Biomarkers in Severe Asthma: The Importance of FeNO

A New Era for Personalized Medicine

Joe Zein, MD, PhD, MBA

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Acknowledgement

- Eugene R. Bleecker, MD

- No conflict of interest

Objectives

- Discuss the importance of understanding **disease heterogeneity** in the assessment of asthma

- Describe the value of predictive biomarkers of asthma **endotypes** and identifying their role in asthma **subphenotypes**

- Demonstrate the overall importance of **FeNO in asthma pathobiology**

Definition and Prevalence of Severe Asthma

Severe Asthma: ***"asthma which requires treatment with guidelines medications such as high-dose ICS and LABA for the previous year or SCS to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy"***

Poor asthma control (ACQ >1.5, ACT <20, or 'not well controlled' according to GINA)

At least 2 oral OCS-requiring exacerbations last year

Serious exacerbations: at least 1 hospitalization, ICU stay or mechanical ventilations in the past year

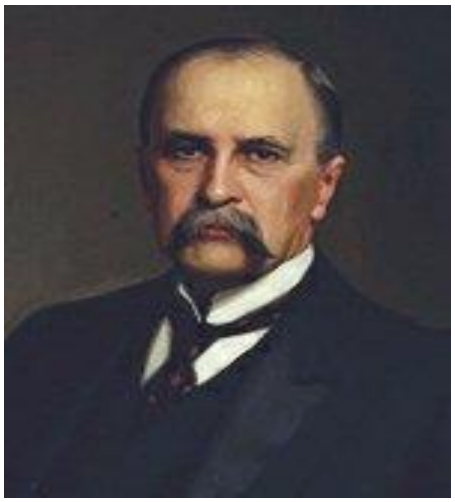
Persistent airflow limitation FEV_1 <80% predicted

Prevalence of severe asthma: *5%-10% of the total asthma population are often estimated*' – Is this an underestimate?

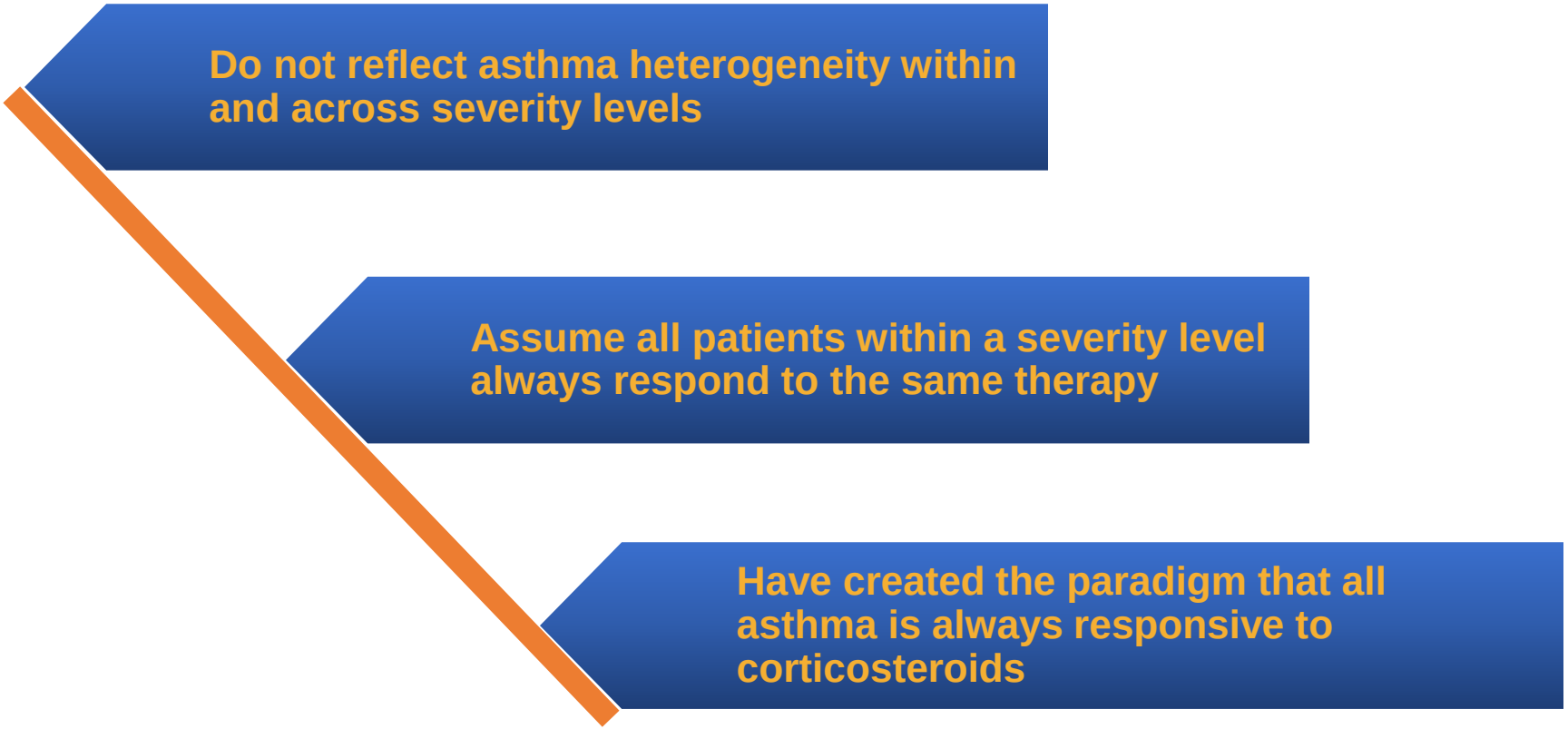
ACO = Asthma Control Questionnaire ACT = asthma control Test FEV_1 = forced expiratory volume in 1 second
GINA = Global Initiative for Asthma ICS = inhaled corticosteroid ICU = Intensive Care Unit LABA = long-acting β_2 agonist
OCS = oral corticosteroid SCS = systemic corticosteroids
Chung KF, et al. *Eur Respir J* 2014; 43:343-73

"If it were not for the great variability among individuals medicine might as well be a science and not an art."

-Sir William Osler



Limitations of Guideline Classifications of Severe Asthma



Moore WC, et al. *Am J Respir Crit Care Med* 2010; 181:315-23
Jarjour NN, et al. *Am J Respir Crit Care Med* 2012; 185:356-62

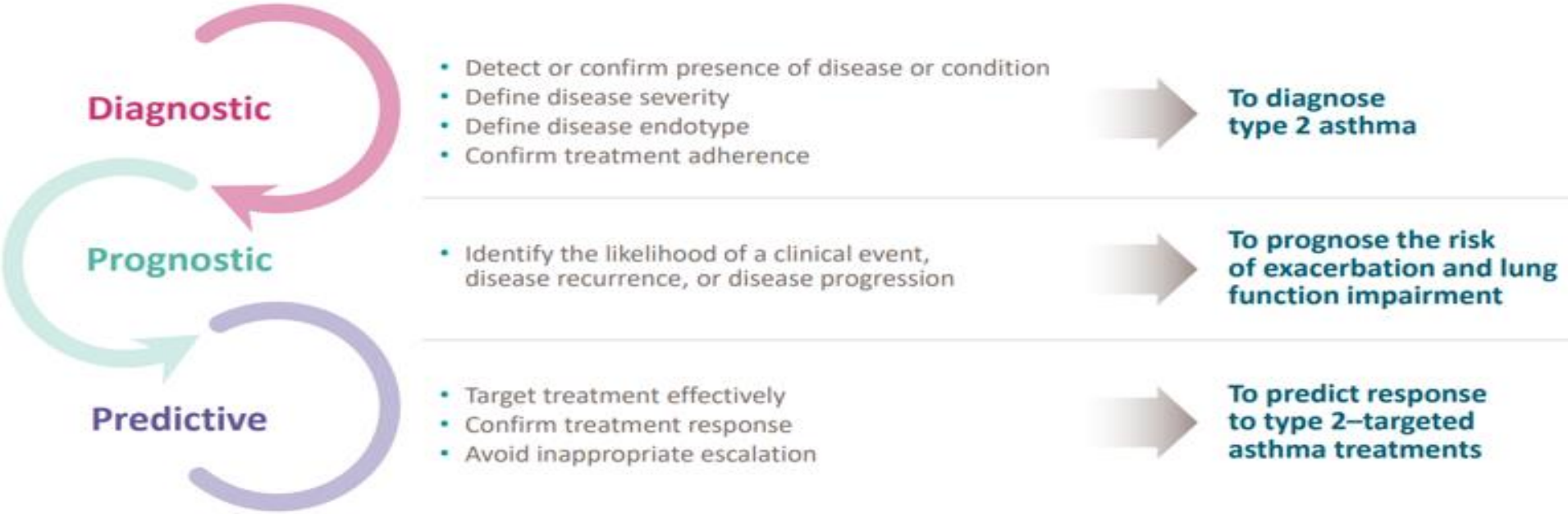
The Approach to Treatment Is Changing

"In the future, the promise of safe and effective biomarker-driven approaches with greater understanding of immunopathobiology of severe asthma" **– Chung et al. 2014**

Muraro A, et al. *J Allergy Clin Immunol* 2016; 137:1347-58
Chung KF, et al. *Eur Respir J* 2014; 43:343-73

Potential Uses of Biomarkers in Asthma

- ***Biomarker:** An objective characteristic that is an indicator of normal biology, pathogenic processes, or pharmacologic responses to a therapeutic intervention*



Fricker M, et al. *Respirology*. 2017;22(3):430-442.

Approaches Classifying Asthma Heterogeneity and Severity

- **"Hypothesis Driven Univariate Based":** (Age of Onset, Allergic, Obesity, Ethnicity, Eosinophilic, Neutrophilic, Mast Cell, Exacerbations, etc)

- **"Model Free" Multivariate: Unbiased Clusters Approaches (Systems Medicine)**

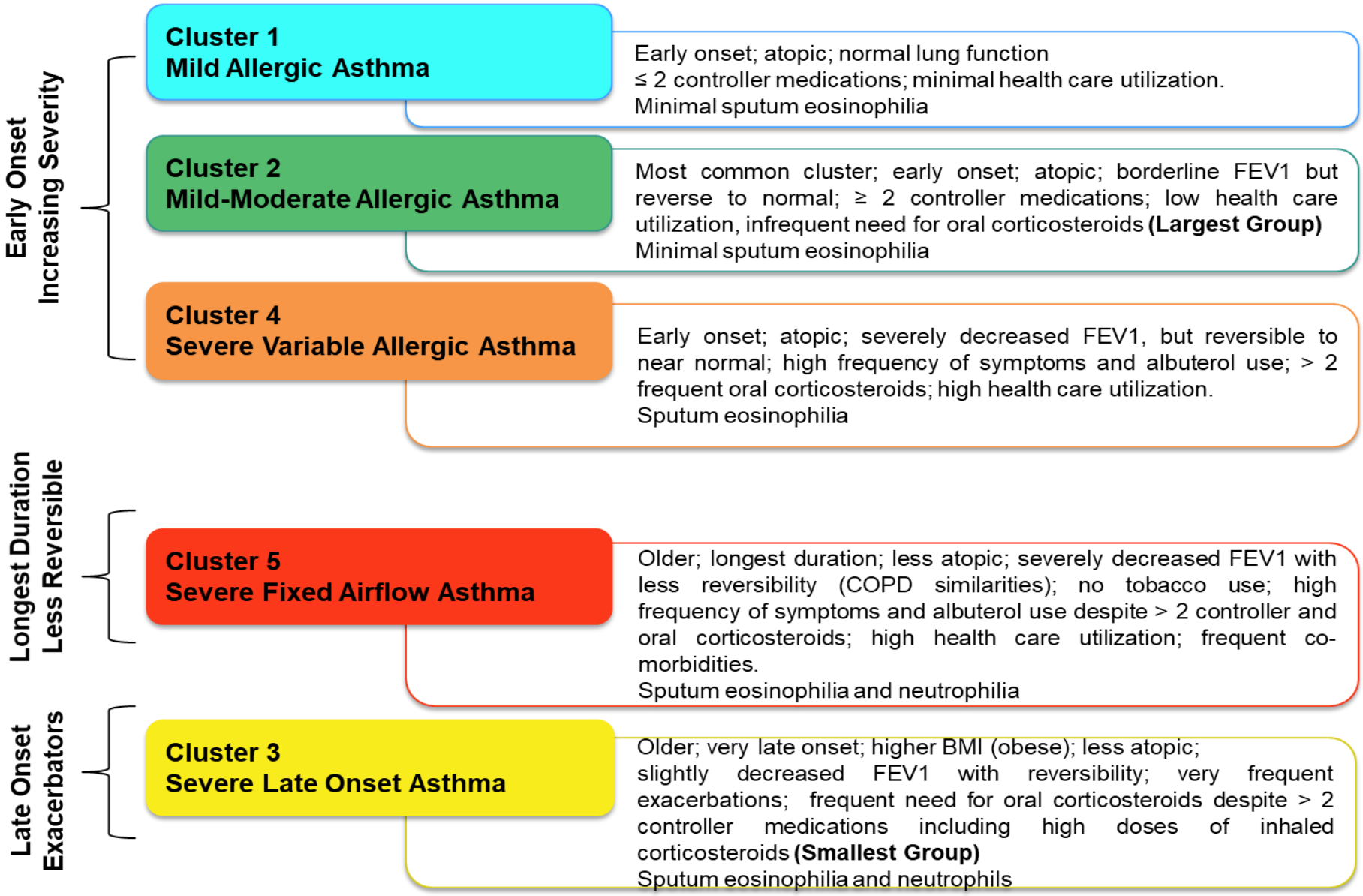
  - Haldar P, et al. *AJRCCM* (2008)

  - Lefaudeux D, JACI (2017)

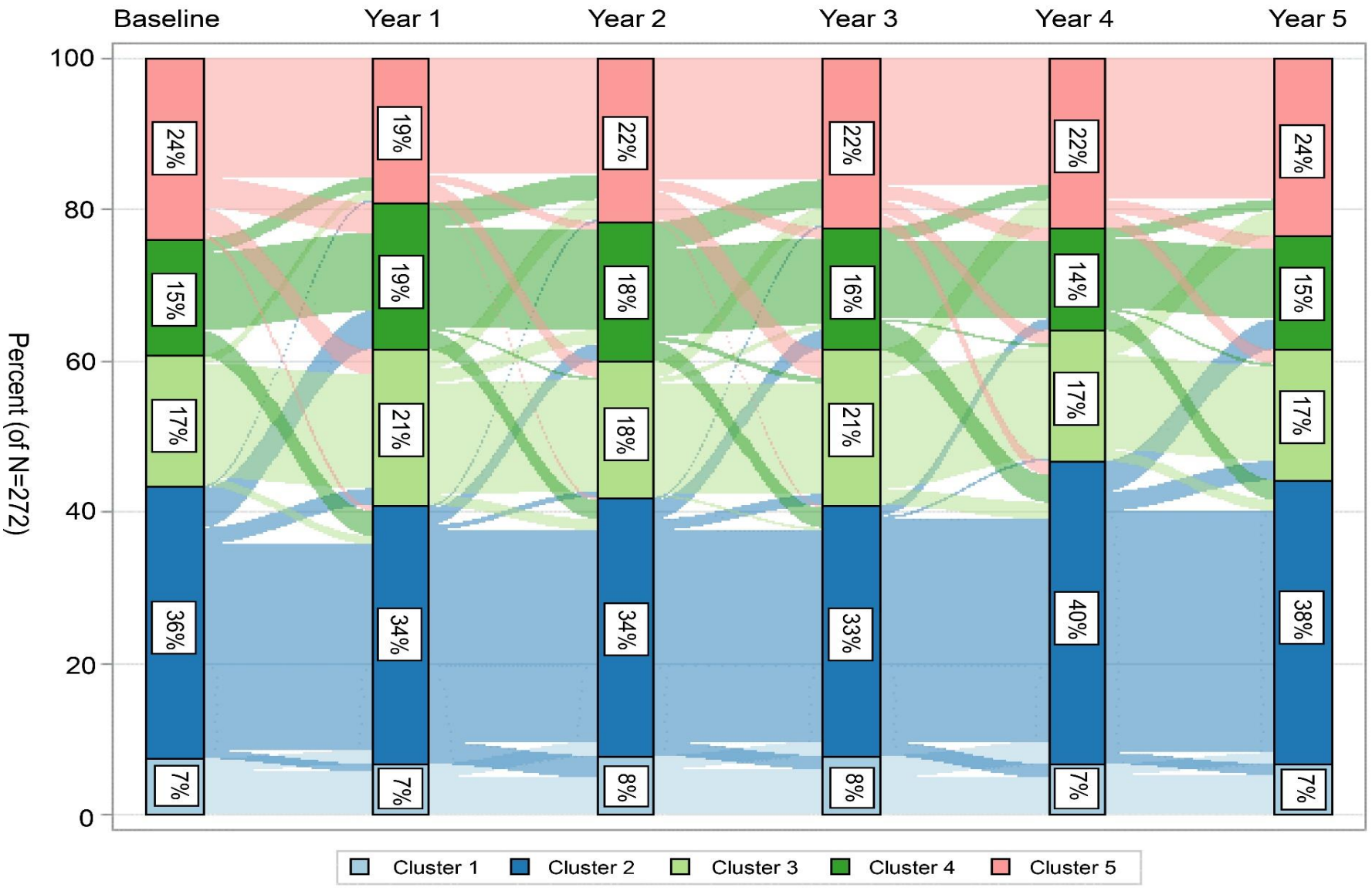
  - **SARP NHLBI :** Moore WC, et al. *AJRCCM* (2010), *Ann Am Thorac Soc* (2013), *JACI* (2014)

Haldar P, et al. *Am J Respir Crit Care Med* 2008; 178:218-24. Moore WC, et al. *Am J Respir Crit Care Med* 2010; 181:315-23. Moore WC, et al. *Ann Am Thorac Soc* 2013; 10:S118-24. Moore WC, et al. *J Allergy Clin Immunol* 2014; 133:1557-63 e5

SARP Asthma Clinical Clusters



Longitudinal Stability of SARP Clinical Clusters Over 5 Years in the SARP 3 Cohort



Asthma, Heterogeneity and Severity

- **Will each of these sub-phenotypes "respond" to a therapy that targets specific inflammatory mechanisms?**

Is severe asthma caused by nonadherence with prescribed corticosteroids?

What are the responses to systemic corticosteroids in severe asthma?

Phipatanakul W, et al. Am J Respir Crit Care Med 2017; 195:1439-48

Many Patients Remain Type 2 High After Intramuscular Triamcinolone (40 mg)

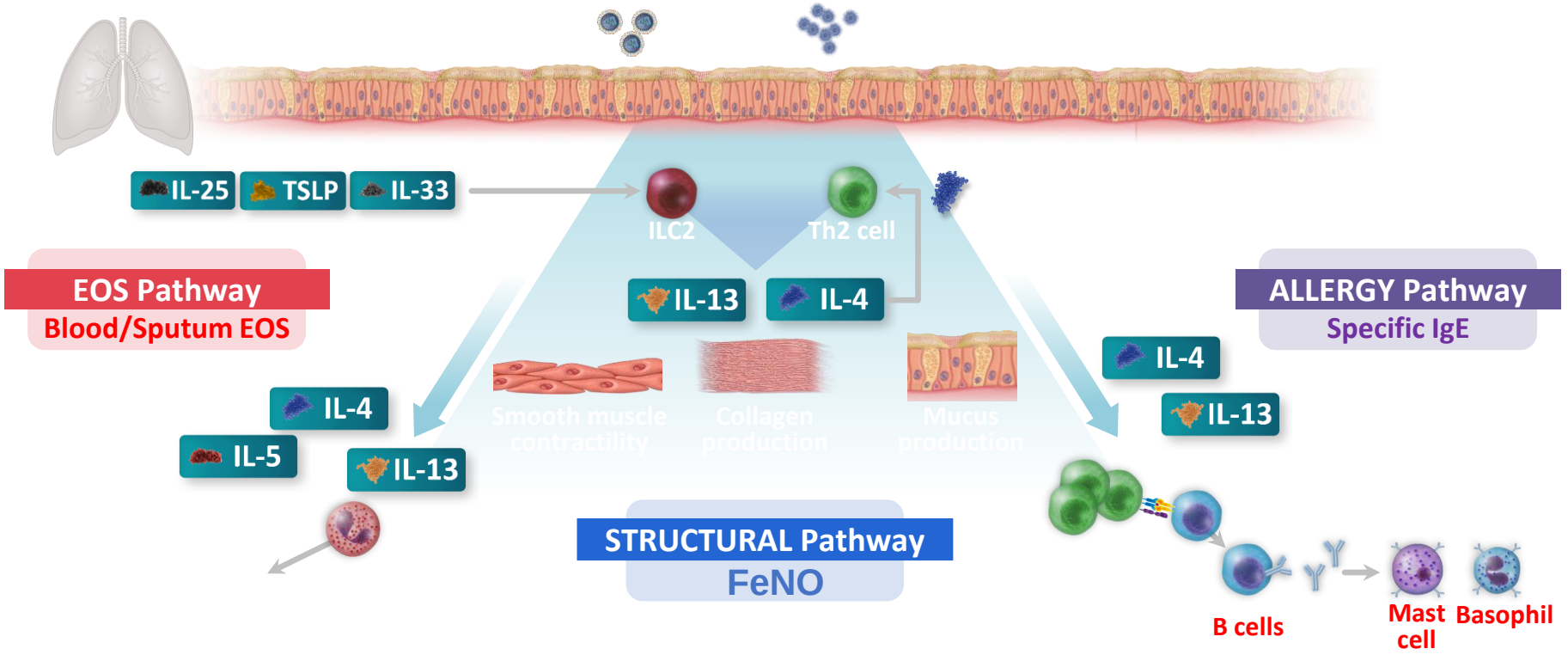
- **Sputum eosinophils remain >2% in 27%**
- **Blood eosinophils >300 in 27%**
- **FeNO >25 ppb in 36%**

  …….*of patients with severe asthma*

Persistent T2 High Asthma had lower lung function, greater reversibility and more frequent exacerbations

Phipatanakul W, et al. *Am J Respir Crit Care Med* 2017; 195:1439-48. Peters MC, et al. *J Allergy Clin Immunol* 2018; 131:1169-79

Unique and Overlapping Biomarkers Reflect Inflammatory Pathways in Type 2 Asthma[1,2]



EOS, eosinophils; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin; ILC2, group 2 innate lymphoid cell; Th2, T helper 2; TSLP, thymic stromal lymphopoietin.

1. Gandhi NA, et al. *Nat Rev Drug Discov*. 2016;15(1):35-50. 2. Gandhi NA, et al. *Expert Rev Clin Immunol.* 2017;13(5):425-437.

Do Current Biomarkers Accurately Predict Asthma Severity Phenotypes?

- **How well do serum IgE levels, blood eosinophil levels and FeNO relate to severity characteristics?**
- **What about other biomarkers: IL6 levels, Sputum eosinophil and neutrophil percent**
- **Data from ~ 700 patients with severe asthma from SARP 1-3 (NHLBI network 2000-Present)**

SARP 1, 2, 3 Severe Asthma: IgE

	IgE < 100 N=261	IgE ≥ 100 N=424	
Severe asthma and ≥ 12 years old	Mean ± std	Mean ± std	P-value
Age of Enroll	46 ± 14	40 ± 17	<0.0001
Age Asthma Onset	**19 ± 17**	**14 ± 16**	**0.0009**
Asthma Duration	28 ± 16	26 ± 16	0.1
BMI	32 ± 9	31 ± 9	0.11
IgE	38 ± 29	632 ± 934	<0.0001
Number + skin test	**1.8 ± 2.4**	**4.8 ± 3.5**	**<0.0001**
Baseline FEV_1 %pred	66 ± 22	67 ± 2	0.87
Steroid Use	**%**	**%**	
High-Dose ICS	96	97	0.66
Other CS (oral or injected)	**41**	**29**	**0.002**
HCU in the Last Year from Asthma			
ER or urgent care	**65**	**54**	**0.007**
OCS bursts 3 or more	**53**	**38**	**0.0003**
ER Visit	**49**	**37**	**0.002**
Hospitalizations	28	22	0.1

Moore WC, et al. J Allergy Clin Immunol 2007; 119:405-13
Moore WC, et al. Ann Am Thorac Soc 2013; S118-24
Moore WC, et al. Am J Resp Crit Care Med 2010; 181:315-323
Teague WG, et al. J Allergy Clin Immunol 2017; 6:545-554

SARP 1, 2, 3 Severe Asthma: Blood Eos

	Blood Eos < 300 N=422	Blood Eos ≥ 300 N=311	
Severe asthma and ≥ 12 years old	Mean ± std	Mean ± std	P-value
Age of Enroll	44 ± 15	42 ± 18	0.34
Age Asthma Onset	16 ± 15	16 ± 17	0.57
Asthma Duration	28 ± 16	25 ± 15	0.02
BMI	**33 ± 9**	**29 ± 7**	**< 0.0001**
Number + skin test	3.5 ± 3	4 ± 3	0.52
Blood EOS µl	133 ± 77	594 ± 805	<0.0001
Baseline FEV_1 %pred	**68 ± 22**	**64 ± 21**	**0.02**
Steroid Use	**%**	**%**	
High-Dose ICS	96	97	0.84
Other CS (oral or injected)	37	31	0.1
HCU in the Last Year for Asthma			
ER or urgent care	60	57	0.4
OCS bursts 3 or more	46	45	0.82
ER Visits	44	42	0.55
Hospitalizations	26	24	0.73

Moore WC, et al. J Allergy Clin Immunol 2007; 119:405-13
Moore WC, et al. Ann Am Thorac Soc 2013; S118-24
Moore WC, et al. Am J Resp Crit Care Med 2010; 181:315-323
Teague WG, et al. J Allergy Clin Immunol 2017; 6:545-554

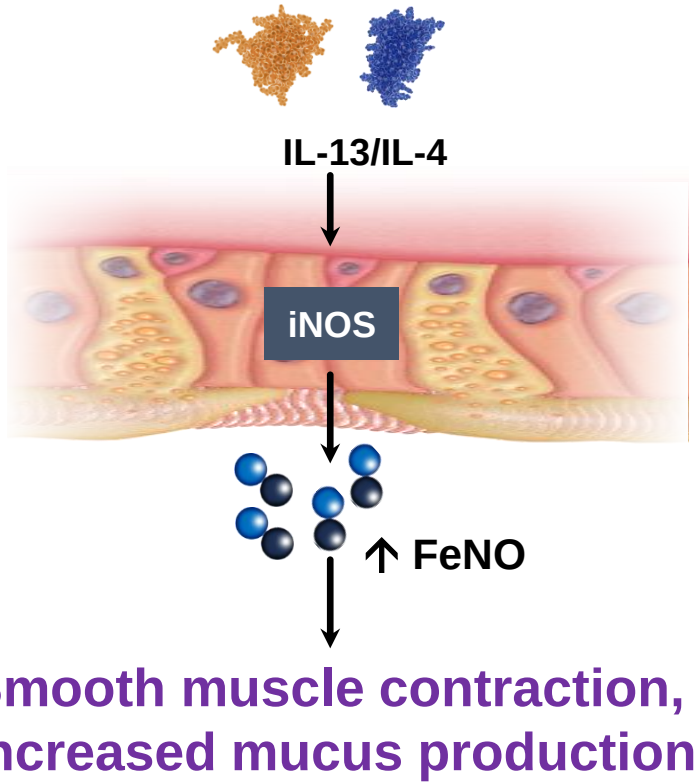
SARP 1, 2, 3 Severe Asthma: FeNO

	FeNO < 30 N=402	FeNO ≥ 30 N=281	
Severe asthma and ≥ 12 years old	Mean ± std	Mean ± std	P-value
Age of Enroll	44 ± 15	41 ± 17	0.06
Age Asthma Onset	15 ± 15	17 ± 17	0.69
Asthma Duration	**29 ± 16**	**24 ± 15**	**0.0002**
BMI	**33 ± 9**	**29 ± 7**	**<0.0001**
Number + skin test	3.5 ± 3.3	3.7 ± 3.6	0.61
FeNO ppb	16 ± 7	68 ± 43	<0.0001
Baseline FEV_1 %pred	**68 ± 21**	**65 ± 22**	**0.08**
Steroid Use	**%**	**%**	
High-Dose ICS	97	97	1
Other CS (oral or injected)	**28**	**38**	**0.004**
HCU in the Last Year for Asthma			
ER or urgent care	**54**	**67**	**0.0005**
OCS bursts 3 or more	**39**	**51**	**0.003**
ER Visits	**37**	**52**	**0.0002**
Hospitalizations	**19**	**31**	**0.0005**

Moore WC, et al. J Allergy Clin Immunol 2007; 119:405-13
Moore WC, et al. Ann Am Thorac Soc 2013; S118-24
Moore WC, et al. Am J Resp Crit Care Med 2010; 181:315-323
Teague WG, et al. J Allergy Clin Immunol 2017; 6:545-554

Elevated FeNO Levels Are Associated With Type 2 Inflammation

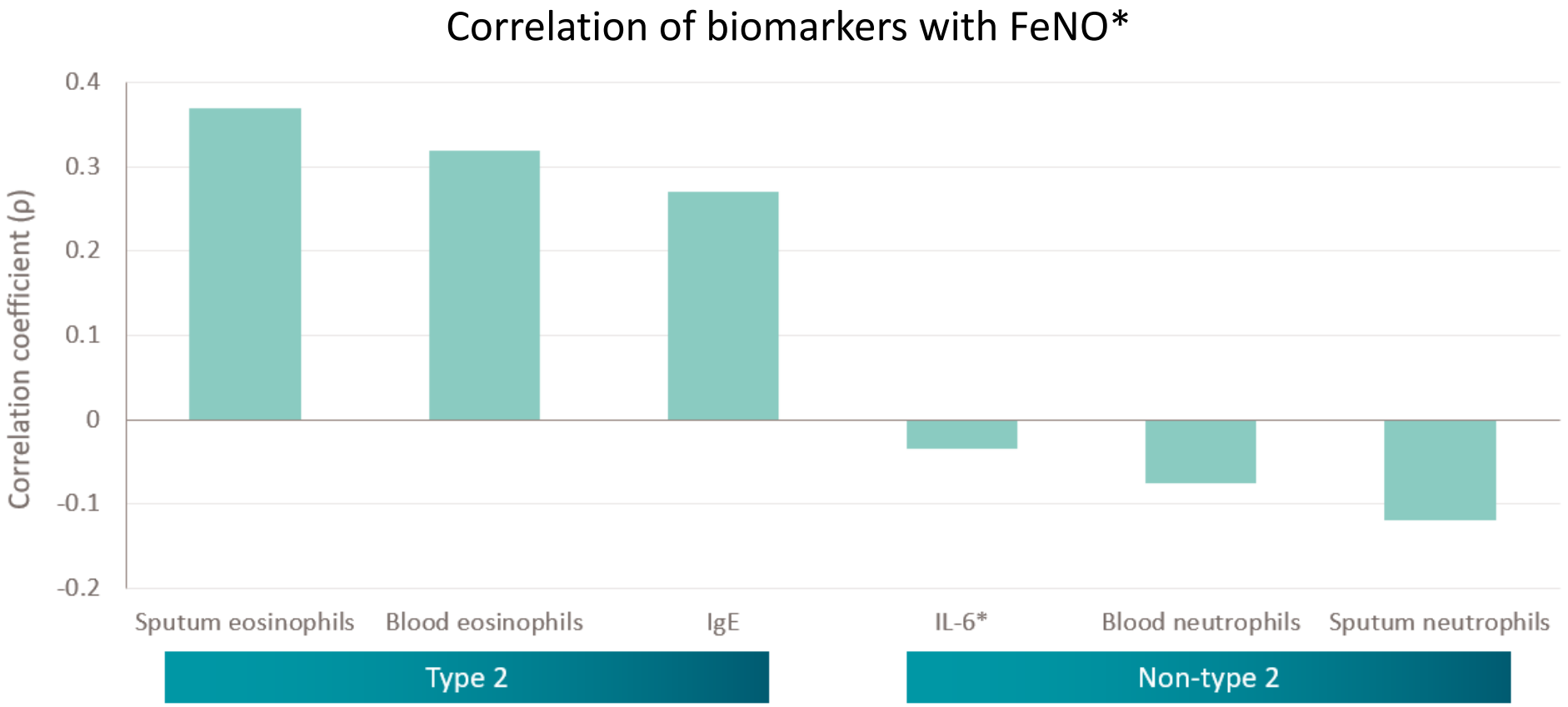
FeNO Production Is Driven by Activity of IL-4 and IL-13[1-3]



FeNO, fractional exhaled nitric oxide; IL, interleukin; iNOS, inducible nitric oxide synthase.

1. Parulekar AD, et al. *Curr Opin Pulm Med*. 2016;22(1):59-68. 2. Prado CM, et al. *ISRN Allergy*. 2011;2011:832560. 3. Alving K, et al. *Eur Respir Mon*. 2010;49:1-31.

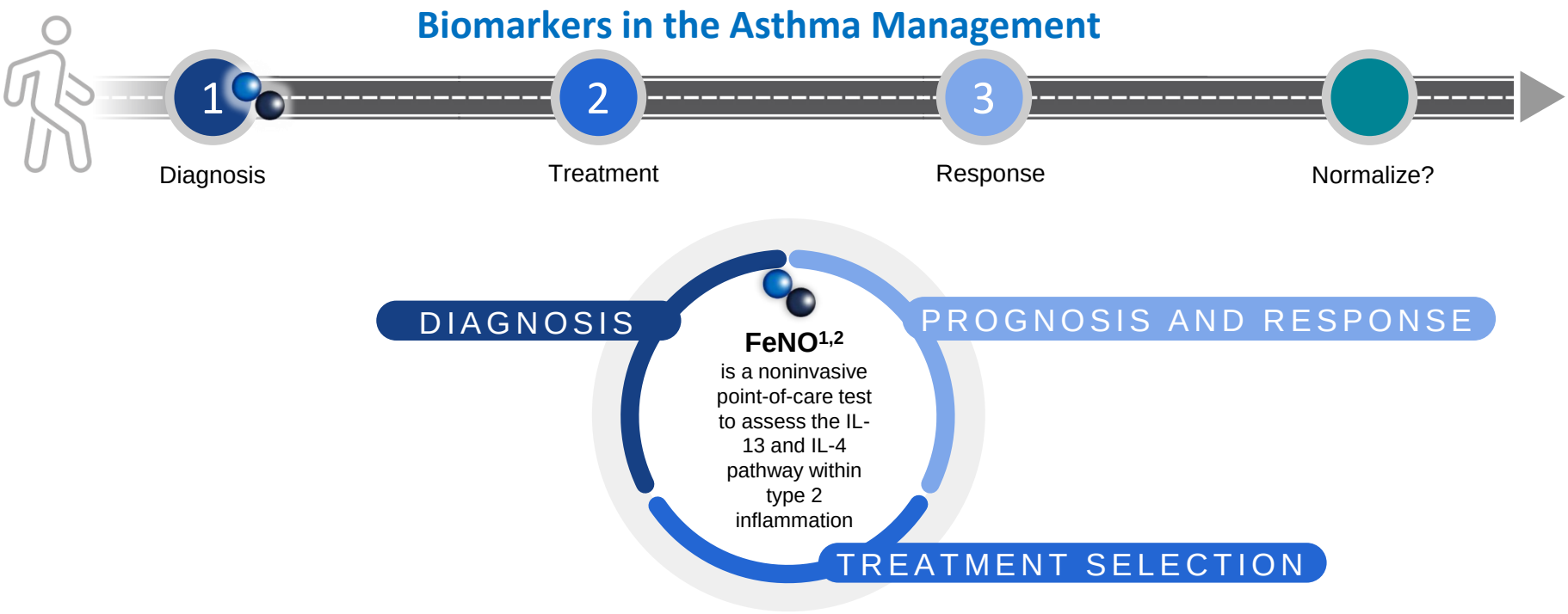
FeNO Positively Correlates With the Presence of Other Type 2 Biomarkers



*IL-6 levels were not significantly correlated with type 2 asthma biomarkers and thus should reflect non–type 2 asthma.
FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin.

Li X, et al. *J Allergy Clin Immunol*. 2020;145(1):430-433.

FeNO Plays a Role in the Asthma Pathobiology



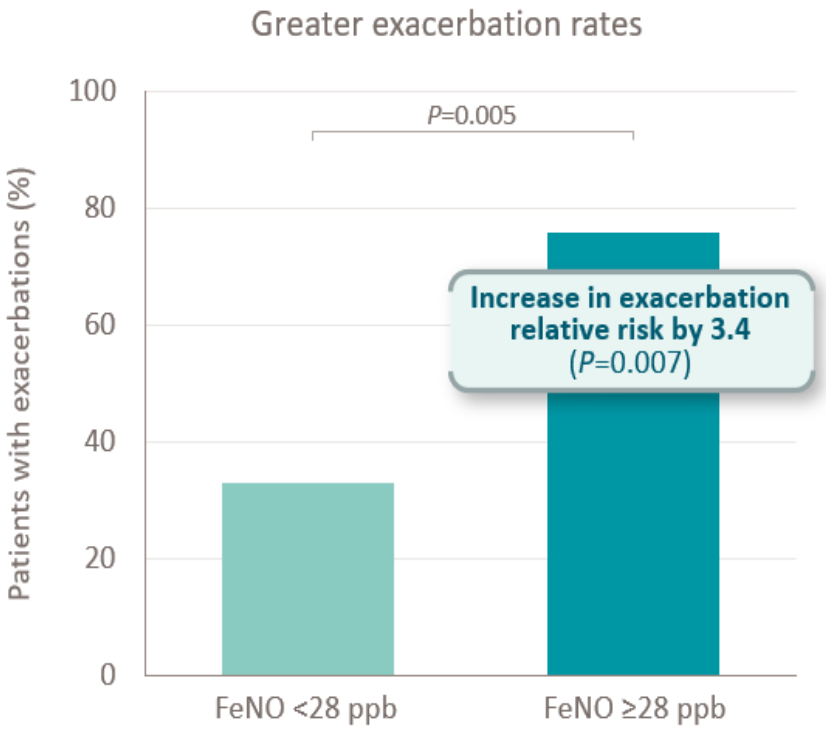
FeNO, fractional exhaled nitric oxide; IL, interleukin.

1. GINA. Global Strategy for Asthma Management and Prevention, 2022. Accessed May 3, 2022. https://ginasthma.org/reports/.
2. Kuo CR, et al. *Respir Med*. 2019;155:54-57.

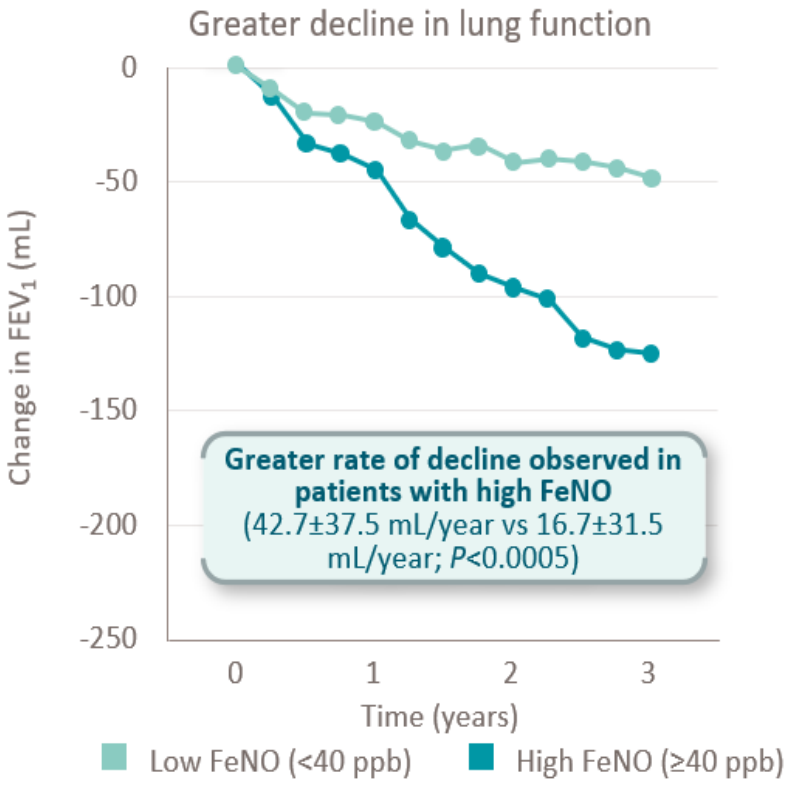
Elevated FeNO Is Associated With Greater Disease Burden

Elevated FeNO Is a Predictor of Asthma Exacerbations and increased Lung Function Decline

18-month prospective study of asthma patients who were clinically stable (n=44)[1*]



3-year follow-up study in patients with stable asthma (n=128)[2†]



*For 6 weeks prior to study start and receiving ICS+LABA (250 µg of fluticasone/50 µg of salmeterol or equivalent)[1]

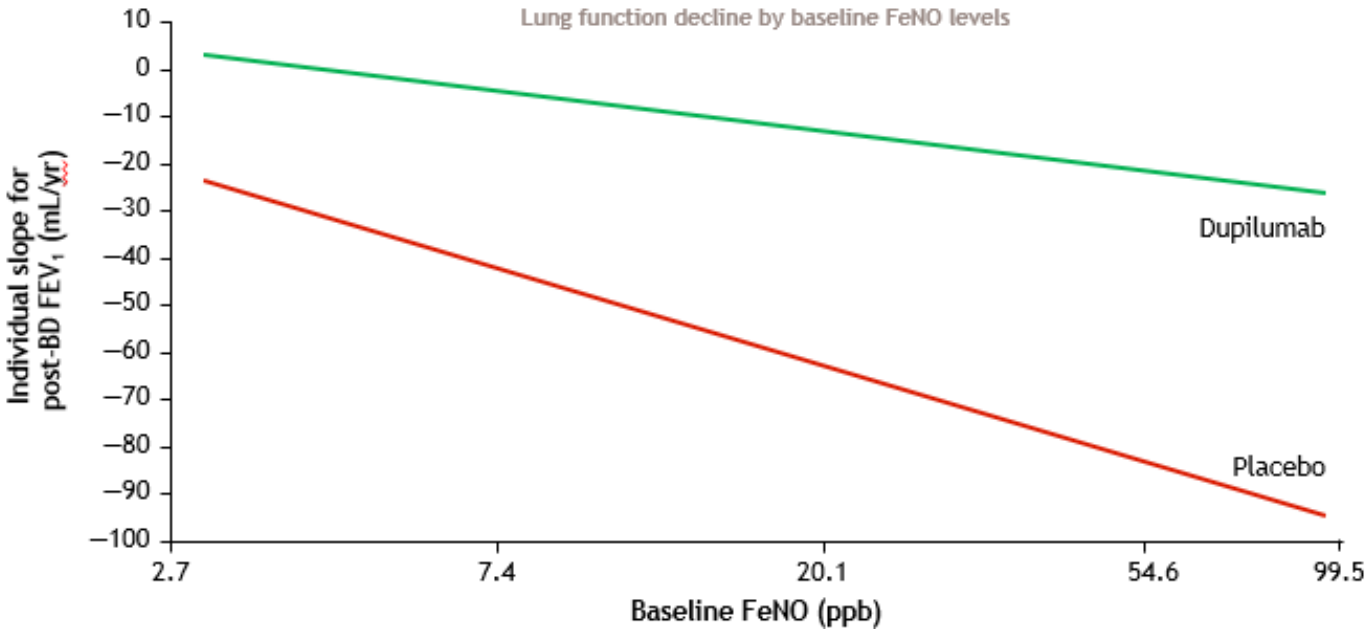
†Following treatment with ICS +/- LABA, leukotriene modifier, or theophylline for more than 4 years.[2]

1. Gelb AF, et al. *Chest*. 2006;129(6):1492-1499.

2. Matsunaga K, et al. *Allergol Int*. 2016;65(3):266-271.

Rate of Lung Function Decline Across FeNO Levels

- Lung function decline consistently increased in patients with higher baseline FeNO levels



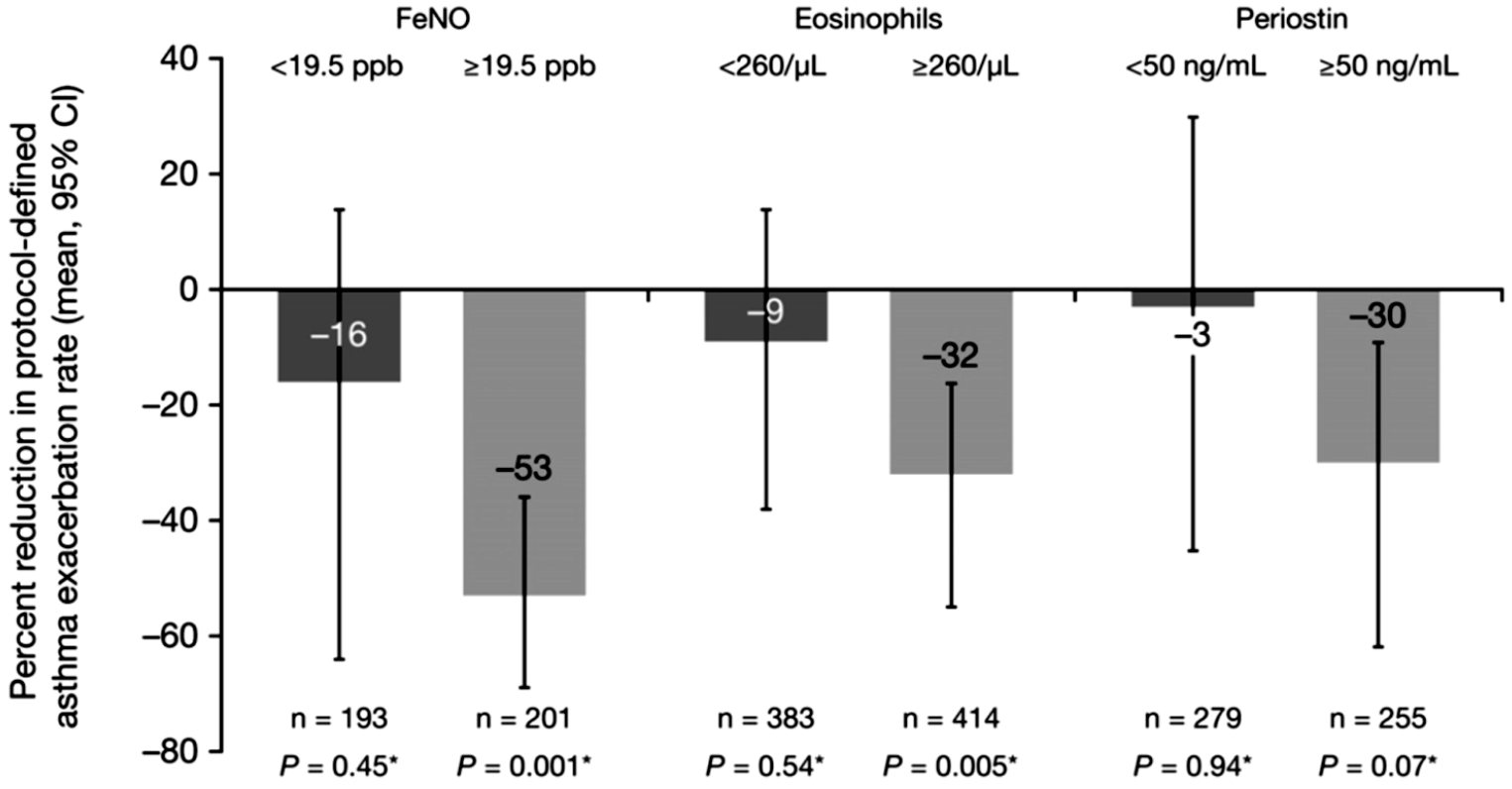
Linear association between individual post-BD FEV_1 slope and baseline FeNO values.

FeNO as a Potential Prognostic and Predictive Marker of Lung Function Decline in Patients With Uncontrolled, Moderate-to-Severe Asthma:

LIBERTY ASTHMA QUEST; Ian D. Pavord et al, Presented at the 118th International Conference of the American Thoracic Society (ATS); San Francisco, CA, USA; May 13–18, 2022

Treatment effect of Omalizumab is greater in all three high baseline biomarker subgroups:

Post-hoc analysis of the EXTRA Omalizumab study



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 NA. Am J Respir Crit Care Med. 2013 Apr 15;187(8):804-11.

EDITORIAL

New Biologics for Asthma

Jeffrey M. Drazen, M.D., and David Harrington, Ph.D.

- Four new biologics —mepolizumab, reslizumab, benralizumab, dupilumab and Tezepelumab directed vs. type 2 inflammation
- **None of therapies have eliminated asthma exacerbations in all patients and normalized the physiological changes that are the core of asthma**
- **Some subjects are "asthma free" and some have no effect whatsoever**
- **"We need to go beyond blood eosinophil counts and nitric oxide. There are other biomarkers, yet to be discovered and validated, that will guide more effective treatment of severe asthma; let's commit to finding them."**

***NEJM*, May, 2018**

Thank you!

Questions and Comments?