)
Displaying high FeNO vs low FeNO	1.23 (0.33, 4.63)	4.10 (1.10, 15.2)	14.0 (1.75, 112)
ACQ at initial visit (per ACQ unit)	3.27 (1.86, 5.76)	5.81 (3.17, 10.7)	1.32 (0.92, 1.88)
Height (per 10 cm)	1.06 (0.47, 2.40)	1.40 (0.65, 3.03)	1.28 (0.67, 2.42)
Age (per 10 years)	1.22 (0.84, 1.77)	1.07 (0.74, 1.55)	1.03 (0.77, 1.37)
FEV_1 (per 10% pred)	1.20 (0.84, 1.70)	1.20 (0.88, 1.65)	1.20 (0.94, 1.54)
Female gender	1.02 (0.23, 4.61)	1.41 (0.34, 5.84)	1.87 (0.59, 5.93)
Atopy	1.31 (0.23, 7.35)	0.34 (0.06, 1.97)	0.73 (0.22, 2.41)
Time to follow-up (per 10 days)	0.99 (0.98, 1.01)	0.99 (0.98, 1.01)	1.00 (0.98, 1.01)
Dose of ICS (per 100 microgram)	1.05 (0.85, 1.30)	0.91 (0.77, 1.08)	0.96 (0.85, 1.10)





Malinovschi A, et al. Nitric Oxide 2014;40:110-6

FENO as a Predictor of Steroid Response

- 94 asthma (65 EA, 29 NEA)

Table 7 Areas under the curve (AUC) for receiver operator characteristic analyses in which measurements of FEV_1 at baseline, FEV_1 at loss of control (LOC) or 28 days after steroid withdrawal, change in FEV_1 with bronchodilator at baseline, AHR as measured by $PD_{15}HS$ and by $PC_{20}AMP$ and F_{ENO} were used as predictors

	EA			NEA		
Predictors	**$\Delta PC_{20}AMP$**	**ΔFEV_1**	**ΔACQ**	**$\Delta PC_{20}AMP$**	**ΔFEV_1**	**ΔACQ**
FEV_1 (baseline)	0.308	0.613	0.254	0.305	**0.849**	0.387
FEV_1 (LOC)	0.426	**0.818**	0.411	0.315	**0.865**	0.379
BD response	0.435	0.609	0.549	0.429	0.616	0.470
$PD_{15}HS$	0.538	0.597	0.558	0.500	0.401	0.641
$PC_{20}AMP$	0.686	0.691	**0.710**	0.656	**0.708**	0.646
F_{ENO}	**0.778**	0.699	**0.727**	**0.810**	0.354	0.631

The outcomes were: change in airway hyper-responsiveness as measured by $PC_{20}AMP$ ($\Delta PC_{20}AMP$), change in FEV_1 (ΔFEV_1) and change in ACQ (ΔACQ) following 28+ days of inhaled fluticasone treatment in 60 patients with eosinophilic asthma (EA) (49 for $PC_{20}AMP$) and 28 patients with non-eosinophilic asthma (NEA). An AUC of >0.7 is considered significant.
ACQ, Asthma Control Questionnaire; BD response, bronchodilator response; FEV_1, forced expiratory volume in 1 s; F_{ENO}, fraction of exhaled nitric oxide; $PC_{20}AMP$, provocation concentration of adenosine monophosphate causing a 20% fall in FEV_1; $PD_{15}HS$, provocation dose of hypertonic saline causing a 15% fall in FEV_1.

In non-eosinophilic asthma, steroid responsiveness is best predicted by baseline exhaled NO.

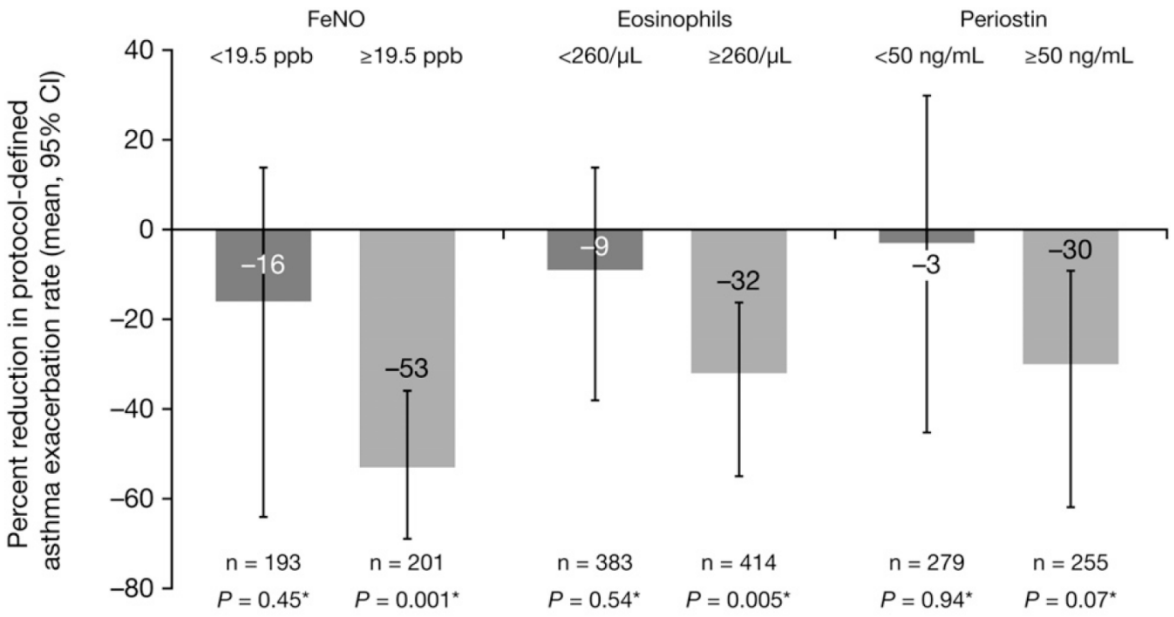
Cowan DC, et al. Thorax 2010;65:384-90

FENO as a Predictor of Treatment Effects of Omalizumab

Exploring the Effects of Omalizumab in Allergic Asthma

An Analysis of Biomarkers in the EXTRA Study

- 850 patients with uncontrolled severe persistent allergic asthma



Exacerbation rates						
	Low FeNO at baseline	High FeNO at baseline	Low eosinophils at baseline	High eosinophils at baseline	Low periostin at baseline	High periostin at baseline
Omalizumab	0.60	0.50	0.65	0.70	0.73	0.66
Placebo	0.71	1.07	0.72	1.03	0.72	0.93

Hanania N, et al. Am J Respir Crit Care Med 2013;187:804-11

Biologic Agents in Asthma and Biomarkers

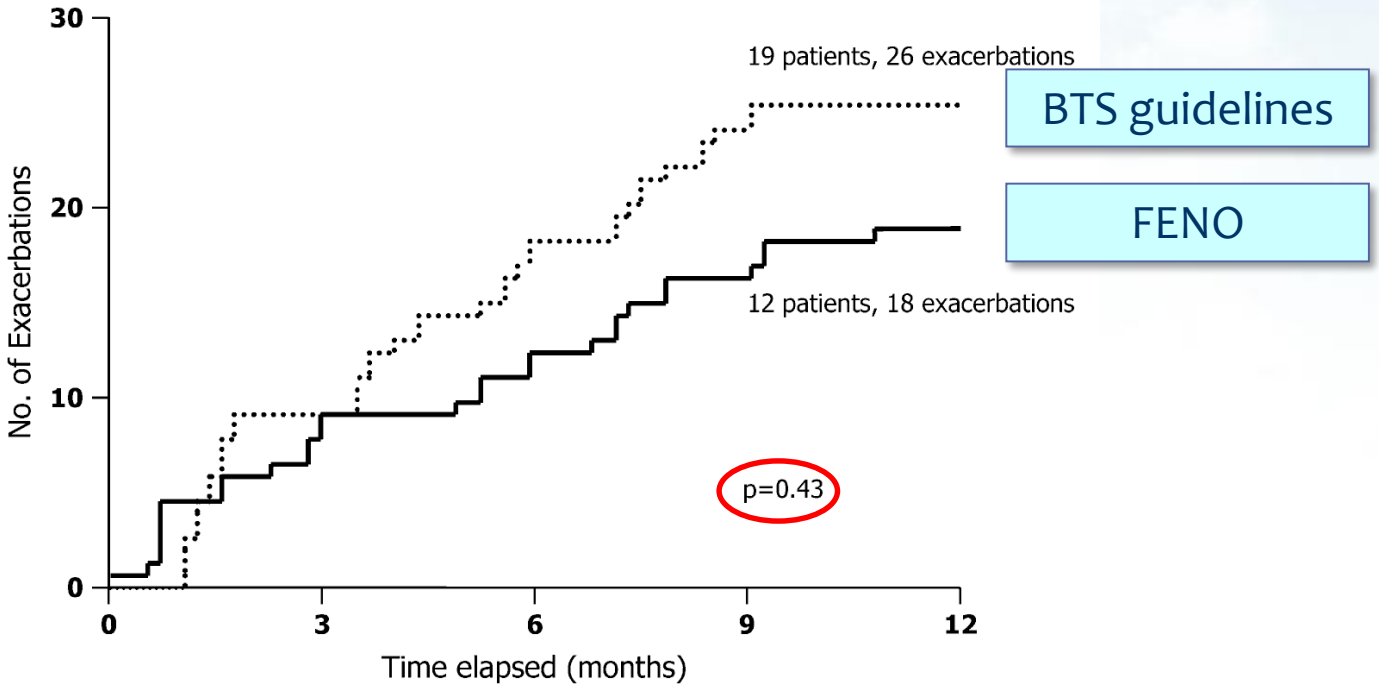
Table 1. Biologic Agents in Asthma and Potential Biomarkers

Pathway	Biologic Agents Approved or in Trials	Biomarkers Predicting Response to Therapy	Biomarkers Modulated by Therapy	Reference(s)
IgE	Omalizumab	F_{ENO} Blood eosinophils Periostin	F_{ENO} Sputum eosinophils	Hanania *et al.*, 2013 (63)
IL-4/IL-13	Pitrakinra (competitive antagonist) Dupilumab (receptor antibody)	F_{ENO} Sputum eosinophils Blood eosinophils	F_{ENO}	Wenzel *et al.*, 2007 (81) Wenzel *et al.*, 2013 (60)
IL-13	Lebrikizumab Tralokinomab	Periostin F_{ENO} Eosinophils Sputum IL-13 (periostin surrogate)	F_{ENO}	Corren *et al.*, 2011 (61) Piper *et al.*, 2013 (62)
IL-5	Mepolizumab Reslizumab Benralizumab	Sputum eosinophils Blood eosinophils	Sputum eosinophils Blood eosinophils	Flood-Page *et al.*, 2007 (25) Haldar *et al.*, 2009 (57) Pavord *et al.*, 2012 (58) Bel *et al.*, 2014 (59) Nair *et al.*, 2009 (66) Ortega *et al.*, 2014 (74) Castro *et al.*, 2011 (75) Castro *et al.*, 2014 (76)

Gauthier M, et al. AJRCCM 2015;192:660-8

FENO to Guide Treatment of Asthma

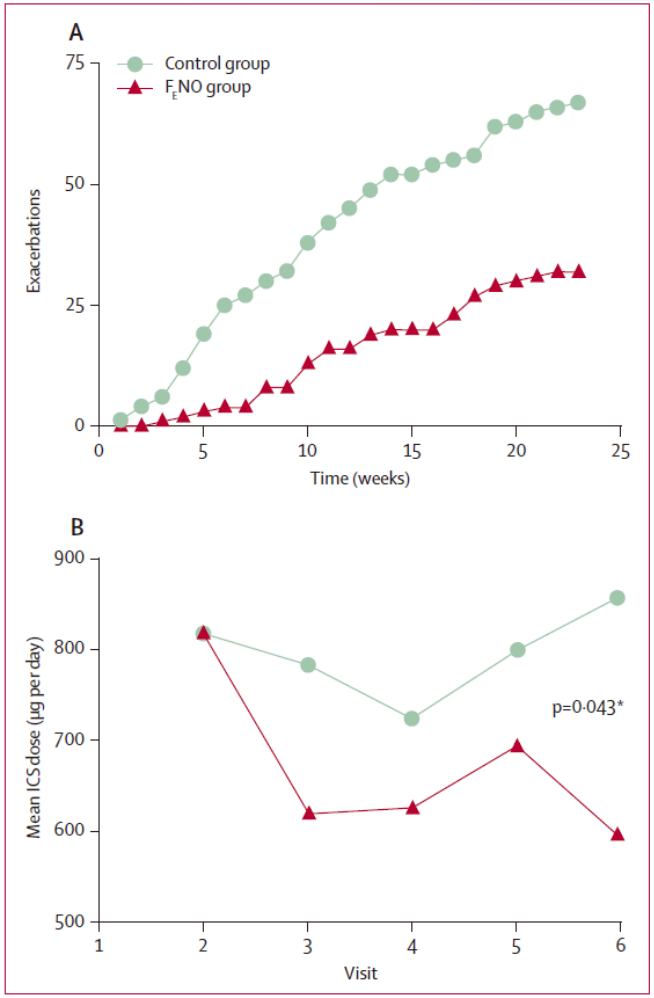
- 118 asthmatics



Shaw DE, et al. Am J Respir Crit Care Med 2007;176:231-7

FENO to Guide Treatment of Asthma

- 220 pregnant subjects with asthma



Exacerbation rate

FENO vs control:

0.288 vs 0.615 exacerbations per pregnancy

Incidence rate ratio:

0.496 (95% CI 0.325-0.755; p=0.001)

In the FENO group,
quality of life was improved (56.9 vs 54.2; p=0.037) and
neonatal hospitalizations were reduced (8 vs 17%; p=0.046).

Powell H, et al. Lancet 2011;378:983-90

FENO to Guide Treatment of Asthma

- Seven RCTs (1,546 patients)

Comparison 1. Asthma treatment tailored on FeNO versus clinical symptoms

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants who had ≥ 1 exacerbations over study period	5	1005	Odds Ratio (Fixed, 95% CI)	0.60 [0.43, 0.84]
2 Number of exacerbations per 52 weeks (exacerbation rates)	5	842	Rate Ratio (Fixed, 95% CI)	0.59 [0.45, 0.77]
3 Severe exacerbations requiring oral corticosteroids	3	495	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.50, 1.48]
4 Severe exacerbations requiring hospitalisation	3	488	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.67]
5 FEV_1 % pred at final visit	4	802	Mean Difference (Fixed, 95% CI)	0.11 [-1.15, 1.37]
6 FeNO level at final visit	5	668	Std. Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.16, 0.15]
7 Symptom score as per Asthma Control Test	4	707	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.18, 0.01]
8 Symptom score as per AQLQ	2		Mean Difference (Fixed, 95% CI)	0.00 [-0.10, 0.10]
9 ICS dose at final visit (microgram per day)	4	582	Mean Difference (IV, Random, 95% CI)	-147.15 [-380.85, 86.56]
10 Subgroup (control guideline use): Number of participants who had ≥ 1 exacerbations over study period	5		Odds Ratio (Fixed, 95% CI)	0.60 [0.43, 0.84]
10.1 Guideline control	2		Odds Ratio (Fixed, 95% CI)	0.87 [0.47, 1.61]
10.2 Other control	3		Odds Ratio (Fixed, 95% CI)	0.51 [0.34, 0.76]

Petsky HL, et al. Cochrane Database Syst Rev 2016: CD011440

FENO as a Predictor of Exacerbation

- 44 nonsmoking asthmatics

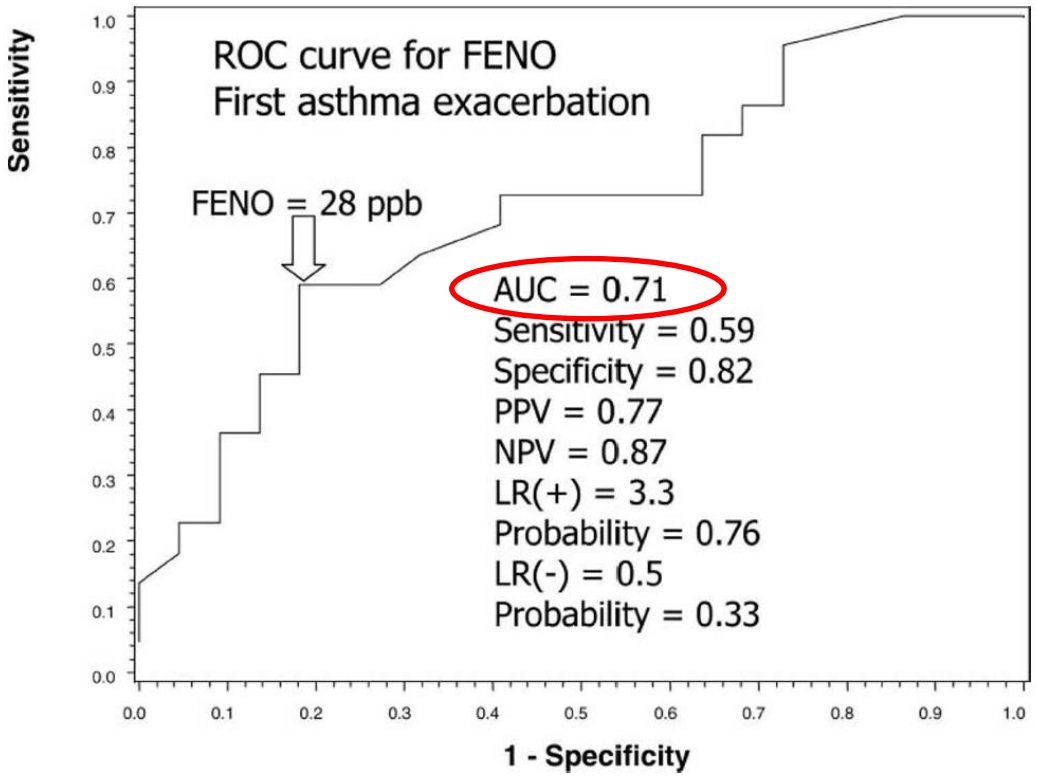


FIGURE 3. ROC curve for FENO for first asthma exacerbation. See Figure 2 for expansion of abbreviations.

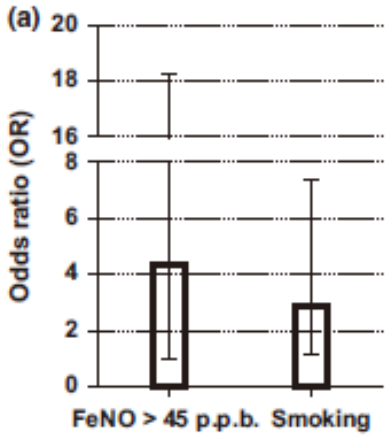
Gelb AF, et al. Chest 2006;129:1492-9

FENO as a Predictor of Exacerbation

- 169 asthmatics (prospectively followed up for 1 year)

Table 3. Adjusted odds ratios in multivariate logistic regression models for factors associated with risk of frequent exacerbations (defined as two or more, and three or more exacerbations during 1 year of follow-up).

Factor	OR	95% CI	*P*	Comments
Frequent exacerbators (two or more exacerbations)				
eNO > 45 p.p.b.	4.32	1.02–18.31	0.047	Adjusted for sex, age, smoking, asthma severity and atopy
Smoking	2.90	1.15–7.35	0.025	Adjusted for sex, age, asthma severity and atopy
Sputum eosinophils ≥ 2%	3.81	0.68–21.43	0.13	Adjusted for sex, age, smoking, asthma severity and atopy
Juniper ACQ > 1.36 (median)	2.92	0.94–90.30	0.063	As above
$FEV_1 \leq 70\%$	1.86	0.70–4.92	0.21	As above
SGRQ>34.6 (median)	1.61	0.52–4.91	0.41	As above
BMI>25	1.16	0.42–3.12	0.77	As above

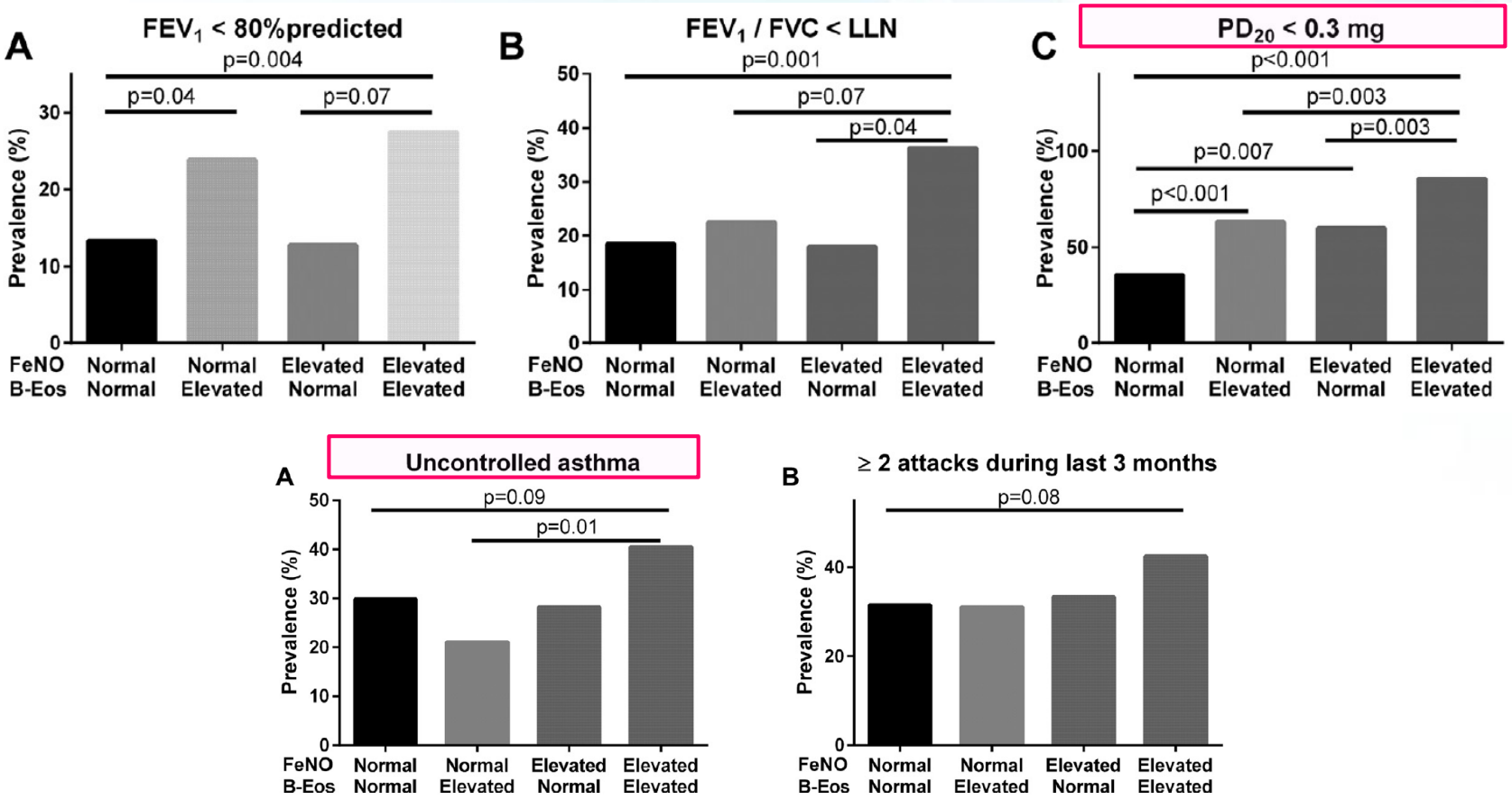


Odds ratio: 4.32

Kupczyk M, et al. Clin Exp Allergy 2014;44:212-21

Relation to Increase in Morbidity

- 406 asthmatics



Malinovschi A, et al. J Allergy Clin Immunol 2016;138:1301-8

1 What is NO?

2 Measuring FENO in Asthma

3 FENO in Asthma Guidelines

Recommendations by ATS

- 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).

Dweik RA, et al. Am J Respir Crit Care Med 2011;184:602-15

FENO Measurement (ATS Guideline)

LOW	INTERMEDIATE	HIGH
	Eosinophilic inflammation	
Unlikely	Present, but mild	Significant
<25 ppb (Children <20 ppb)	25-50 ppb (Children 20-35 ppb)	>50 ppb (Children >35 ppb)
Responsiveness to corticosteroids are less likely	Should be interpreted cautiously and with reference to the clinical context	Responsiveness to corticosteroids are likely in symptomatic patients

Note: account for age as a factor affecting FENO in children younger than 12 years of age.

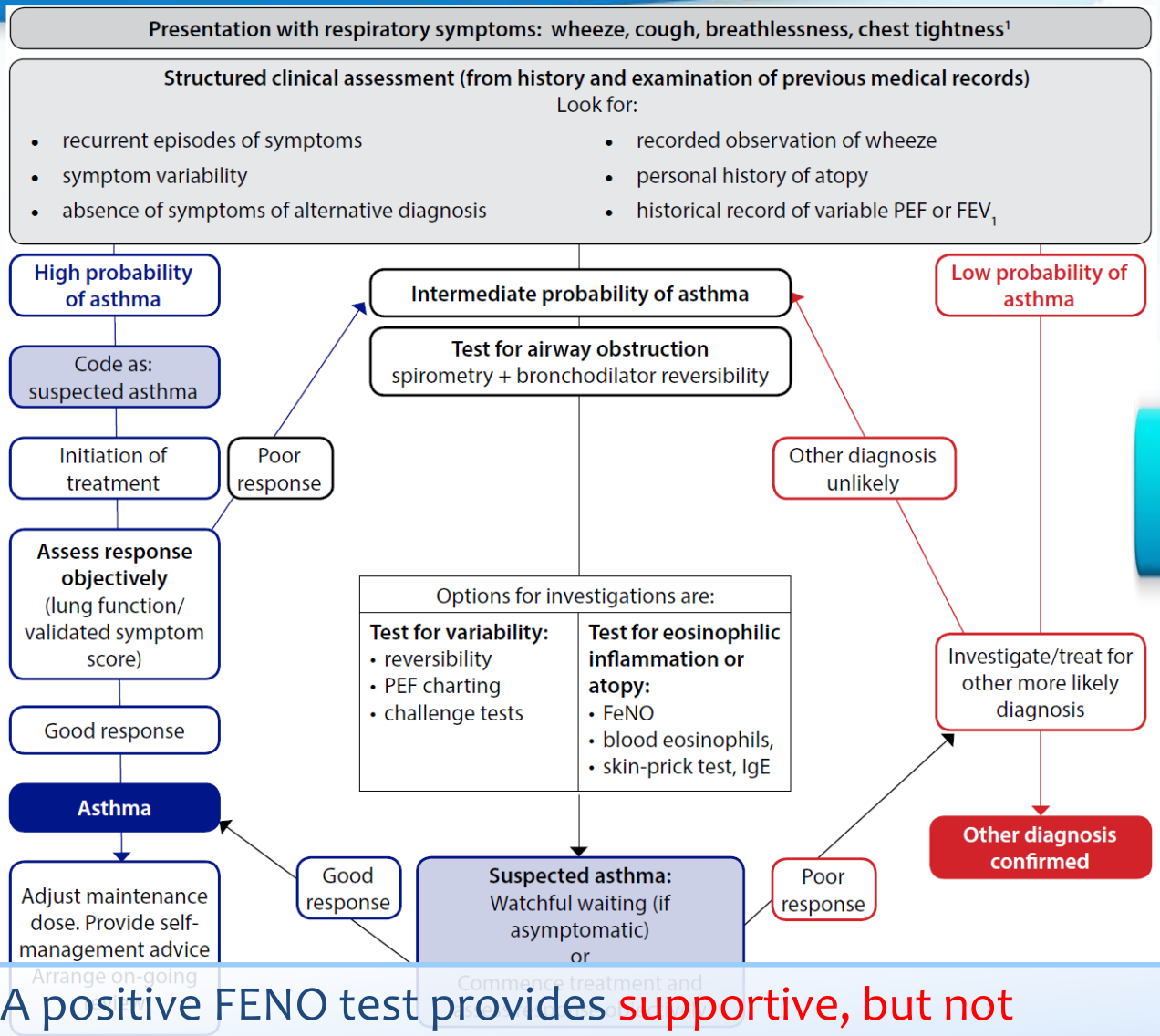
An Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications
Am J Respir Crit Care Med. 2011 184: 602-615

Common Reasons for Measuring FENO

- To assist in assessing the etiology of respiratory symptoms
- To help identify the eosinophilic asthma phenotype
- To assess potential response or failure to respond to anti-inflammatory agents, notably ICS
- To establish a baseline FENO during clinical stability for subsequent monitoring of chronic persistent asthma
- To guide changes in doses of anti-inflammatory medications
- To assist in the evaluation of adherence to anti-inflammatory medications
- To assess whether airway inflammation is contributing to poor asthma control particularly in the presence of other contributors (e.g., rhinosinusitis, anxiety, gastro-esophageal reflux, obesity, or continued allergen exposure).

Dweik RA, et al. Am J Respir Crit Care Med 2011;184:602-15

BTS/SIGN Guideline (2016)



A positive FENO test provides supportive, but not conclusive, evidence for an asthma diagnosis.

FENO in GINA Guideline (2017)

- What's new in GINA 2017?
  - Additional information has been added about factors affecting the FENO, its relationship with eosinophilic airway inflammation, and its predictive value (P20, 29, 38, 41, and 104)

B. Risk factors for poor asthma outcomes	
Assess risk factors at diagnosis and periodically, particularly for patients experiencing exacerbations. Measure FEV_1 at start of treatment, after 3–6 months of controller treatment to record the patient's personal best lung function, then periodically for ongoing risk assessment.	
Potentially modifiable independent risk factors for flare-ups (exacerbations) • Uncontrolled asthma symptoms[78] • High SABA use[79] (with increased mortality if >1 x 200-dose canister/month[80]) • Inadequate ICS: not prescribed ICS; poor adherence;[81] incorrect inhaler technique[82] • Low FEV_1, especially if <60% predicted[83,84] • Major psychological or socioeconomic problems[85] • Exposures: smoking;[84] allergen exposure if sensitized[84] • Comorbidities: obesity;[86] rhinosinusitis;[87] confirmed food allergy[88] • Sputum or blood eosinophilia;[89,90] elevated FENO (in adults with allergic asthma)[91] • Pregnancy[92]	**Having one or more of these risk factors increases the risk of exacerbations even if symptoms are well controlled.**

FENO >50 parts per billion (ppb) has been associated with a good short-term response to ICS.[28] However, there are no studies examining the long-term safety of withholding ICS in patients with low initial FENO. Consequently, in patients with a diagnosis or suspected diagnosis of asthma, FENO cannot be recommended at present for deciding against treatment with ICS. Based on current evidence, GINA recommends treatment with low-dose ICS for most patients with

FENO Measurement

NIOX MINO
(Aerocrine, Sweden)

NIOX VERO
(Aerocrine, Sweden)

Nobreath
(Bedfont, UK)

Noninvasive, easy to perform, objective, and safe method

Asthma Biomarkers as a Predictors of Response to Specific Therapies

Biomarker	Predictor of Response	Strengths	Weakness
Total IgE	Omalizumab	Easy to obtain, inexpensive, sensitive	Not specific for all asthma types
Specific IgE	IT, Omalizumab	Easy to obtain, inexpensive, good correlation with atopy	Not specific for all asthma types
FeNO > 50 ppb	ICS	Easy to obtain, correlation with airway eosinophilic inflammation and IL-13 production	Expensive, not specific for all asthma types
Sputum eosinophils (>3%)	ICS	Correlation with airway eosinophilic inflammation, decreased FEV1, and increased BHR	Difficult to obtain
Blood eosinophils (300/µL)	Anti-IL-5	Inexpensive, easy to obtain, Responds to multiple therapies	Not sensitive or specific for asthma or atopy
Periostin	Anti-IL-13 and IL-4	Sensitive indicator of Th2 airway inflammation	Expensive, not readily available

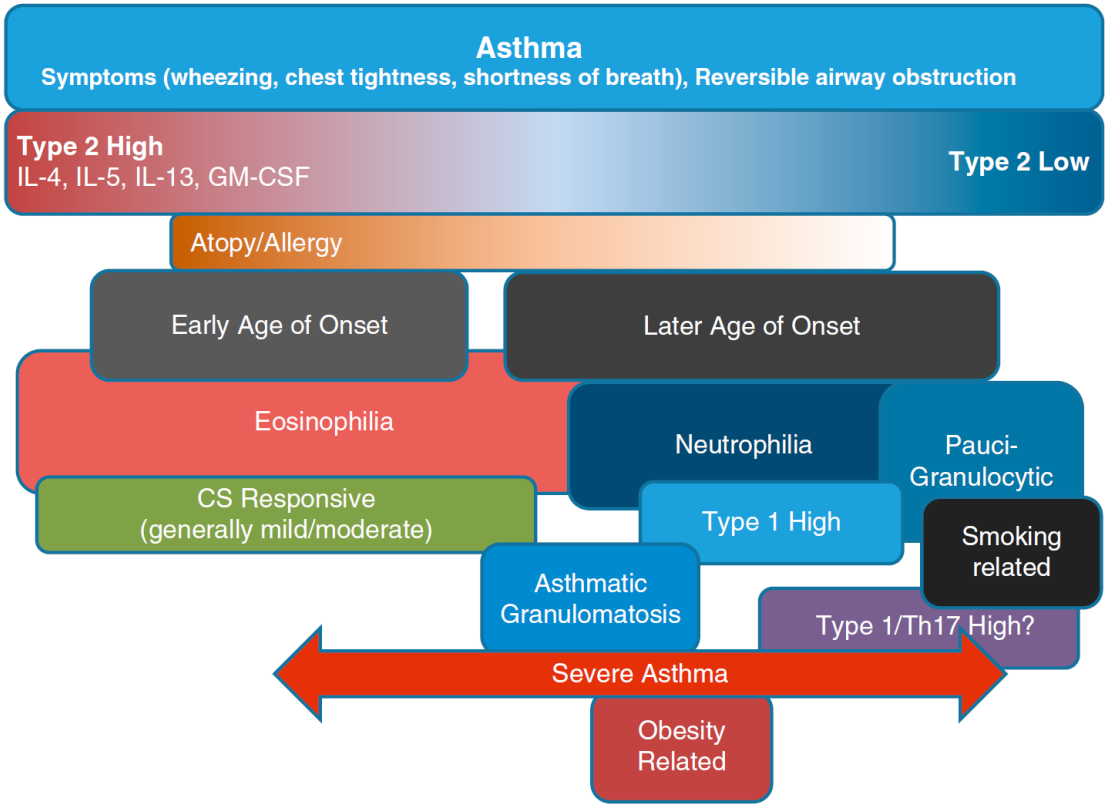
Limitation of FENO for Asthma Diagnosis

- Not associated with neutrophilic airway inflammation
- Children younger than 4 years
- False negative in patient already treated with ICS
- Cut-off values
- Adding costs to the care of asthmatic patients

- Problems encountered
  - Poor comprehension
  - Inability to maintain required flow rate
  - Inability to exhale for required time
  - Patient unwilling to comply with test

Consideration

- Asthma is a complex disease, and single measures cannot be used to assess, manage, and treat this disease.
- FENO measurement is no exception.



SUMMARY

- FeNO is a noninvasive, simple, objective, and safe method of measuring airway eosinophilic inflammation.

- FENO provides supportive evidence for an asthma diagnosis.
- FENO is used in determining the likelihood of steroid responsiveness.
- FENO can be used to guide changes
  in doses of anti-inflammatory medications and
  to predict future exacerbations in asthma.

- FENO measurement can be more widely available.

Thank You for Your Attention