2022.07.09
천식연구회 Workshop 2022

Role of FeNO in Asthma

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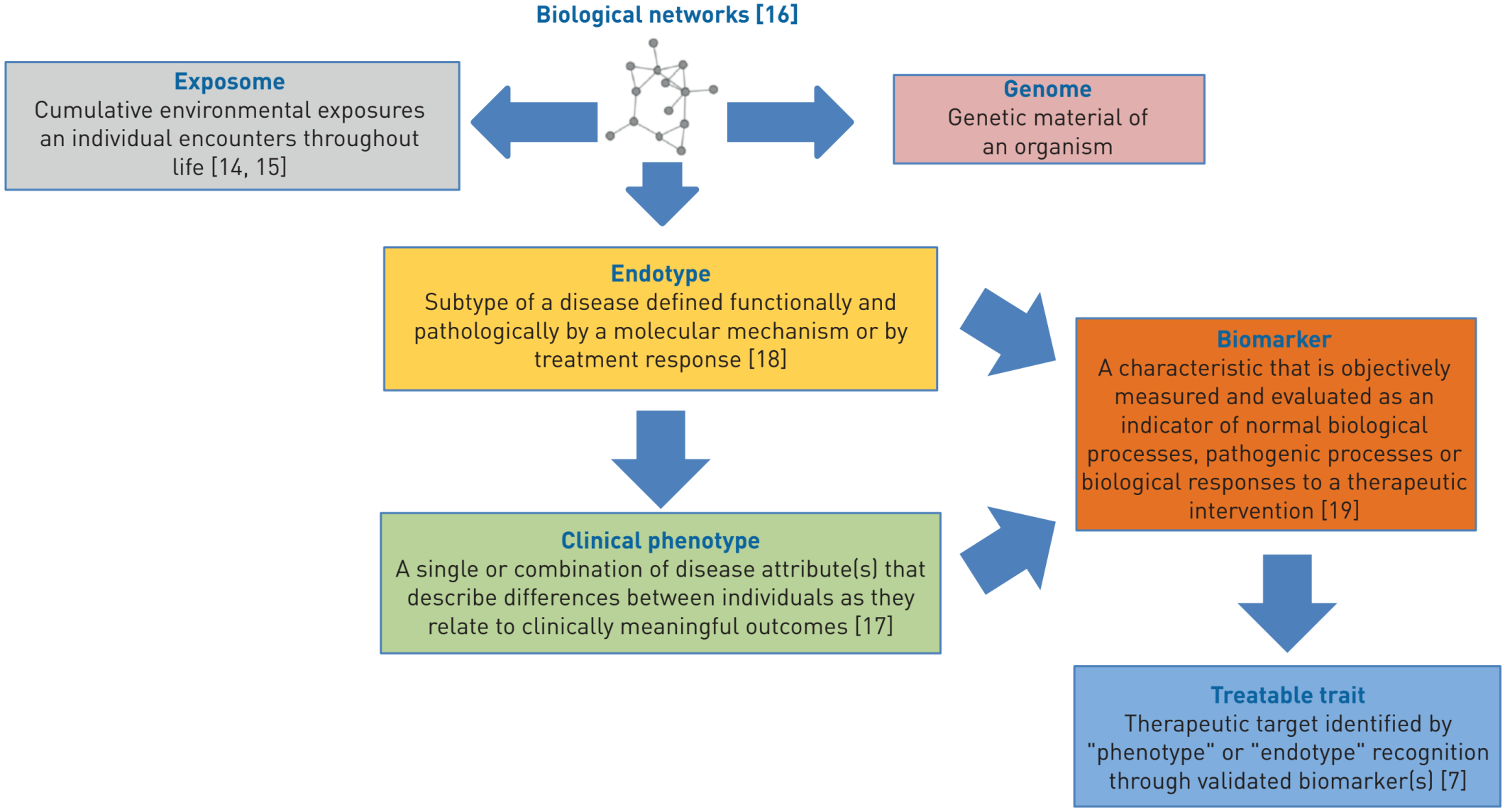
Contents

Schematic of the Relationships Between the Exposome and the Genome (Via Complex Biological Networks), the Emergence of Endotypes and Phenotypes, and the Possibility of Identifying Them Through Validated Biomarkers of Treatable Traits



Agusti A et al. Eur Respir J 2017;50. [PMID: 29051276]

WHAT IS A BIOMARKER?

A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.

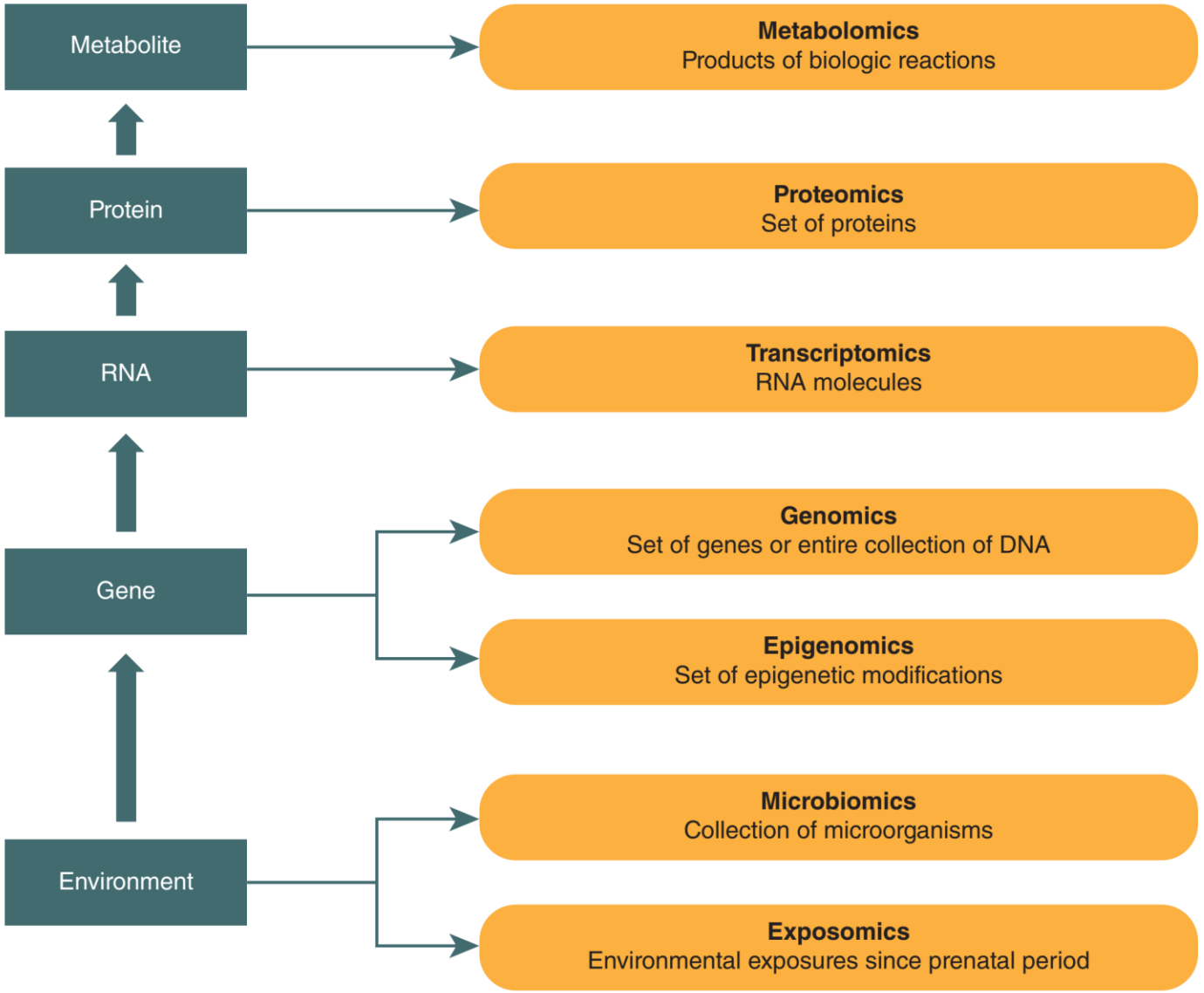
Types: Molecular, histologic, radiographic, and physiologic characteristics are types of biomarkers.

Examples:

- Blood glucose (molecular)
- Tumor size (radiographic)
- Blood pressure (physiologic)

IgE (molecular)
FeNO (molecular)
Blood eosinophil (cellular)
Sputum eosinophil (cellular)
Mucus plugging (radiographic)
FEV1 (physiologic)

Example of Biologic/Pathological Processes and Corresponding Kinds of Omics



Moon JY et al. BRN Rev 2018;4:84-107

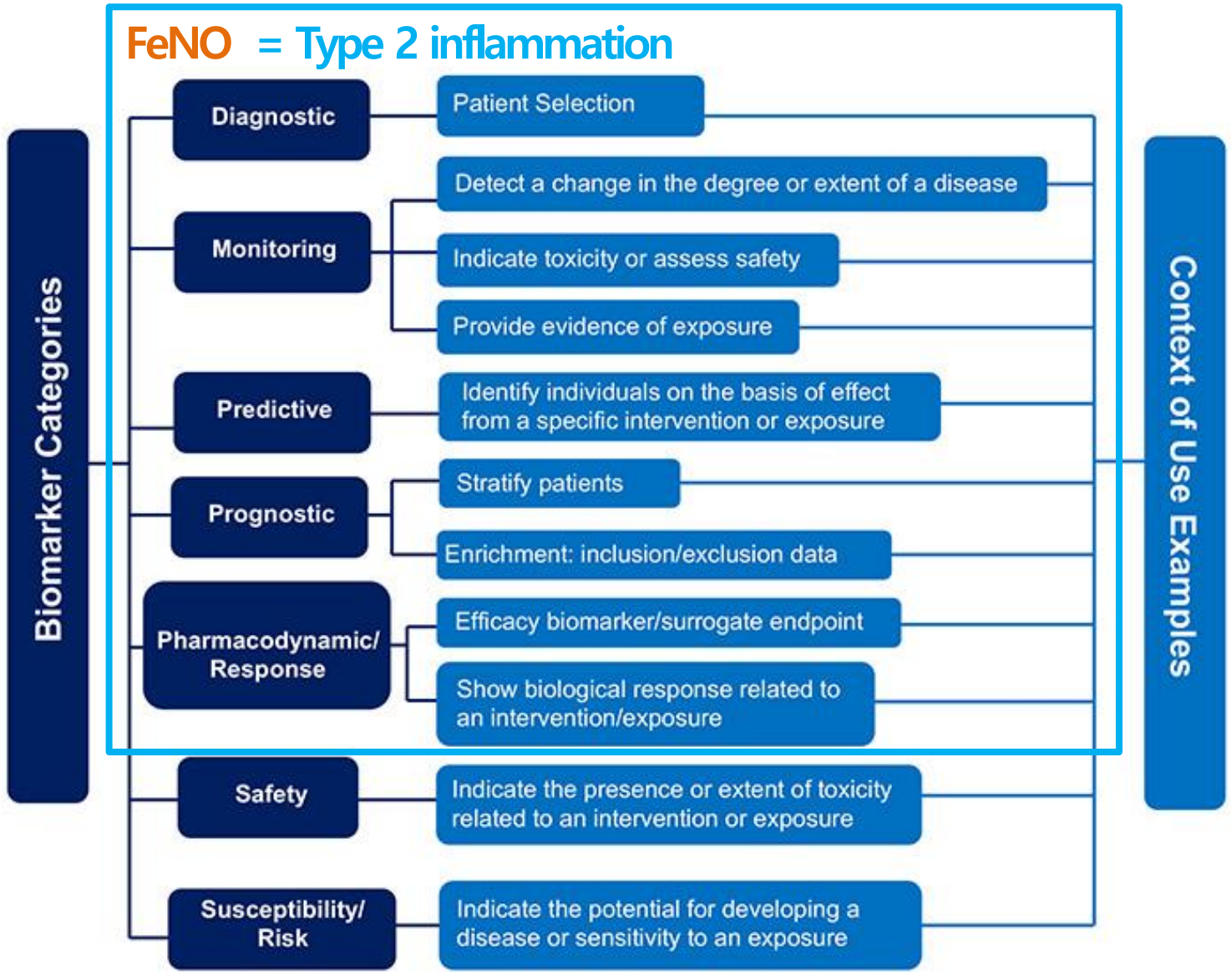
Invasive vs. Non-invasive / Systemic vs Local

- Invasive
  - Blood
  - Bronchoalveolar lavage
  - Biopsy
- Non-invasive
  - Urine
  - Sputum
  - Exhaled
    - Exhaled breath condensate (EBC)
    - Volatile organic compounds (VOCs)
    - Fraction of nitric oxide in expired gas (**FeNO**)

Systemic biomarkers

Local biomarkers

Different Categories of Biomarkers



https://www.fda.gov/drugs/biomarker-qualification-program/context-use

Categories of Biomarker related to Natural History

Susceptibility/risk biomarker

Indicating the potential for developing asthma

Diagnostic biomarker

Detecting presence of asthma

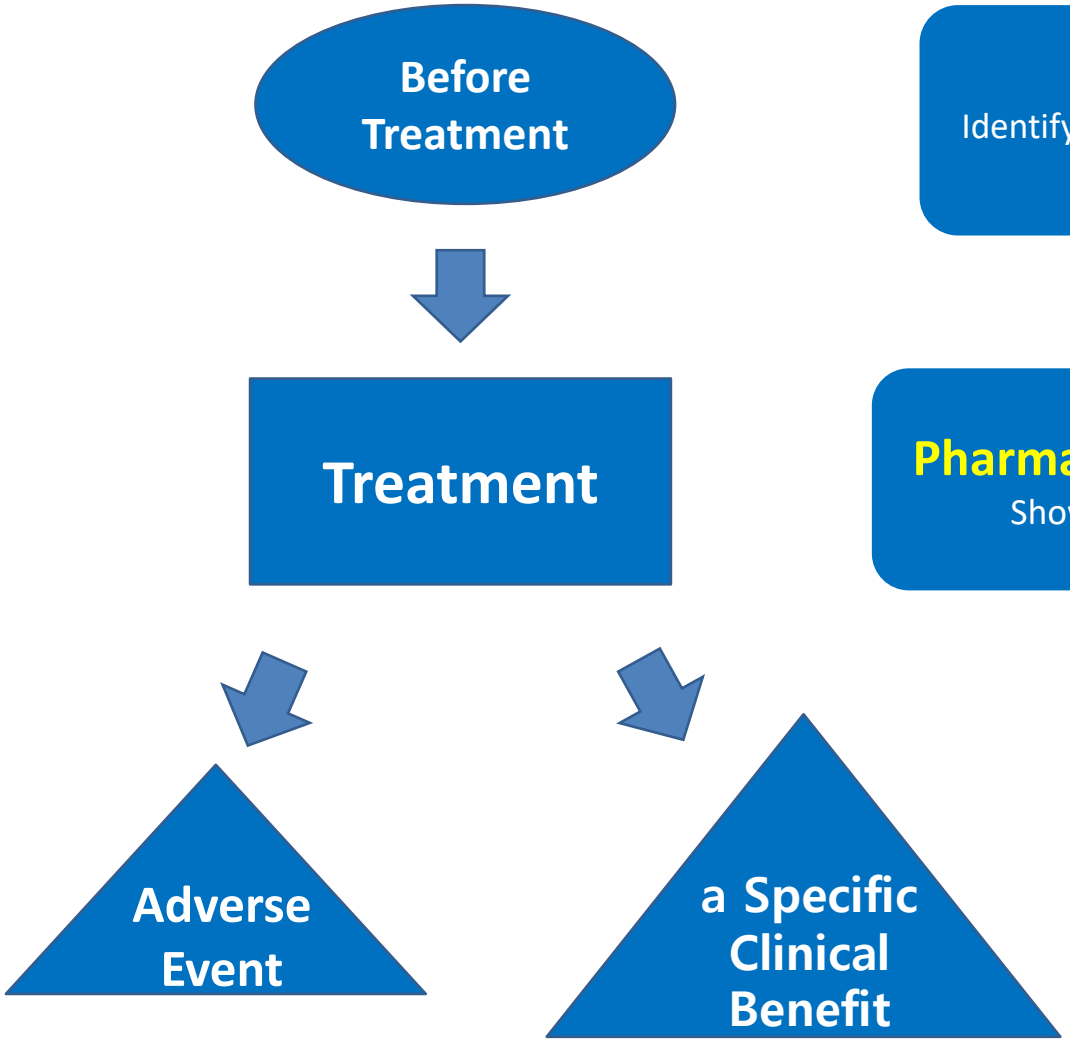
Monitoring biomarker

Assessing status of asthma

Prognostic biomarker

Identifying likelihood of asthma **progression, exacerbation, or death**

Categories of Biomarker related to Treatment



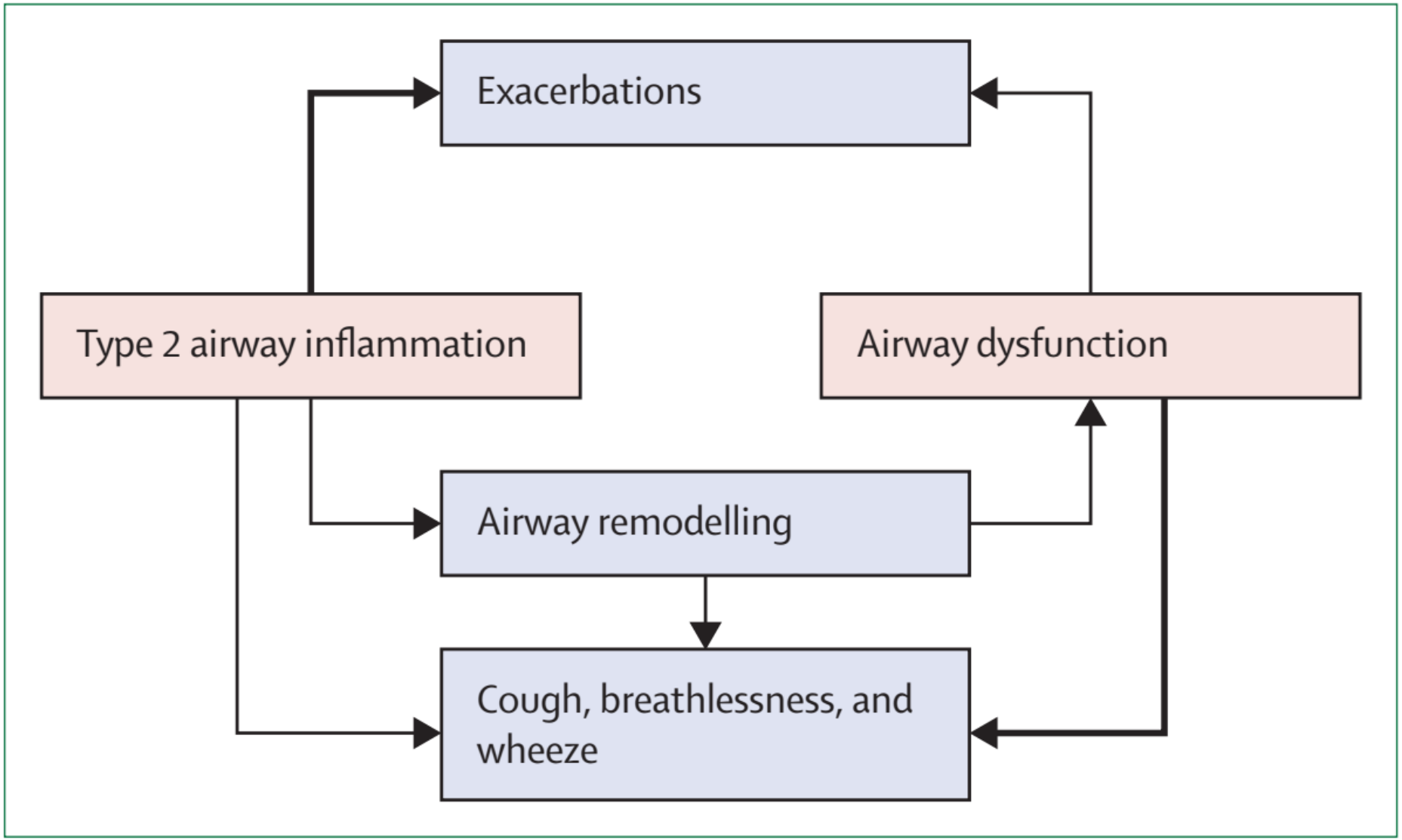
Predictive biomarker
Identifying individuals who are more likely to have the benefits of treatment

Pharmacodynamic/response biomarker
Showing a biological response to treatment

Safety biomarker
Indicating an adverse effect of treatment

Validated Surrogate Endpoint
An endpoint supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate endpoint predicts a specific clinical benefit.

Type 2 Airway Inflammation and Airway Dysfunction



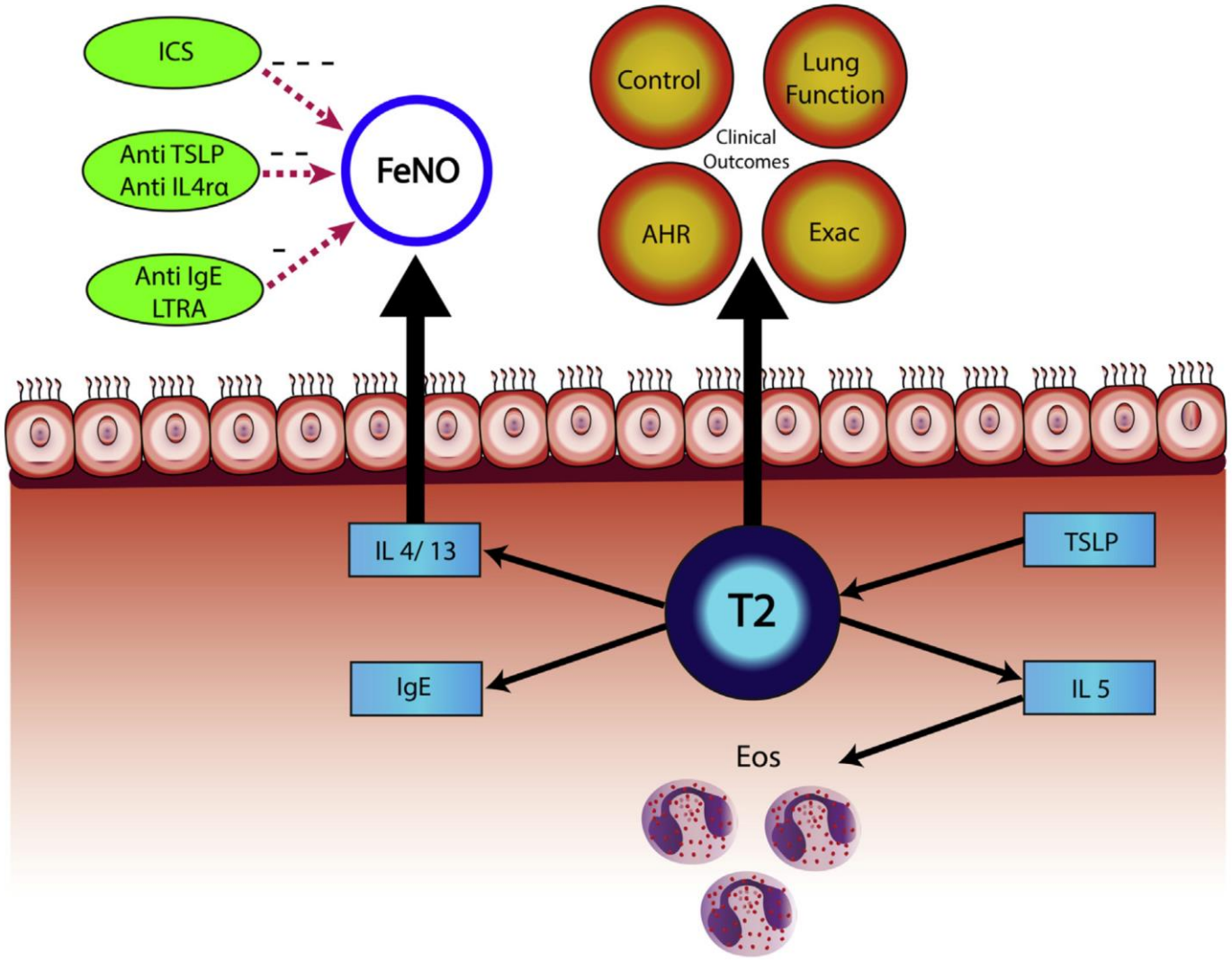
Shaw DE et al. Lancet Respir Med 2021;9:786-94. [PMID: 33639099]

Biomarkers of Type-2 Airway Inflammation

Biomarker	Cutoffs	Association With Treatment Response	Comments
IgE	Variable	Anti-IgE	IgE levels do not consistently predict clinical outcomes nor treatment responsiveness
Blood eosinophil count	$\geq 0.15 \times 10^9$ per L	Corticosteroids Anti-IL-5/5R Anti-IL4Rα Anti-IgE Anti-TSLP	Generally available, cheap, directly relates to asthma control and risk of asthma attacks
Sputum eosinophils	≥2%	Corticosteroids Anti-IL-5 Anti-IL4Rα	Not routinely available, tissue-specific, time-consuming
FENO	≥25 ppb	ICS Anti-IL-4Rα Anti-TSLP	Quick, cheap, noninvasive, associated with increased risk of asthma attacks; increases probability of ICS responsiveness

Pavord ID et al. Lancet 2018;391:350-400 [PMID 28911920]

Schematic Figure to Portray the Pivotal Role of T2 Inflammation



Lipworth B et al. J Allergy Clin Immunol 2020;146:1281-2 [PMID 33280711]

FeNO Cut-offs in Different Guidelines

Guidelines	F_{eNO} cut-offs	Justification
NICE [28]	**Adults**	
	Positive: >40 ppb	
	Children (5–16 years)	
	Positive: >35 ppb	
Scottish consensus statement [65]	**ICS-naïve patients**	
	>40 ppb	
	Patients taking ICS	
	>25 ppb	
GINA [15]	**Adults**	Associated with eosinophilic inflammation (in non-smokers)
	⩾20 ppb	
ATS/ERS [40]	**Adults**	Eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids likely
	High: >50 ppb	
	Intermediate: 25–50 ppb	Cautious interpretation required Eosinophilic inflammation and responsiveness to corticosteroids less likely
	Low: <25 ppb	
ATS/ERS [40]	**Children**	Eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids likely
	High: >35 ppb	
	Intermediate: 20–35 ppb	Cautious interpretation required Eosinophilic inflammation and responsiveness to corticosteroids less likely
	Low: <20 ppb	

Menzies-Gow A et al. Eur Respir J 2020;55 [PMID 31949116]

Confounding Factors to Be Considered When Interpreting FENO Levels in Patients With Asthma

- Factors That Increase FENO
  - Chronic rhinosinusitis, nasal polyposis, or both
  - Allergic rhinitis
  - Atopy
  - Rhinovirus respiratory infections
  - Intake of nitrate-containing food, eg, beetroot
  - Air pollution (particulate matter and ozone)
  - Male sex
  - HIV infection
  - Increasing age (>60)
  - Increased height
  - Morning

- Factors That Decrease FENO
  - Cigarette smoking
    - Decreases FENO by 40%-60%
    - Magnitude of reduction correlates with the cumulative lifetime cigarette consumption
  - Inhaled steroid use
  - Alcohol ingestion
  - Spirometry
  - Certain drugs
    - LTRA, prostaglandins
  - Physical exercise
  - Obesity

Rupani H et al. Chest 2022;161:906-17 [PMID 34673021]
Loewenthal L et al. Semin Respir Crit Care Med 2022; [PMID 35253144]

Contents

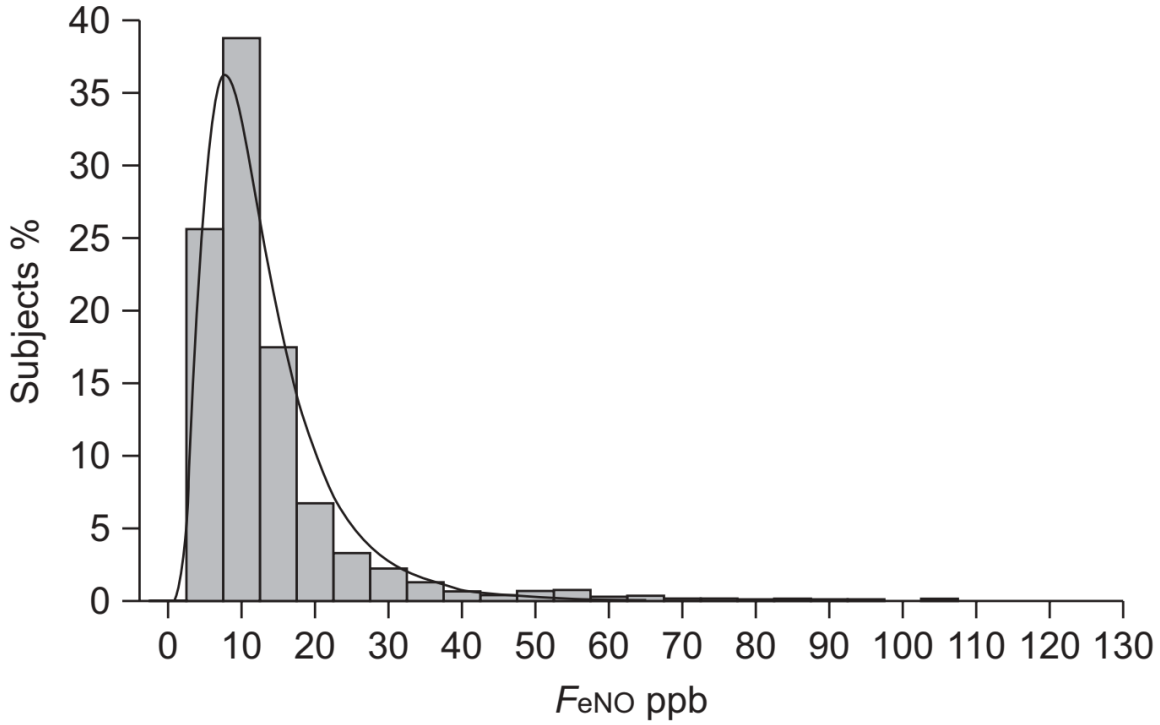
FeNO, an Exhaled Biomarker

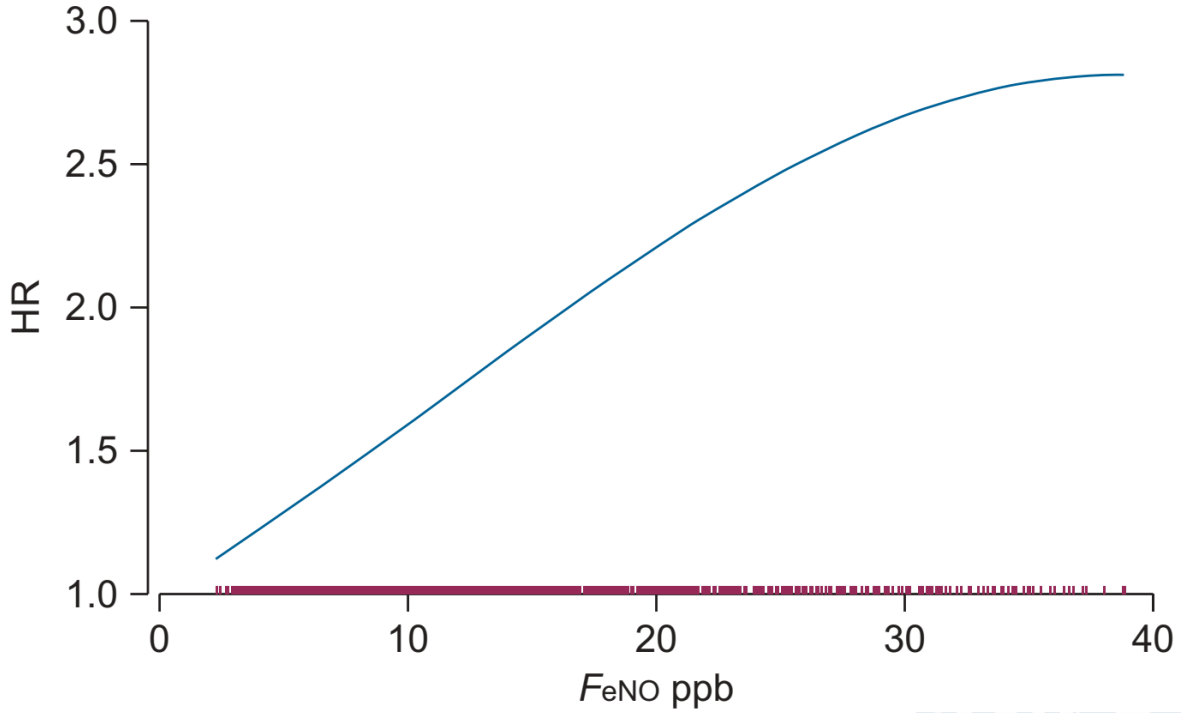
FeNO, a Biomarker for Natural History of Asthma

FeNO, a Biomarker for Pharmacologic Treatment

Exhaled nitric oxide, susceptibility and new-onset asthma in the Children's Health Study

T.M. Bastain, T. Islam, K.T. Berhane, R.S. McConnell, E.B. Rappaport, M.T. Salam, W.S. Linn, E.L. Avol, Y. Zhang and F.D. Gilliland





Bastain TM et al. Eur Respir J 2011;37:523-31 [PMID 20634264]

TABLE 6 Association of exhaled nitric oxide (F_{ENO}) with new-onset asthma by parental history of asthma

Age-specific quartiles of F_{ENO} at baseline	Parental history of asthma					
	No			Yes		
	New-onset asthma	No asthma	HR[#] (95% CI)	New-onset asthma	No asthma	HR[#] (95% CI)
Quartile 1	13	393	1	9	81	2.55 (1.08–6.04)
Quartile 2	19	408	1.66 (0.82–3.39)	9	61	3.97 (1.67–9.41)
Quartile 3	18	395	1.80 (0.87–3.73)	7	65	3.77 (1.48–9.61)
Quartile 4	36	380	3.18 (1.66–6.08)	8	77	2.17 (0.88–5.34)
p_{trend}			<0.001[¶]			0.33[¶]
$p_{interaction}$			<0.05[+]			

Data are presented as n, unless otherwise stated. HR: hazard ratio; p_{trend}: p-value for trend; $p_{interaction}$: p-value for interaction. [#]: adjusted for race/ethnicity, lifetime wheeze and community with baseline strata for age and sex; [¶]: trend tests conducted in stratified models; [+]: based on the Chi-squared statistic using the likelihood ratio test to compare a model with base terms to a model containing the interaction term.

Bastain TM et al. Eur Respir J 2011;37:523-31 [PMID 20634264]

Accuracy of FE_{NO} for diagnosing asthma: a systematic review

Stefan Karrasch,[1,2,3] Klaus Linde,[1] Gerta Rücker,[4,5] Harriet Sommer,[4,5] Marlies Karsch-Völk,[1] Jos Kleijnen,[6,7] Rudolf A Jörres,[3] Antonius Schneider[1]

Table 2 Meta-regression for FE_{NO} devices

FE_{NO} device (measurement technique)	n	Sensitivity (95% CI)	Specificity (95% CI)
Niox Flex (chemoluminescence)	12	0.58 (0.27 to 0.83)	0.88 (0.59 to 0.97)
Other chemoluminescence	8	0.84 (0.76 to 0.90)	0.77 (0.65 to 0.86)
Niox Mino (electrochemical)	5	0.59 (0.31 to 0.82)	0.81 (0.51 to 0.94)
Other electrochemical	1	0.16 (0.02 to 0.63)	0.98 (0.48 to 1.00)

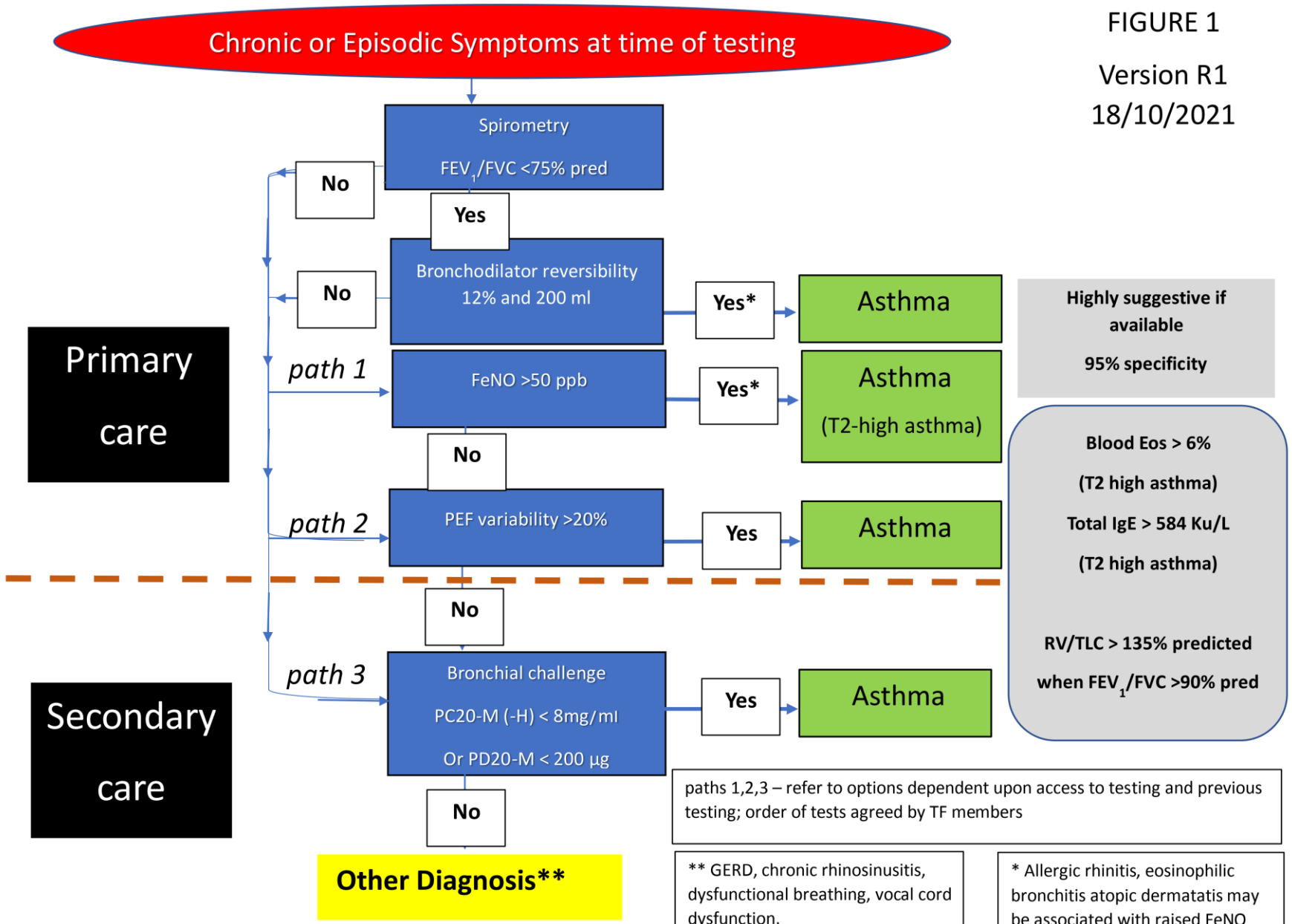
n, number of data sets in analysis (two studies/three data sets without sufficient information).

Karrasch S et al. Thorax 2017;72:109-16 [PMID 27388487]

FIGURE 1

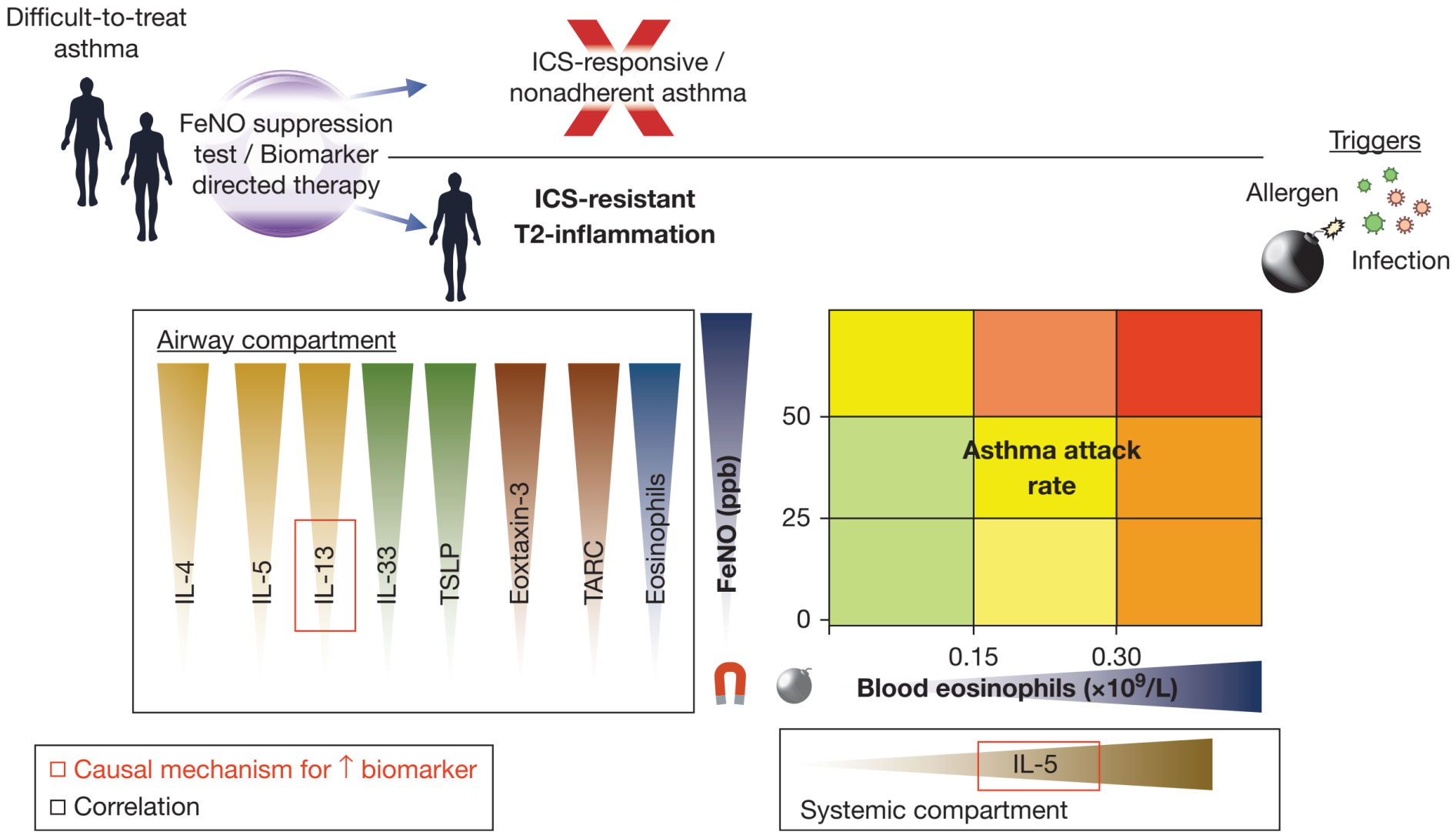
Version R1

18/10/2021



Louis R et al. Eur Respir J 2022. [PMID: 35169025]

Translating Type 2 (T2) Biomarkers in Severe Asthma

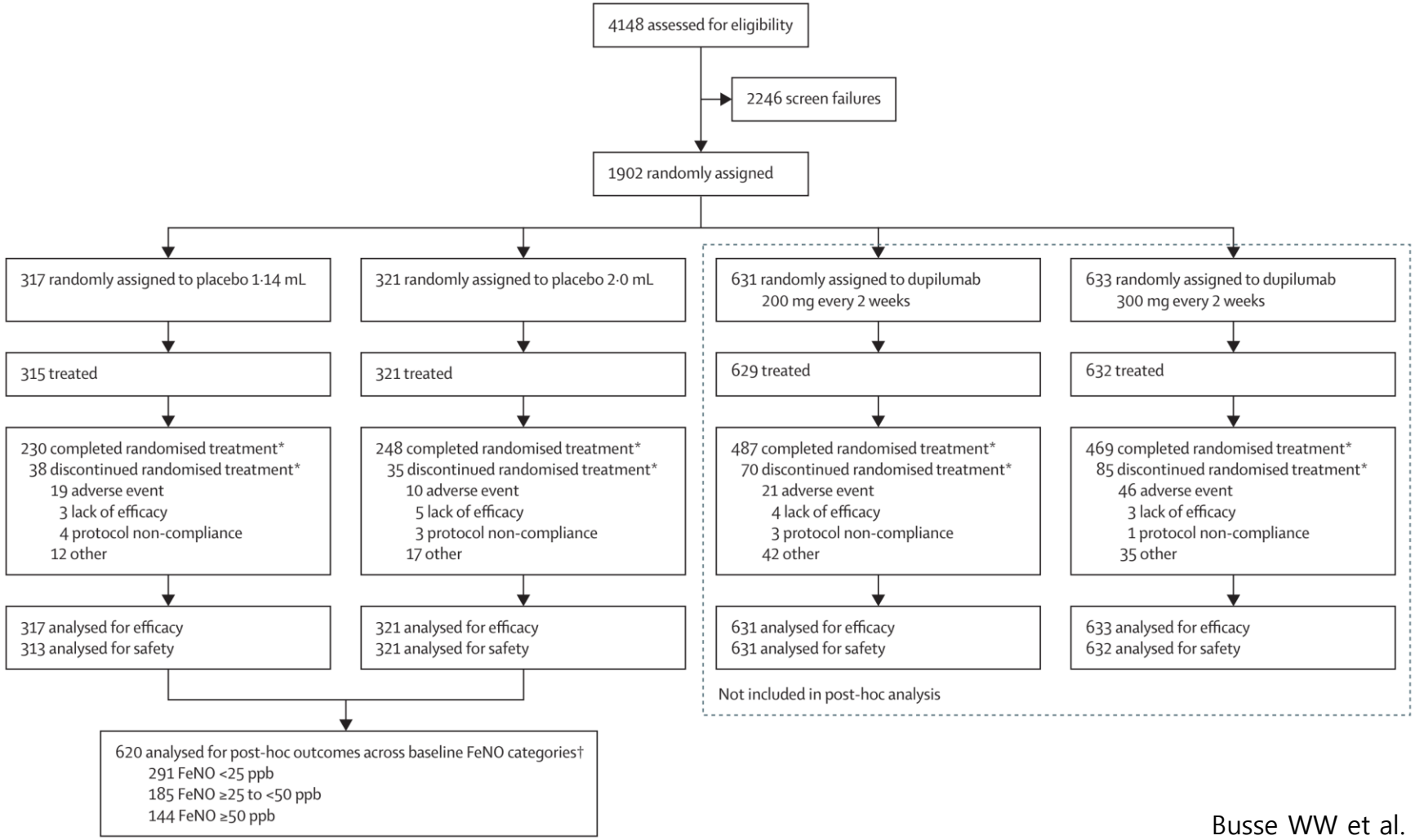


- **FENO** reflects **airway** type 2 activity and the chemotactic pull to the airway compartment, whereas **blood eosinophils** reflect the **systemic** pool of available effector cells and circulating IL-5.
- These biomarkers have **additive value** in predicting **asthma attacks** and the benefits of **T2 targeted anti-inflammatory treatment** in clinical trials

Couillard S et al. Chest 2021;160:2019-29 [PMID 34265308]

Baseline FeNO as a prognostic biomarker for subsequent severe asthma exacerbations in patients with uncontrolled, moderate-to-severe asthma receiving placebo in the LIBERTY ASTHMA QUEST study: a post-hoc analysis

William W Busse, Sally E Wenzel, Thomas B Casale, J Mark FitzGerald, Megan S Rice, Nadia Daizadeh, Yamo Deniz, Naimish Patel, Sivan Harel, Paul J Rowe, Neil M H Graham, Thomas O'Riordan, Ian D Pavord



- post-hoc analysis of the 52-week, double-blind, phase 3 LIBERTY ASTHMA QUEST study
- Uncontrolled asthma with
  - inhaled glucocorticoids plus up to two controllers;
  - one or more exacerbations in the previous year;
  - FEV1 percent predicted 40–80%; FEV1 reversibility of 12% or higher and 200 mL;
  - Asthma Control Questionnaire (ACQ-5) score of 1·5 or higher

Busse WW et al. Lancet Respir Med 2021;9:1165-73 [PMID 34181876]

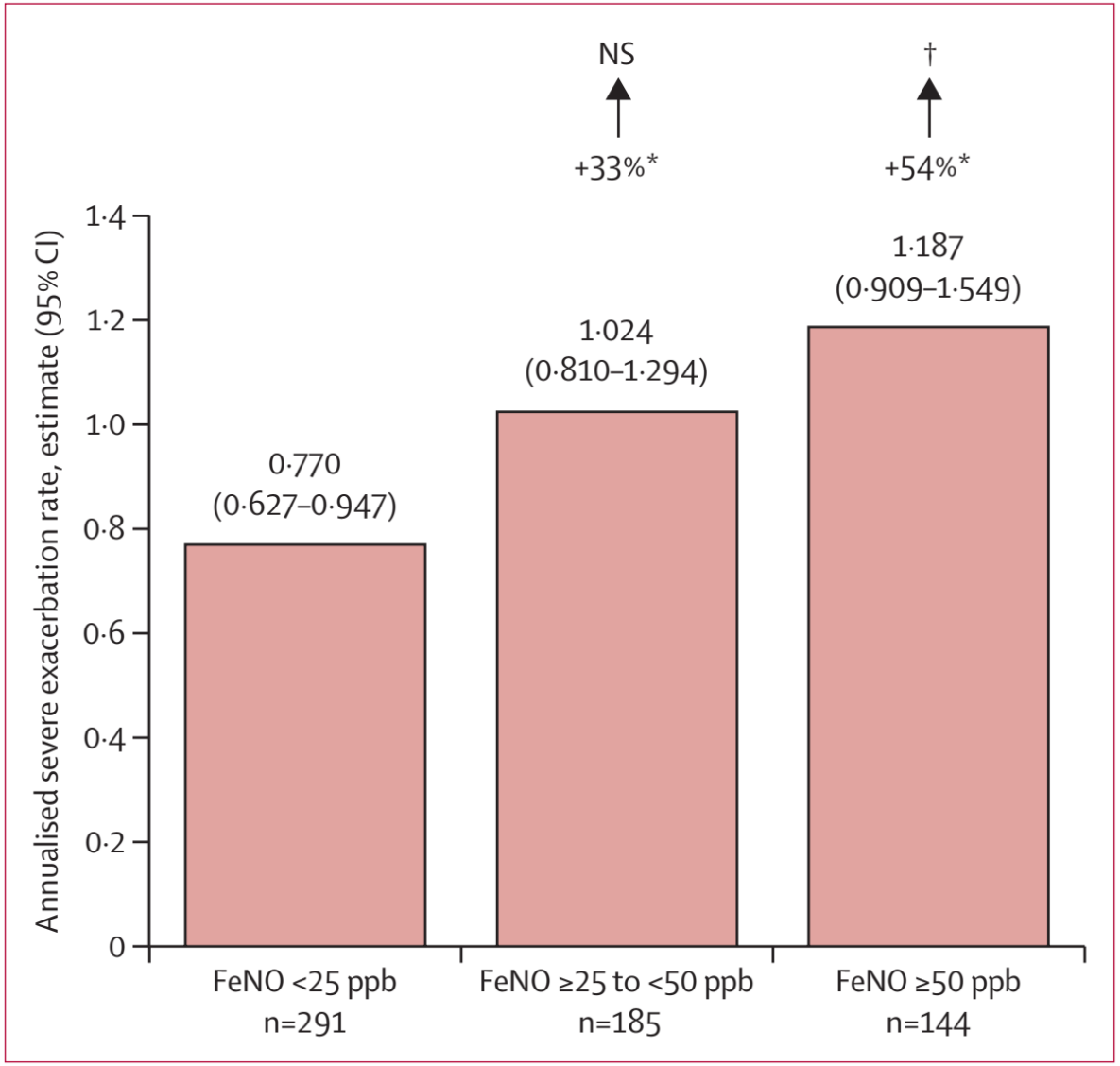


Figure 2: **Multivariable analyses of baseline FeNO level and the estimated annualised severe exacerbation rate over the following 52 weeks in placebo-treated patients**

Blood eosinophil count (cells per µL)	<25 FeNO (ppb)	≥25 to <50 FeNO (ppb)	≥50 FeNO (ppb)
≥300	n=89 0·844 (0·589–1·210) p=0·2083*	n=97 1·235 (0·869–1·755) p=0·0186*	n=98 1.777 (1·245–2·536) p=0·0008*
≥150 to <300	n=96 0·818 (0·591–1·131) p=0·1504*	n=53 1·138 (0·761–1·701) p=0·0164*	n=25 0·475 (0·226–0·999) p=0·7164*
<150	n=106 0·556 (0·353–0·877)	n=35 0·616 (0·328–1·158) p=0·7490*	n=21 0·530 (0·235–1·195) p=0·9083*

Figure 3: **Multivariable analyses of baseline FeNO level and the estimated annualised severe exacerbation rate (95% CI) over the following 52 weeks in placebo-treated patients further stratified by baseline blood eosinophil count**

FeNO=fractional exhaled nitric oxide. *p value versus patients with baseline FeNO of less than 25 ppb and blood eosinophil count of less than 150 cells per µL.

Busse WW et al. Lancet Respir Med 2021;9:1165-73 [PMID 34181876]

Derivation of a prototype asthma attack risk scale centred on blood eosinophils and exhaled nitric oxide

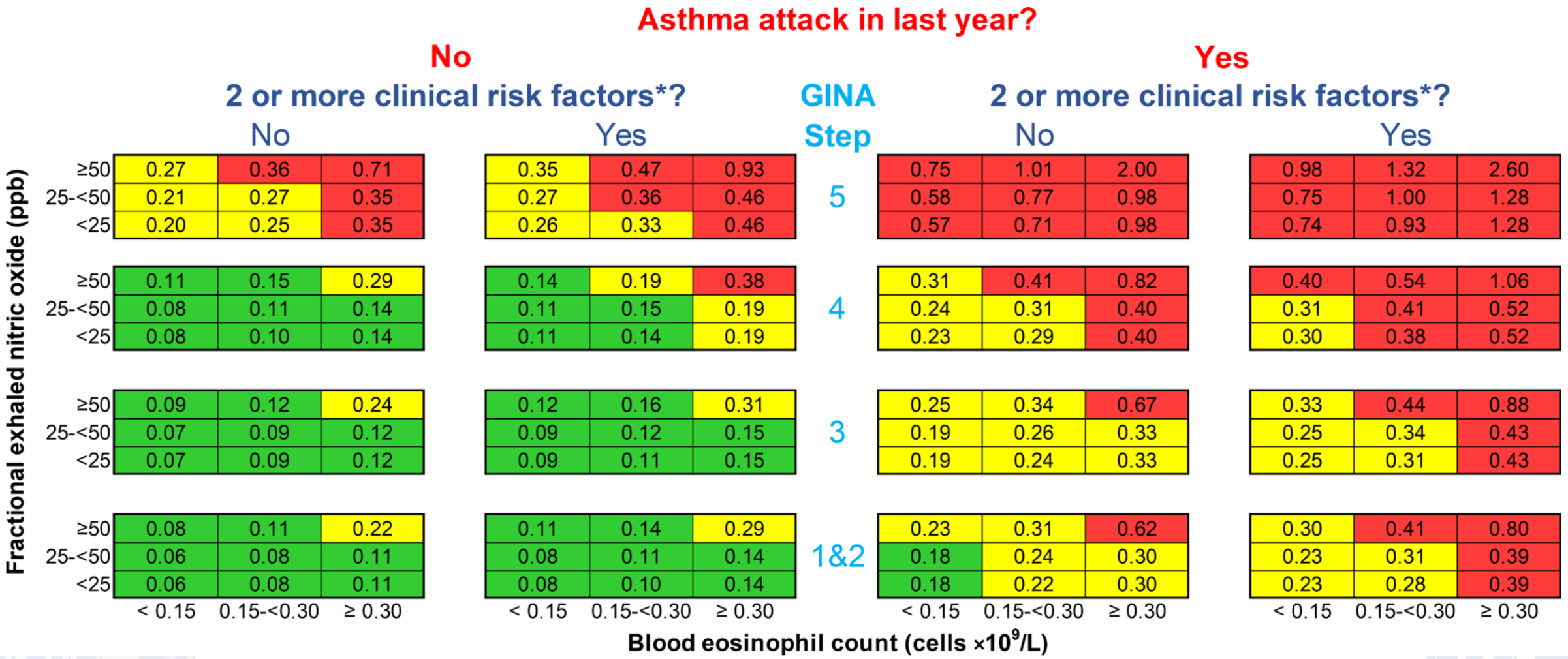
Simon Couillard [1,2] Annette Laugerud,[3] Maisha Jabeen [1] Sanjay Ramakrishnan [1,4] James Melhorn [1] Timothy Hinks [1] Ian Pavord [1]

Table 1 Biomarker-stratified data and rate ratios derived from included trials

		Novel START[4]			CAPTAIN[5]			Pooled AZ trials: Benralizumab 2b, PATHWAY, STRATOS 1–2[7]			QUEST[6]			DREAM[3]				
		Step 1 asthma; low risk; 9% with attack in past 12 months			Step 4 asthma; high risk; 62% with attack in past 12 months			1% step 3 asthma, 50% step 4 asthma, 49% step 5 asthma; high risk; with attack in past 12 months			47% step 4 asthma, 53% step 5 asthma; high risk; with attack in past 12 months			Step 5 asthma; high risk; with attack in past 12 months			Aggregate data for the prototype risk scale	
Blood Eos ($\times 10^9$/L)	FeNO (ppb)	N†	Attack rate‡	Rate ratio	N	Attack rate‡	Rate ratio	N†	Attack rate	Rate ratio	N	Attack rate	Rate ratio	N	Attack rate	Rate ratio	N	Rate ratio
<0.15	<25	18	0.05	0.98	228	0.85	0.54	199	0.58	0.81	106	0.56	0.52	23	1.98	0.76	574	**0.65**
	25–<50	23	0.00	0.00	40	0.10	1.11	82	0.46	0.64	35	0.62	0.61	(9)	(1.78)	(0.71)	180	**0.66**
	≥50	8	0.00	0.00	17	0.15	1.74	23	0.57	0.81	21	0.53	0.53				69	**0.86**
0.15–<0.30	<25	19	0.07	1.50	240	0.07	0.82	191	0.56	0.76	96	0.82	0.80	12	1.54	0.59	558	**0.81**
	25–<50	42	0.02	0.36	87	0.07	0.79	173	0.67	0.96	53	1.14	1.17	(23)	(2.70)	(1.07)	355	**0.88**
	≥50	32	0.01	0.24	24	0.12	1.43	52	1.29	1.93	25	0.48	0.47				133	**1.16**
≥0.30	<25	4	0.30	6.35	248	0.11	1.29	102	0.58	0.82	89	0.84	0.84	18	1.95	0.75	461	**1.12**
	25–<50	22	0.00	0.00	147	0.09	1.00	133	0.87	1.30	97	1.24	1.31	(66)	(3.08)	(1.22)	399	**1.12**
	≥50	51	0.13	4.40	66	0.18	2.14	107	1.01	1.53	98	1.78	2.12				322	**2.29**
Analysed		219	0.05	1.00	1097	0.09	1.00	1062	0.70	1.00	620	0.99	1.00	151	2.52	1.00	3051	1.00
Missing*		4			121			120			14			4			262	
Total		223			1218			1182			634			155			3313	

Couillard S et al. Thorax 2022;77:199-202 [PMID 34362839]

Prototype asthma attack risk scale



Couillard S et al. Thorax 2022;77:199-202 [PMID 34362839]

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FeNO, an Exhaled Biomarker

FeNO, a Biomarker for Natural History of Asthma

FeNO, a Biomarker for Pharmacologic Treatment

Summary of studies investigating the prognostic and predictive ability of the combination of blood eosinophil count and FENO

	Intervention	Prestudy exacerbation rate	FEV_1 (% predicted)	Definition of type 2 status*	Number of patients with type 2 low and high/total number in control group	Severe exacerbations in type 2 low in control group†	Severe exacerbation rate of type 2 high in control group‡	Percentage reduction in annualised exacerbation rate achieved by active treatment	Percentage reduction in proportion of patients having a severe exacerbation achieved with active treatment
Mild asthma									
Novel-START[29,30]	Budesonide 200 µg inhaled twice daily for 52 weeks and as needed *vs* budesonide 100 µg and formoterol 6 µg for 52 weeks *vs* as-needed salbutamol	17§ *vs* 12§ *vs* 20§	90·3 *vs* 89·8 *vs* 89·2	Low: FENO <25 ppb and blood eosinophils <150 cells per µL; high: FENO>50 ppb and blood eosinophils >300 cells per µL	Low: 16/217, high: 51/217	12·5%	25·5%	..	Regular budesonide: low biomarkers: –214%, high biomarkers: 78%; as-needed budesonide and formoterol: low biomarkers: 0%, high biomarkers: 81%
Moderate or moderate-to-severe asthma									
CAPTAIN[31]	Fluticasone furoate 100 µg and vilanterol 25 µg with or without umeclidinium 31·25 µg or 61·50 µg per day *vs* fluticasone furoate 200 µg and vilanterol 25 µg with or without umeclidinium 31·25 µg or 61·50 µg per day	63¶	58·4	Low: FENO <20 ppb and blood eosinophils <150 cells per µL; high: FENO >50 ppb and blood eosinophils >300 cells per µL	Low: 194/1097, high: 67/1097	12%	33%	..	High-dose fluticasone furoate *vs* low dose fluticasone furoate: low biomarkers: –16%, high biomarkers: 100%

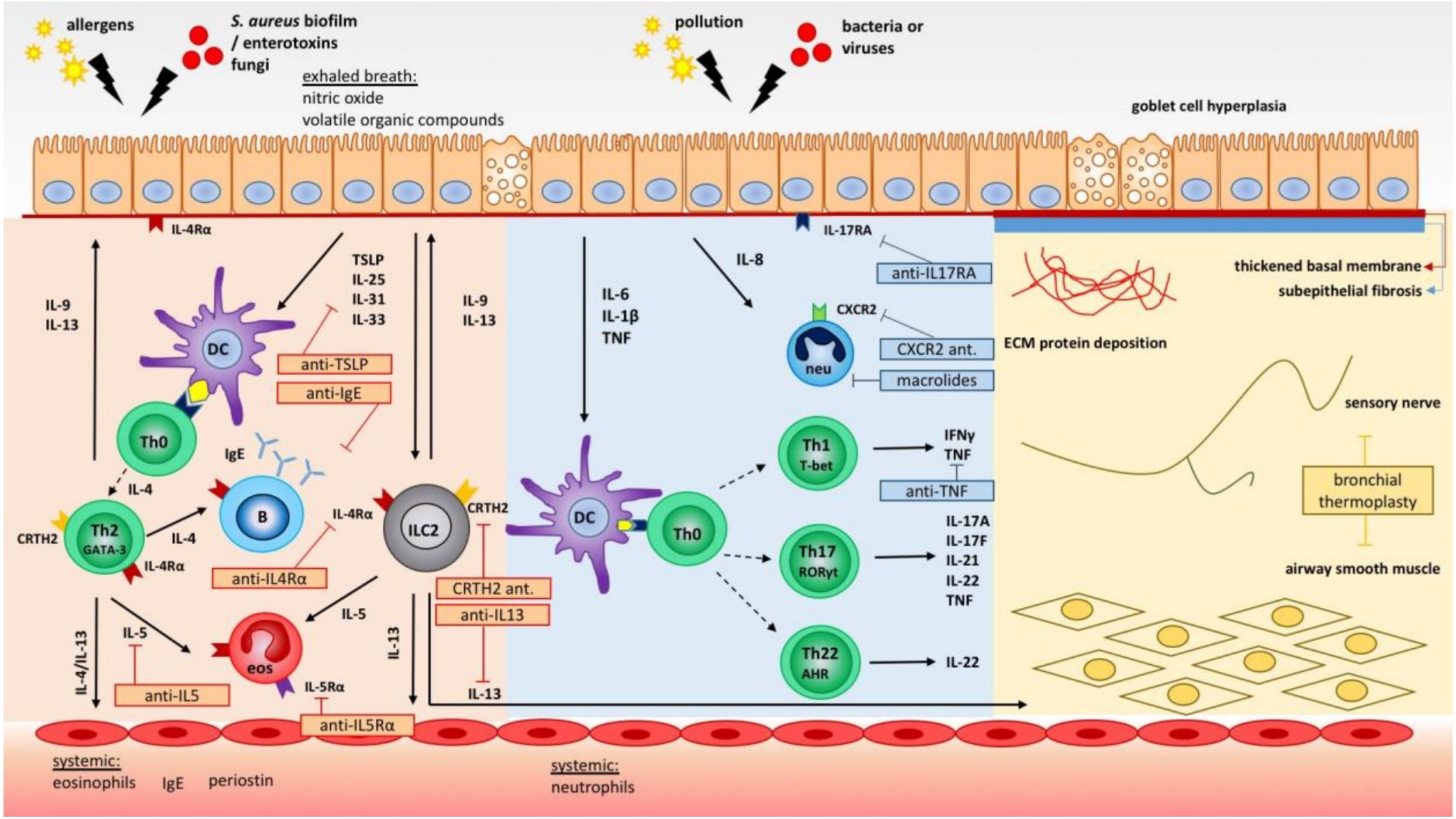
Shaw DE et al. Lancet Respir Med 2021;9:786-94. [PMID: 33639099]

Summary of studies investigating the prognostic and predictive ability of the combination of blood eosinophil count and FENO

	Intervention	Prestudy exacerbation rate	FEV_1 (% predicted)	Definition of type 2 status*	Number of patients with type 2 low and high/total number in control group	Severe exacerbations in type 2 low in control group†	Severe exacerbation rate of type 2 high in control group‡	Percentage reduction in annualised exacerbation rate achieved by active treatment	Percentage reduction in proportion of patients having a severe exacerbation achieved with active treatment
QUEST[32]	Dupilumab 200 mg subcutaneous injection every 2 weeks for 52 weeks *vs* placebo; dupilumab 300 mg subcutaneous injection every 2 weeks for 52 weeks *vs* placebo	2·07 *vs* 2·07; 2·02 *vs* 2·31	58·4 *vs* 58·4; 58·5 *vs* 58·3	Low: FENO <25 ppb and blood eosinophils <150 cells per µL	Low: 55/311 high: 134/311; low: 52/315, high: 142/315	0·58 *vs* 0·61	1·16 *vs* 1·18	Low biomarkers: 9%, high biomarkers: 68%; low biomarkers: –35%, high biomarkers: 65%	..
LAVOLTA I and II[33]	Lebrikizumab 37·5 mg and 125 mg subcutaneous injection every month for 12 months *vs* placebo	64¶ *vs* 64¶	61 *vs* 61	Low: FENO <30 ppb and blood eosinophils <300 cells per µL	Unknown	0·61	1·19	Unknown	..
Severe asthma									
DREAM[12,34]	Mepolizumab 75 mg, 250 mg, and 750 mg intravenous infusion monthly for 12 months combined *vs* placebo	3·7 *vs* 3·7	60 *vs* 59	Low: FENO <25 ppb and blood eosinophils <150 cells per µL	Low: 23/150 high:72/150	1·98	3·14	Low biomarkers: 12%, high biomarkers: 62%	..

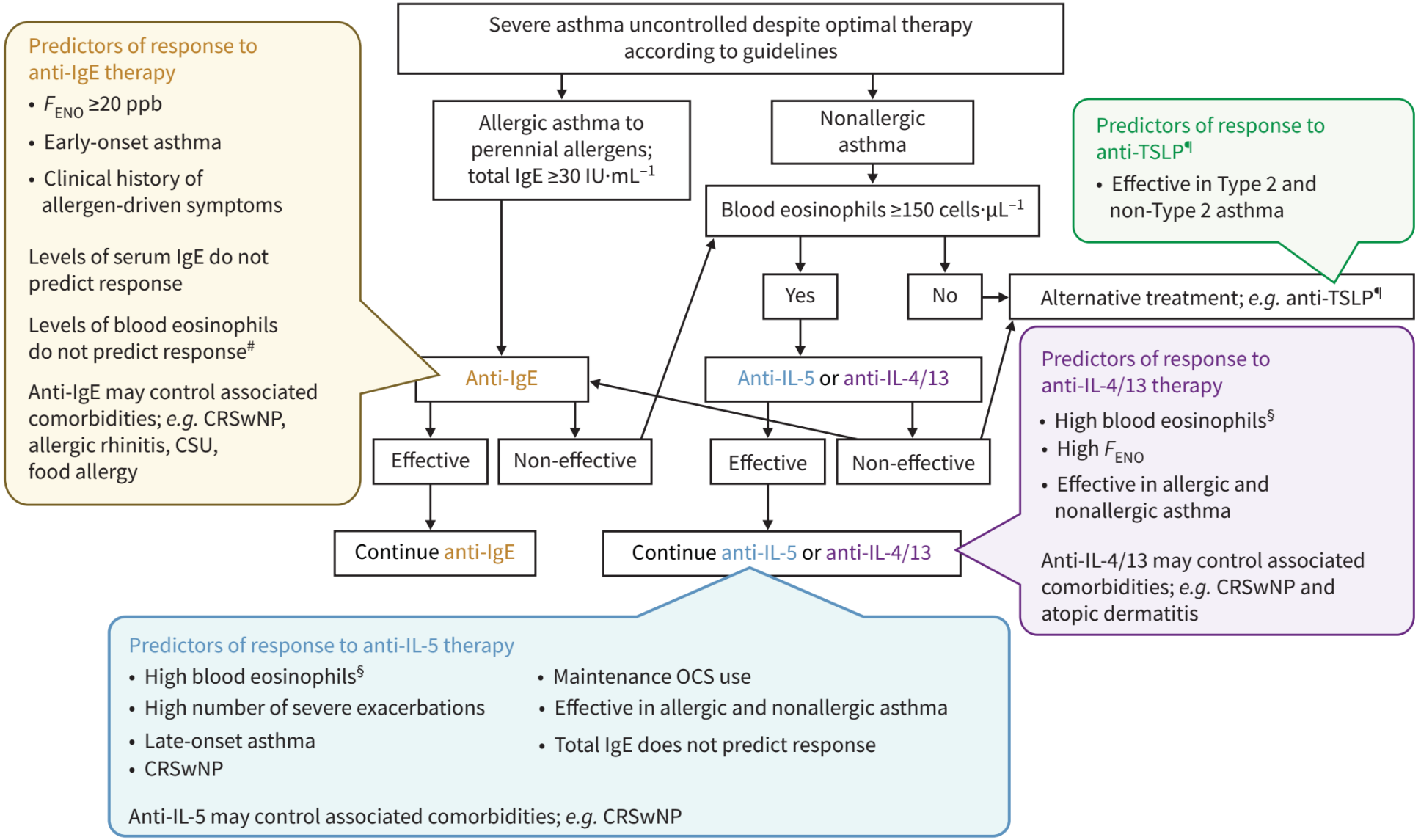
Shaw DE et al. Lancet Respir Med 2021;9:786-94. [PMID: 33639099]

Asthma endotypes and targeted treatment approaches



Diamant Z et al. Allergy 2019;74:1835-51 [PMID 30953574]

Care pathways and predictors of response for biologics in asthma



Busse WW et al. Eur Respir Rev 2022;31 [PMID 35082128]

Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: a prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial

Ian D Pavord, Mark Holliday, Helen K Reddel, Irene Braithwaite, Stefan Ebmeier, Robert J Hancox, Tim Harrison, Claire Houghton, Karen Oldfield, Alberto Papi, Mathew Williams, Mark Weatherall, Richard Beasley, on behalf of the Novel START Study Team

- in this prespecified subgroup analysis, we assessed whether **annual exacerbation rates** in each treatment group were significantly different depending on levels of **blood eosinophil count**, **FeNO**, or a **composite score** of both

Blood eosinophil count (×10⁹/L)		
<0·15 (n=184)	0·15 to <0·30 (n=256)	≥0·30 (n=216)

FeNO (ppb)		
<20 (n=159)	20 to 50 (n=249)	>50 (n=260)

Composite score		
1: blood eosinophils <0·15×10⁹/L and FeNO <20 ppb (n=78)	2: any pattern other than scores 1 or 3 (n=432)	3: blood eosinophils ≥0·3×10⁹/L and FeNO >50 ppb (n=146)

Pavord ID, Lancet Respir Med 2020;8:671-80.

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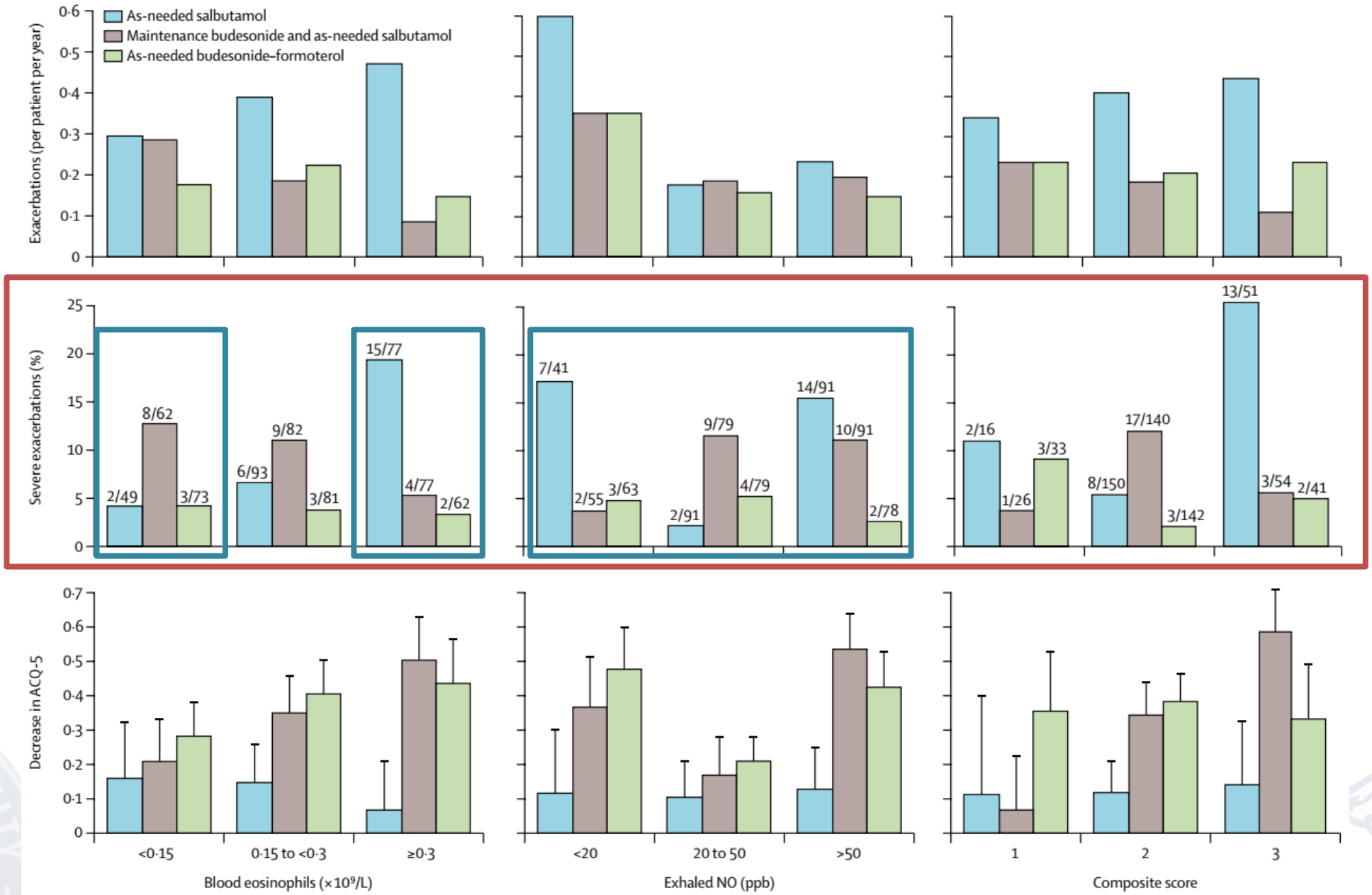
- in this prespecified subgroup analysis, we assessed whether **annual exacerbation rates** in each treatment group were significantly different depending on levels of **blood eosinophil count**, **FeNO**, or a **composite score** of both

	Blood eosinophil count (×10⁹/L)			FeNO (ppb)			Composite score		
	<0·15 (n=184)	0·15 to <0·30 (n=256)	≥0·30 (n=216)	<20 (n=159)	20 to 50 (n=249)	>50 (n=260)	1: blood eosinophils <0·15×10⁹/L and FeNO <20 ppb (n=78)	2: any pattern other than scores 1 or 3 (n=432)	3: blood eosinophils ≥0·3×10⁹/L and FeNO >50 ppb (n=146)
Sex									
Female	114 (62%)	132 (52%)	111 (51%)	117 (74%)	130 (52%)	117 (45%)	61 (78%)	223 (52%)	73 (50%)
Male	70 (38%)	124 (48%)	105 (49%)	42 (26%)	119 (48%)	143 (55%)	17 (22%)	211 (48%)	73 (50%)
Current smoker	19 (10%)	24 (9%)	21 (10%)	31 (19%)	17 (7%)	16 (6%)	12 (15%)	42 (10%)	10 (7%)
≥1 exacerbation in past year	16 (9%)	14 (5%)	18 (8%)	9 (6%)	23 (9%)	17 (7%)	6 (8%)	30 (7%)	12 (8%)
Hospitalisation with asthma ever	10 (5%)	41 (16%)	44 (20%)	15 (9%)	44 (18%)	48 (18%)	5 (6%)	69 (16%)	30 (21%)
Age, years	36·0 (14·9)	38·1 (14·4)	31·9 (12·3)	36·1 (14·2)	38·0 (14·9)	33·0 (12·9)	36·2 (15·1)	36·7 (14·3)	31·2 (12·1)
Age at onset of asthma, years	16·0 (12·9)	15·0 (14·9)	12·3 (11·9)	18·3 (13·9)	14·6 (14·0)	12·0 (12·5)	19·2 (14·1)	14·4 (13·8)	11·7 (11·5)
Body-mass index	27·3 (7·0)	28·1 (6·5)	26·6 (5·8)	28·7 (7·6)	28·0 (6·5)	26·0 (5·2)	27·7 (7·8)	27·9 (6·5)	25·7 (5·2)
SABA puffs per week	3·5 (3·3)	3·4 (3·3)	3·6 (3·3)	3·8 (3·7)	3·2 (2·9)	3·6 (3·3)	3·9 (3·5)	3·4 (3·3)	3·6 (3·2)
ACQ-5	1·0 (0·7)	1·1 (0·7)	1·2 (0·7)	1·2 (0·8)	1·0 (0·7)	1·1 (0·7)	1·1 (0·7)	1·1 (0·7)	1·2 (0·7)
FEV_1, % predicted	92·6 (14·3)	89·2 (13·9)	88·0 (13·0)	92·3 (14·3)	89·1 (13·8)	88·9 (13·4)	95·3 (14·0)	89·5 (13·8)	87·5 (13·0)
FeNO (ppb)	30·4 (24·8)	45·9 (38·8)	82·9 (50·7)	12·9 (4·0)	33·2 (8·2)	97·7 (42·1)	12·9 (3·9)	42·8 (33·2)	107·3 (42·8)
Blood eosinophil count (×10⁹/L)	0·10 (0·03)	0·22 (0·04)	0·51 (0·22)	0·18 (0·15)	0·24 (0·17)	0·38 (0·24)	0·09 (0·03)	0·23 (0·15)	0·52 (0·22)

Data are n (%) or mean (SD), unless otherwise stated. FeNO=fraction of exhaled nitric oxide. ppb=parts per billion. SABA=short-acting β agonist. ACQ-5=Asthma Control Questionnaire 5-item version.

Table 1: **Baseline characteristics by baseline biomarker group**

Pavord ID, Lancet Respir Med 2020;8:671-80.



Pavord ID, Lancet Respir Med 2020;8:671-80.

	Exacerbation rate ratios (95% CI)			Severe exacerbation risk odds ratios (95% CI)		
	As-needed budesonide–formoterol *vs* as-needed salbutamol	Maintenance budesonide plus as-needed salbutamol *vs* as-needed salbutamol	$p_{interaction}$	As-needed budesonide–formoterol *vs* as-needed salbutamol	Maintenance budesonide plus as-needed salbutamol *vs* as-needed salbutamol	$p_{interaction}$
FeNO	..	..	0·28	..	..	0·009
High (>50 ppb)	0·53 (0·24–1·15)	0·72 (0·35–1·50)	..	0·32 (0·06–1·75)	1·93 (0·62–5·92)	..
Low (<20 ppb)	0·36 (0·17–0·76)	0·19 (0·08–0·47)	..	0·18 (0·04–0·84)	0·09 (0·02–0·50)	..
p value (high *vs* low)	0·51	0·028	..	0·65	0·0040	..
Blood eosinophils count	..	..	0·014	..	..	0·009
High (≥0·3 × 10^9/L)	0·28 (0·12–0·63)	0·13 (0·05–0·33)	..	0·15 (0·03–0·79)	0·11 (0·03–0·45)	..
Low (<0·15 × 10^9/L)	0·63 (0·27–1·44)	1·15 (0·51–1·28)	..	1·42 (0·19–10·50)	5·72 (0·97–33·60)	..
p value (high *vs* low)	0·18	0·0006	..	0·10	0·0007	..
Composite score	..	..	0·54	..	..	0·005
High (FeNO >50 ppb and eosinophils ≥0·3 × 10^9/L)	0·52 (0·23–1·22)	0·24 (0·90–0·65)	..	0·15 (0·03–0·71)	0·17 (0·05–0·65)	..
Low (FeNO <20 ppb and eosinophils <0·15 × 10^9/L)	0·68 (0·22–2·14)	0·68 (0·20–2·35)	..	0·17 (0·05–0·65)	0·31 (0·03–3·67)	..
p value (high *vs* low)	0·73	0·20	..	0·18	0·68	..

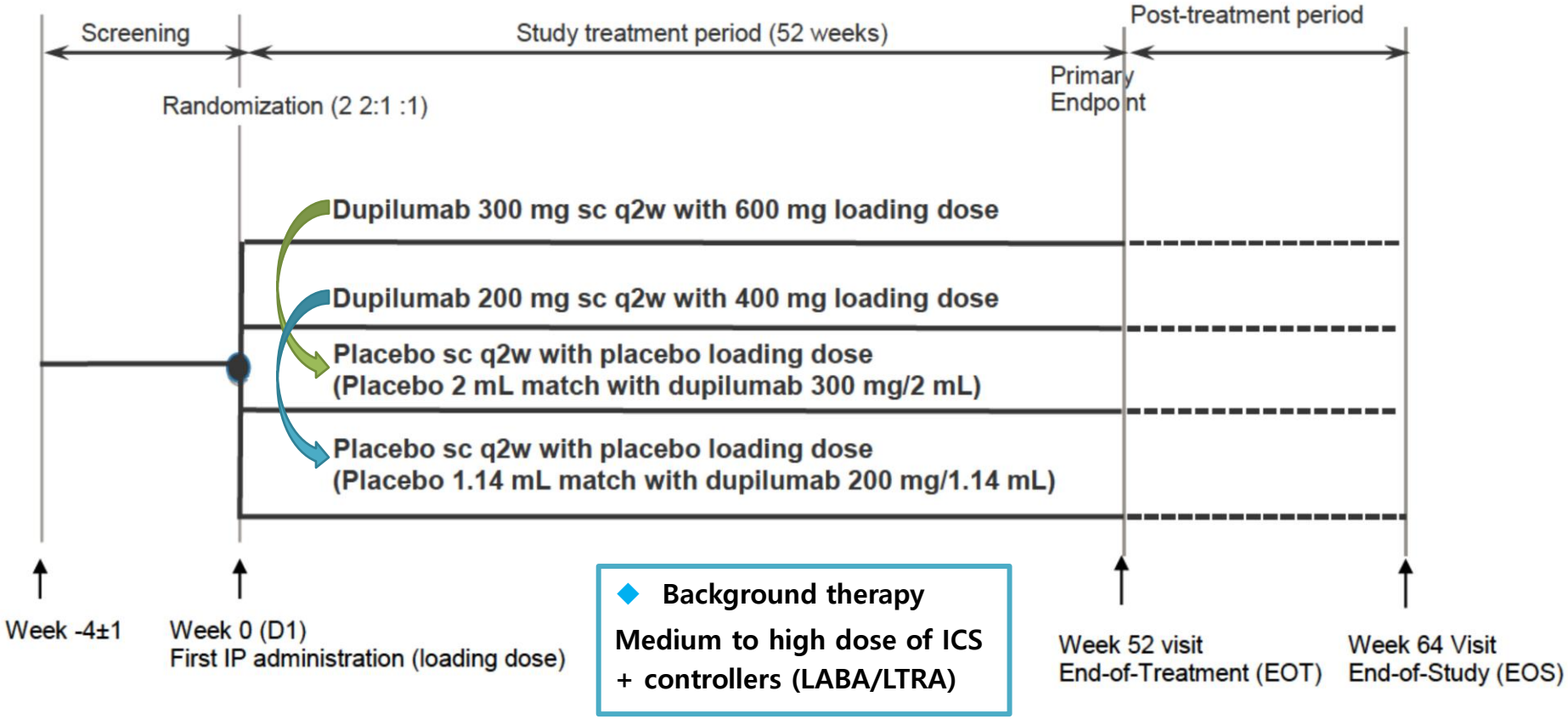
$p_{interaction}$ refers to the interaction between any treatment effect and the biomarker status. p values between treatment comparisons were only considered further if this interaction was significant. FeNO=fraction of exhaled nitric oxide. ppb=parts per billion.

***Table 3*: Exacerbation and severe exacerbation interaction analysis for the change in treatment effect for treatments containing budesonide compared with as-needed salbutamol**

Pavord ID, Lancet Respir Med 2020;8:671-80.

LIBERTY ASTHMA QUEST

- 1902 patients 12 years of age or older with uncontrolled asthma
- The primary **end points**: the annualized **rate** of severe asthma **exacerbations**
  the absolute change from baseline to week 12 in the **FEV1**



- **Background therapy**

Medium to high dose of ICS + controllers (LABA/LTRA)

Castro M, N Engl J Med 2018;378:2486-96.

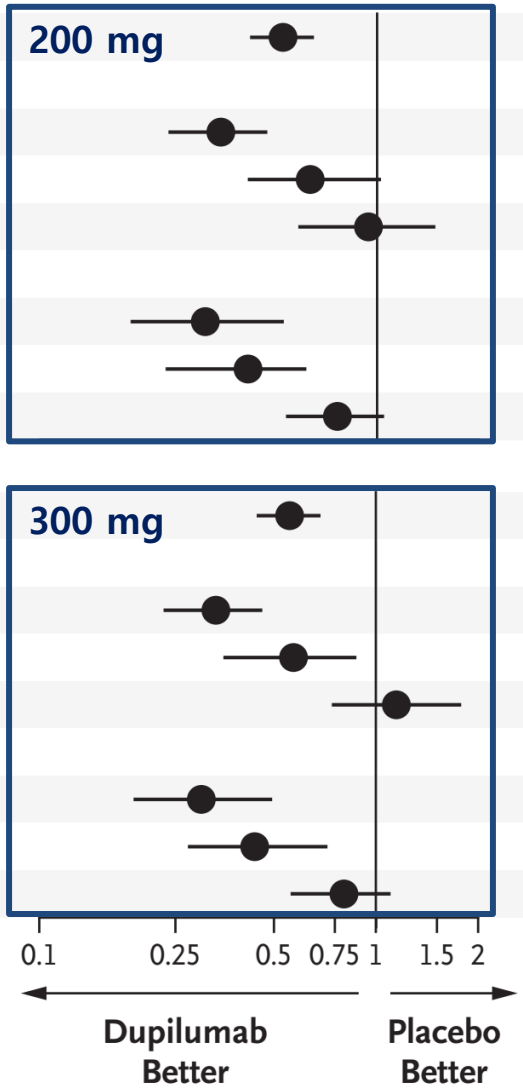
Baseline Characteristics

Characteristic	Placebo, 1.14 ml (N=317)	Dupilumab, 200 mg (N=631)	Placebo, 2.00 ml (N=321)	Dupilumab, 300 mg (N=633)	Overall Population (N=1902)
Age — yr	48.2±15.6	47.9±15.3	48.2±14.7	47.7±15.6	47.9±15.3
Female sex — no. (%)	198 (62.5)	387 (61.3)	218 (67.9)	394 (62.2)	1197 (62.9)
Prebronchodilator FEV_1 — liters	1.76±0.61	1.78±0.62	1.75±0.57	1.78±0.60	1.78±0.60
Percent of predicted normal value	58.43±13.22	58.38±13.52	58.35±13.87	58.51±13.52	58.43±13.52
FEV_1 reversibility — %	25.06±18.76	27.39±22.79	26.45±17.65	25.73±23.79	26.29±21.73
No. of exacerbations in past year	2.07±1.58	2.07±2.66	2.31±2.07	2.02±1.86	2.09±2.15
Use of high-dose inhaled glucocorticoid — no. (%)	172 (54.3)	317 (50.2)	167 (52.0)	323 (51.0)	979 (51.5)
ACQ-5 score†	2.71±0.73	2.76±0.80	2.77±0.77	2.77±0.76	2.76±0.77
Ongoing atopic or allergic condition — no. (%)	266 (83.9)	509 (80.7)	266 (82.9)	524 (82.8)	1565 (82.3)
Nasal polyposis or chronic rhinosinusitis — no. (%)	73 (23.0)	141 (22.3)	80 (24.9)	145 (22.9)	439 (23.1)
Former smoker — no. (%)	59 (18.6)	126 (20.0)	67 (20.9)	116 (18.3)	368 (19.3)
No. of pack-yr	3.96±2.81	3.89±2.69	4.07±3.12	4.15±3.04	4.02±2.89
Biomarker levels					
Blood eosinophil count — cells/mm^3					
Mean	370±338	349±345	391±419	351±369	360±366
Median (range)	270 (0–2200)	250 (0–3610)	265 (0–3580)	250 (0–4330)	255 (0–4330)
F_{ENO} — ppb	34.47±28.54	34.45±34.91	38.39±38.00	34.01±29.74	34.97±32.85
Total IgE — IU/ml	394±625	461±818	448±797	415±701	432±747

Castro M, N Engl J Med 2018;378:2486-96.

Forest Plots of the Risk of Severe Exacerbation

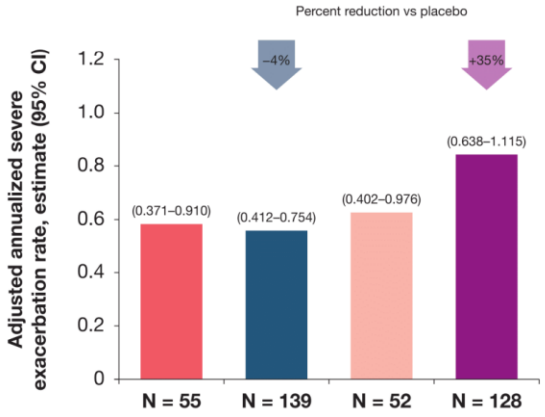
Subgroup	No. of Patients	
	Placebo	Dupilumab
Overall	317	631
Eosinophil count		
≥300 cells/mm^3	148	264
≥150 to <300 cells/mm^3	84	173
<150 cells/mm^3	85	193
FE_{NO}		
≥50 ppb	71	119
≥25 to <50 ppb	91	180
<25 ppb	149	325
Overall	321	633
Eosinophil count		
≥300 cells/mm^3	142	277
≥150 to <300 cells/mm^3	95	175
<150 cells/mm^3	83	181
FE_{NO}		
≥50 ppb	75	124
≥25 to <50 ppb	97	186
<25 ppb	144	317



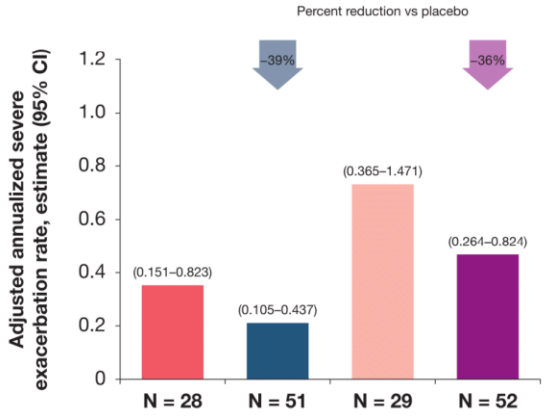
Castro M, N Engl J Med 2018;378:2486-96.

Severe Exacerbation by Baseline FENO & Blood Eosinophil Subgroups

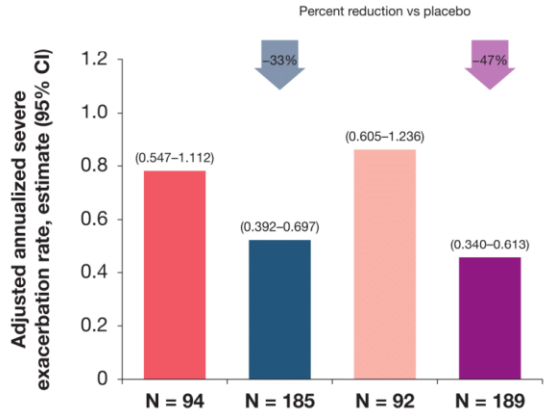
FE_{NO} <25 ppb and eosinophils <150 cells/μL (19.9% of ITT population)



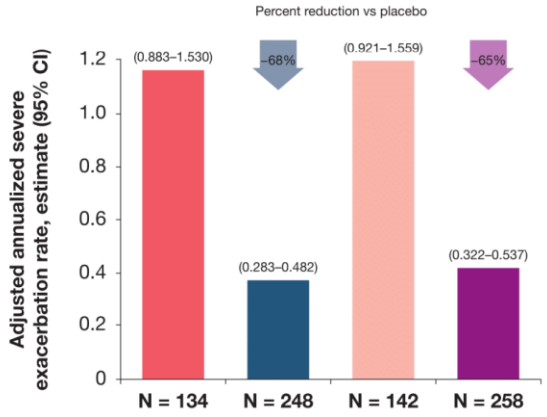
FE_{NO} ≥25 ppb and eosinophils <150 cells/μL (8.5% of ITT population)



FE_{NO} <25 ppb and eosinophils ≥150 cells/μL (29.9% of ITT population)

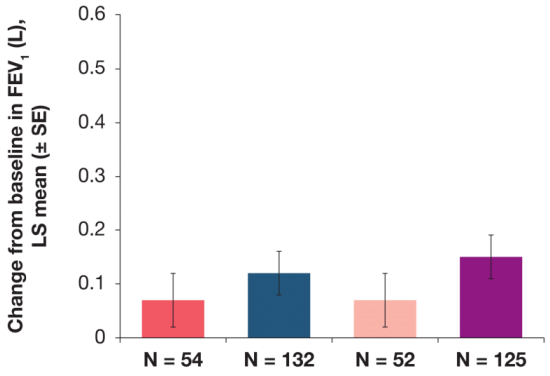


FE_{NO} ≥25 ppb and eosinophils ≥150 cells/μL (41.7% of ITT population)

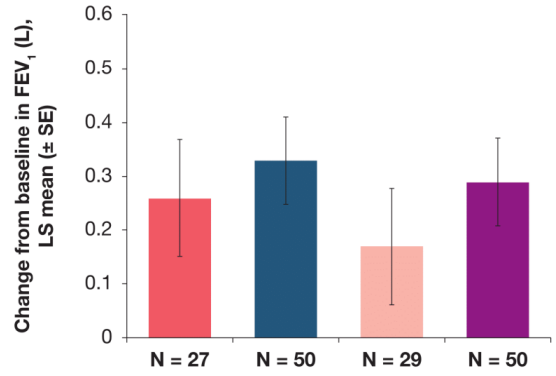


Change of FEV_1 by Baseline FENO & Blood Eosinophil Subgroups

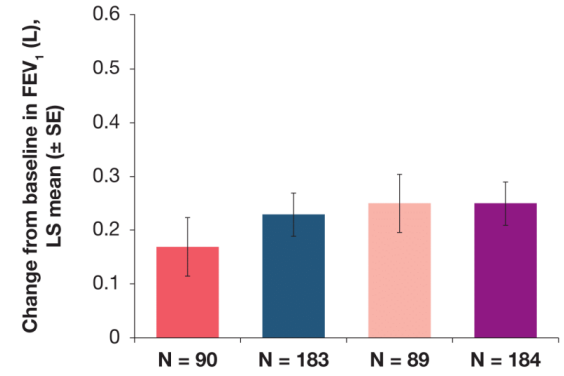
FE_{NO} <25 ppb and eosinophils <150 cells/μL (19.9% of ITT population)



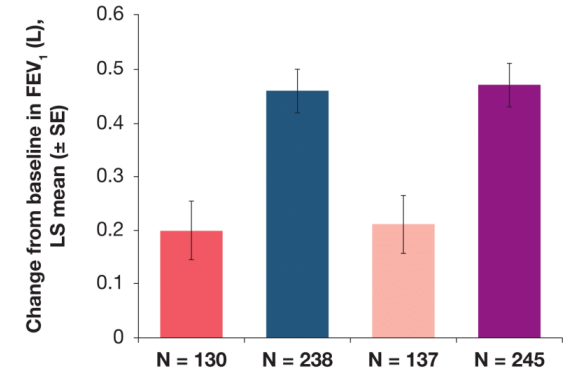
FE_{NO} ≥25 ppb and eosinophils <150 cells/μL (8.5% of ITT population)



FE_{NO} <25 ppb and eosinophils ≥150 cells/μL (29.9% of ITT population)



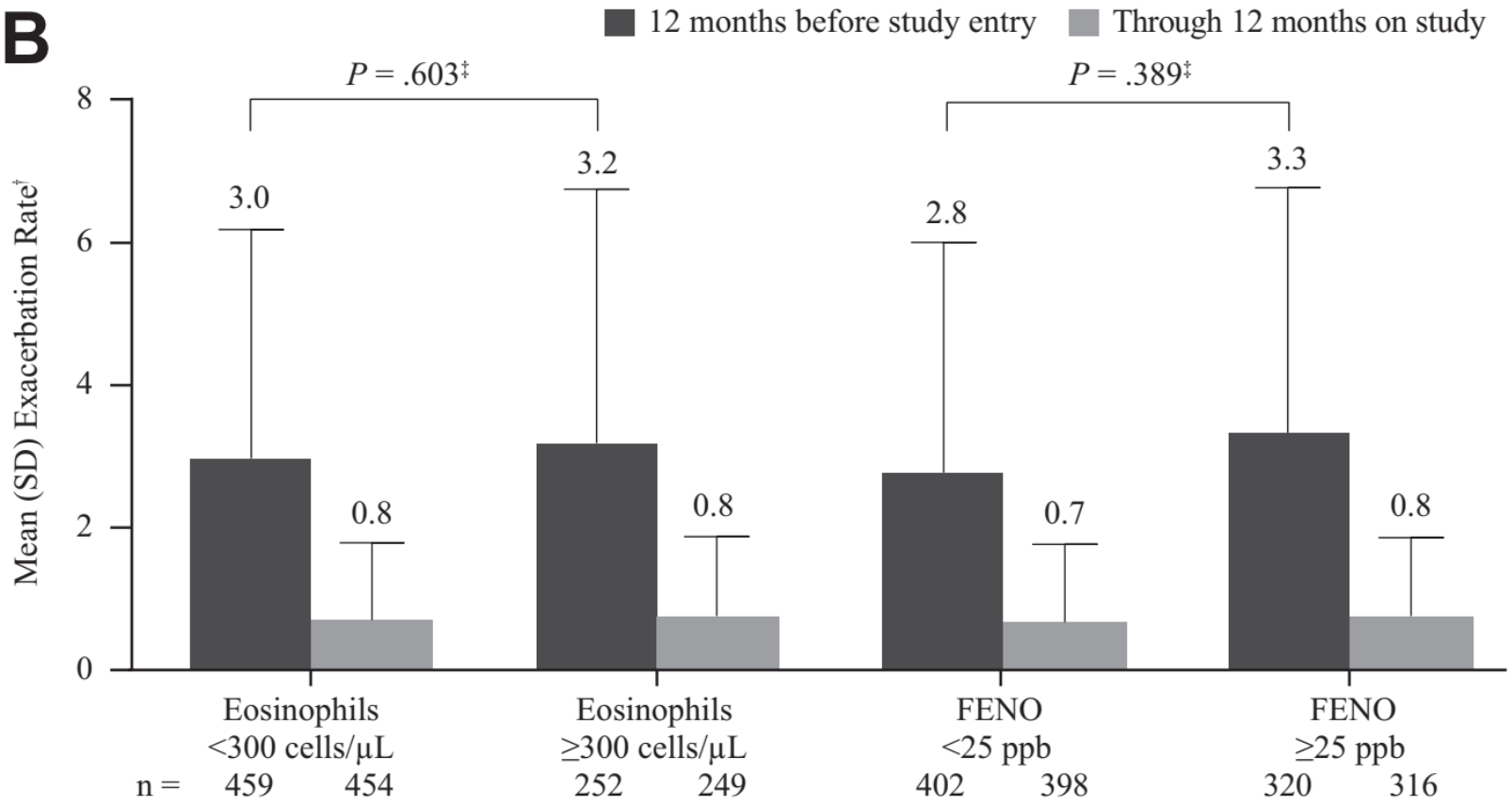
FE_{NO} ≥25 ppb and eosinophils ≥150 cells/μL (41.7% of ITT population)



Castro M, N Engl J Med 2018;378:2486-96.

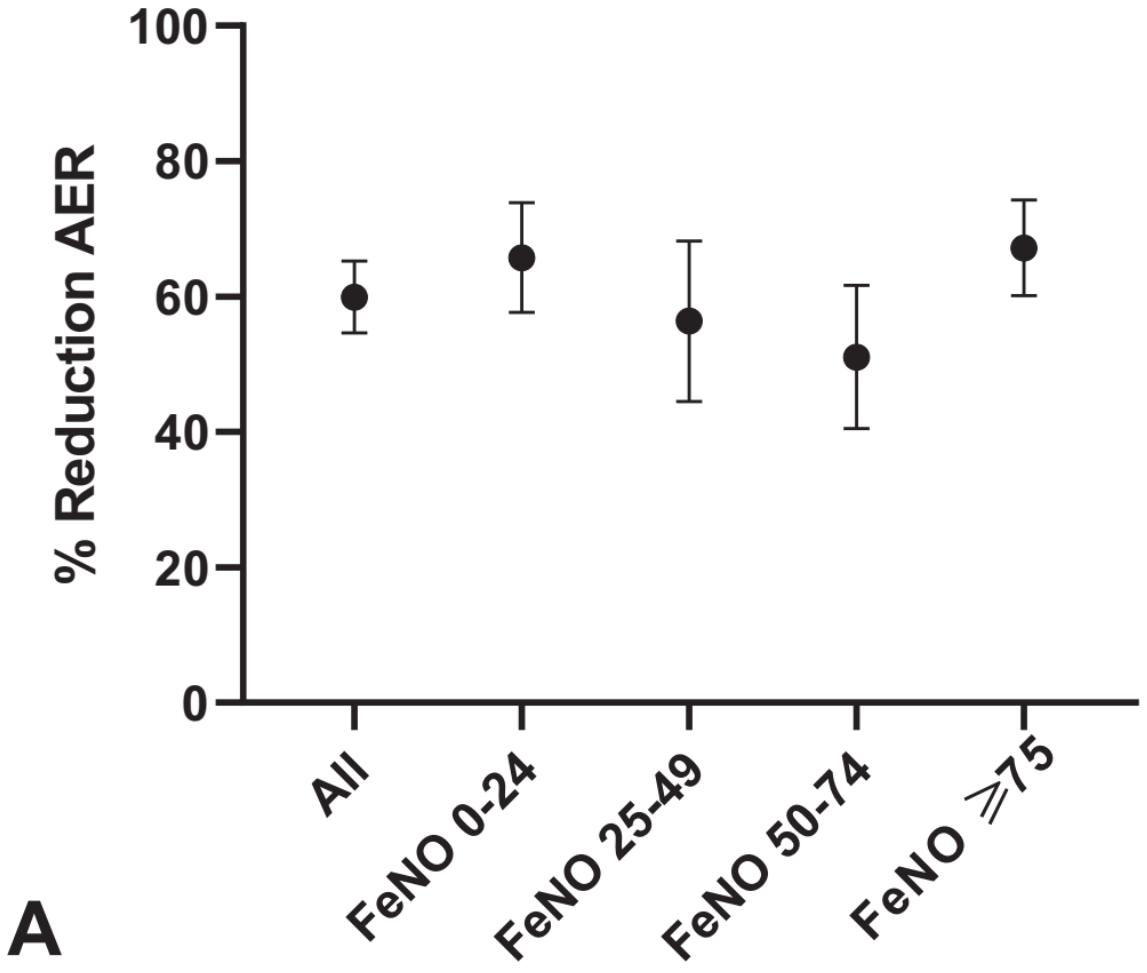
Omalizumab Effectiveness by Biomarker Status in Patients with Asthma: Evidence From PROSPERO, A Prospective Real-World Study

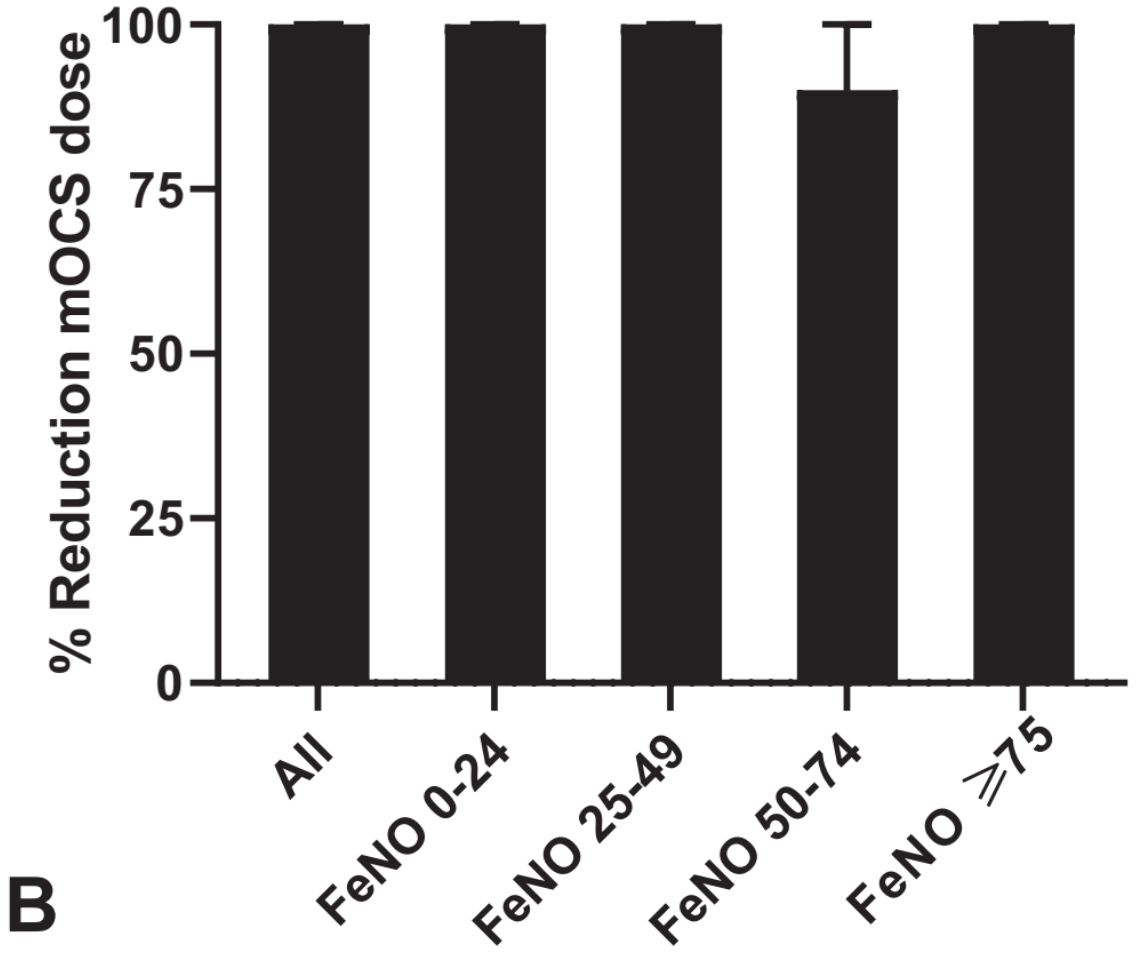
Thomas B. Casale, MD[a], Allan T. Luskin, MD[b], William Busse, MD[c], Robert S. Zeiger, MD, PhD[d,e], Benjamin Trzaskoma, MS[f], Ming Yang, PhD[f], Noelle M. Griffin, PhD[f,*], and Bradley E. Chipps, MD[g] *Tampa, Fla; Madison, Wis; and San Diego, Pasadena, South San Francisco, and Sacramento, Calif*



Casale TB et al. J Allergy Clin Immunol Pract 2019;7:156-64 e1 [PMID 29800752]

Relationship between baseline FENO and clinical effectiveness of anti-IL-5/5R therapy (Mepolizumab & Benralizumab)



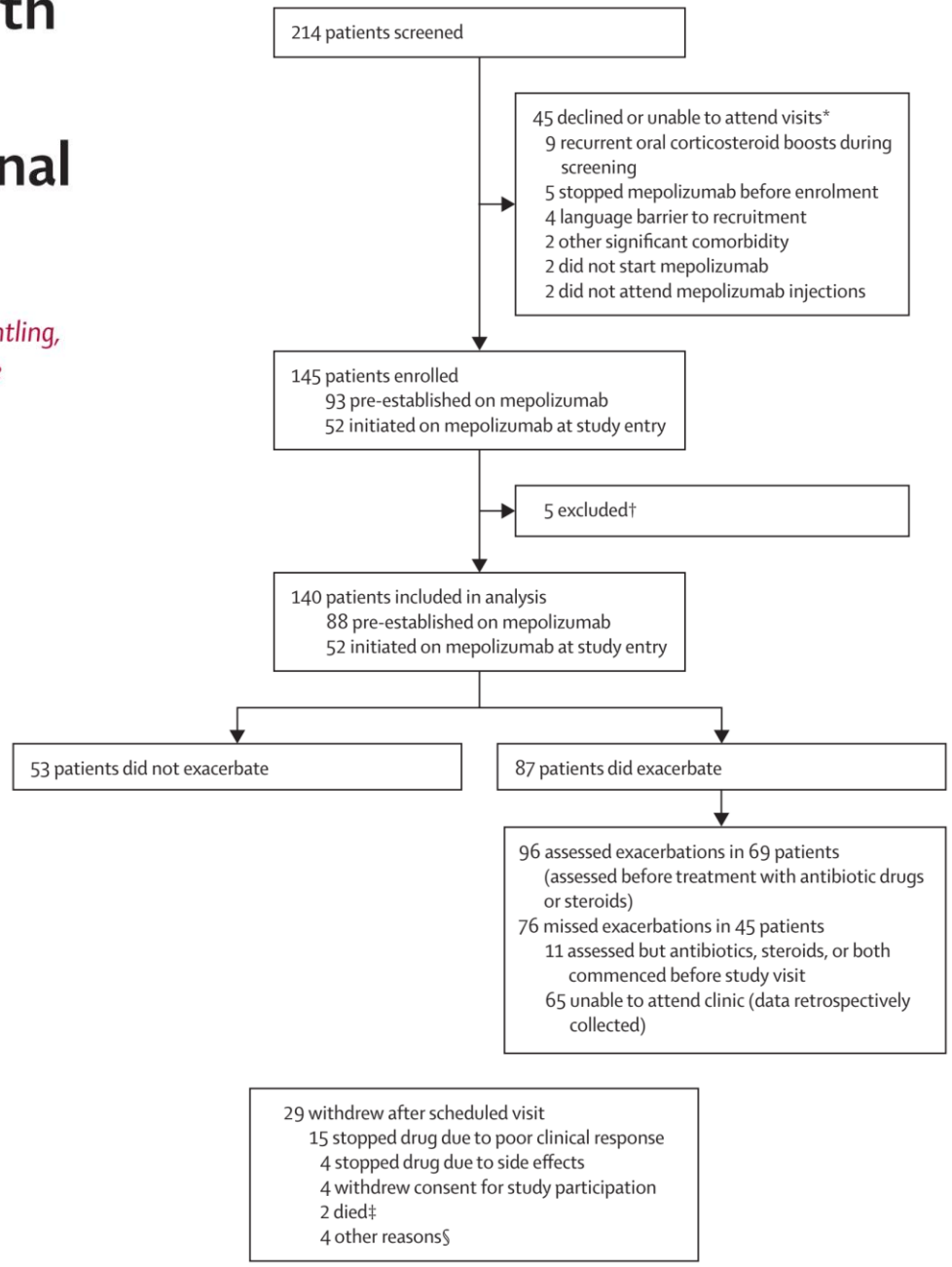


Hearn AP et al. J Allergy Clin Immunol Pract 2021;9:2093-6 e1. [PMID: 33486140]

The inflammatory profile of exacerbations in patients with severe refractory eosinophilic asthma receiving mepolizumab (the MEX study): a prospective observational study

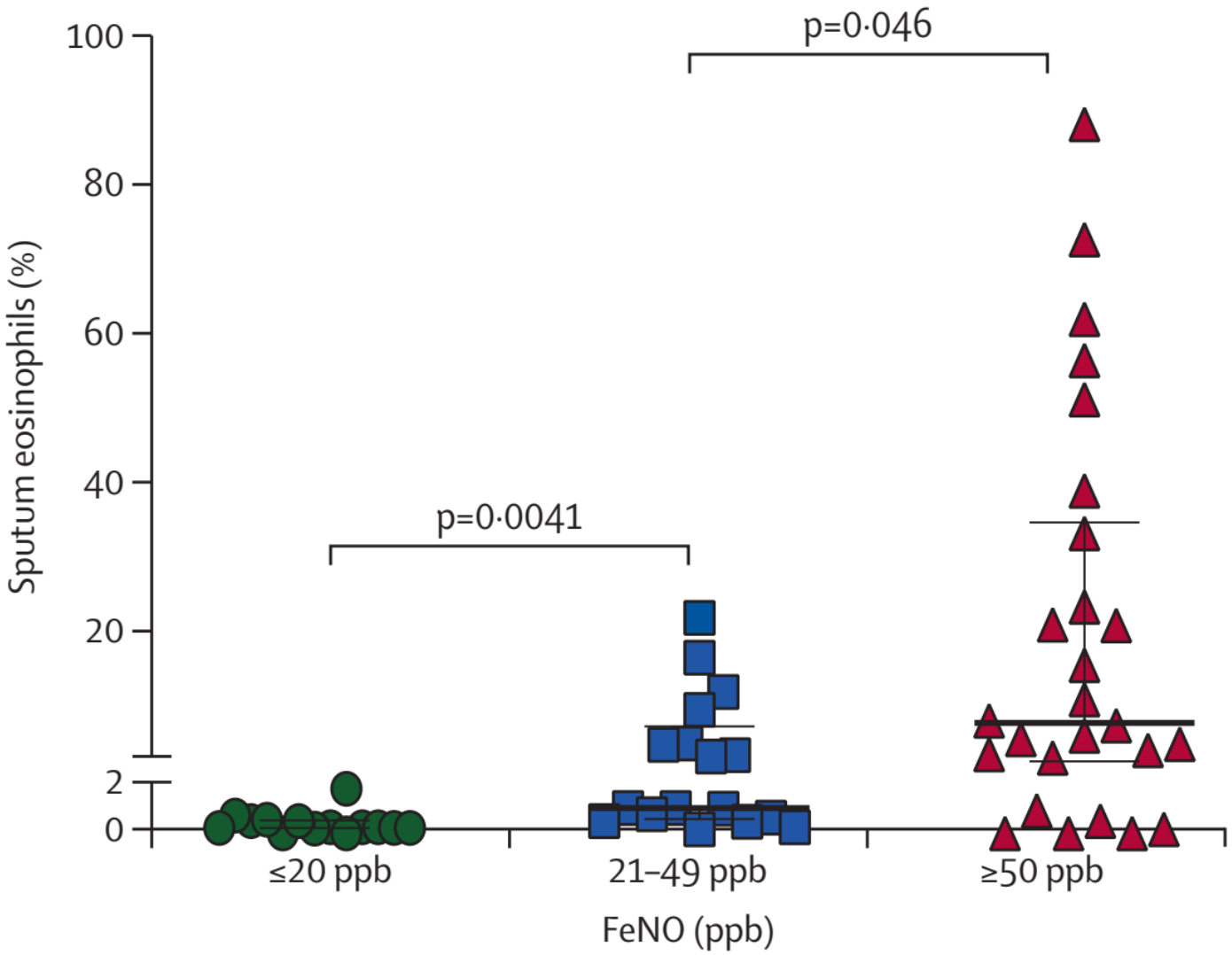
P Jane McDowell, Sarah Diver, Freda Yang, Catherine Borg, John Busby, Vanessa Brown, Rahul Shrimanker, Ciara Cox, Christopher E Brightling, Rekha Chaudhuri, Ian D Pavord, Liam G Heaney on behalf of the Medical Research Council: Refractory Asthma Stratification Programme (RASP-UK Consortium)

- Participants
  - were aged 18–80 years;
  - had a diagnosis of severe asthma (Global Initiative for Asthma [GINA] treatment **steps 4 and 5**);
  - were eligible for treatment with mepolizumab in line with UK clinical guidelines, including having an oral corticosteroid requirement of either
    - **maintenance oral corticosteroids** or
    - **at least four exacerbations** requiring oral corticosteroids in the preceding year



McDowell PJ et al. Lancet Respir Med 2021;9:1174-84 [PMID 33971168]

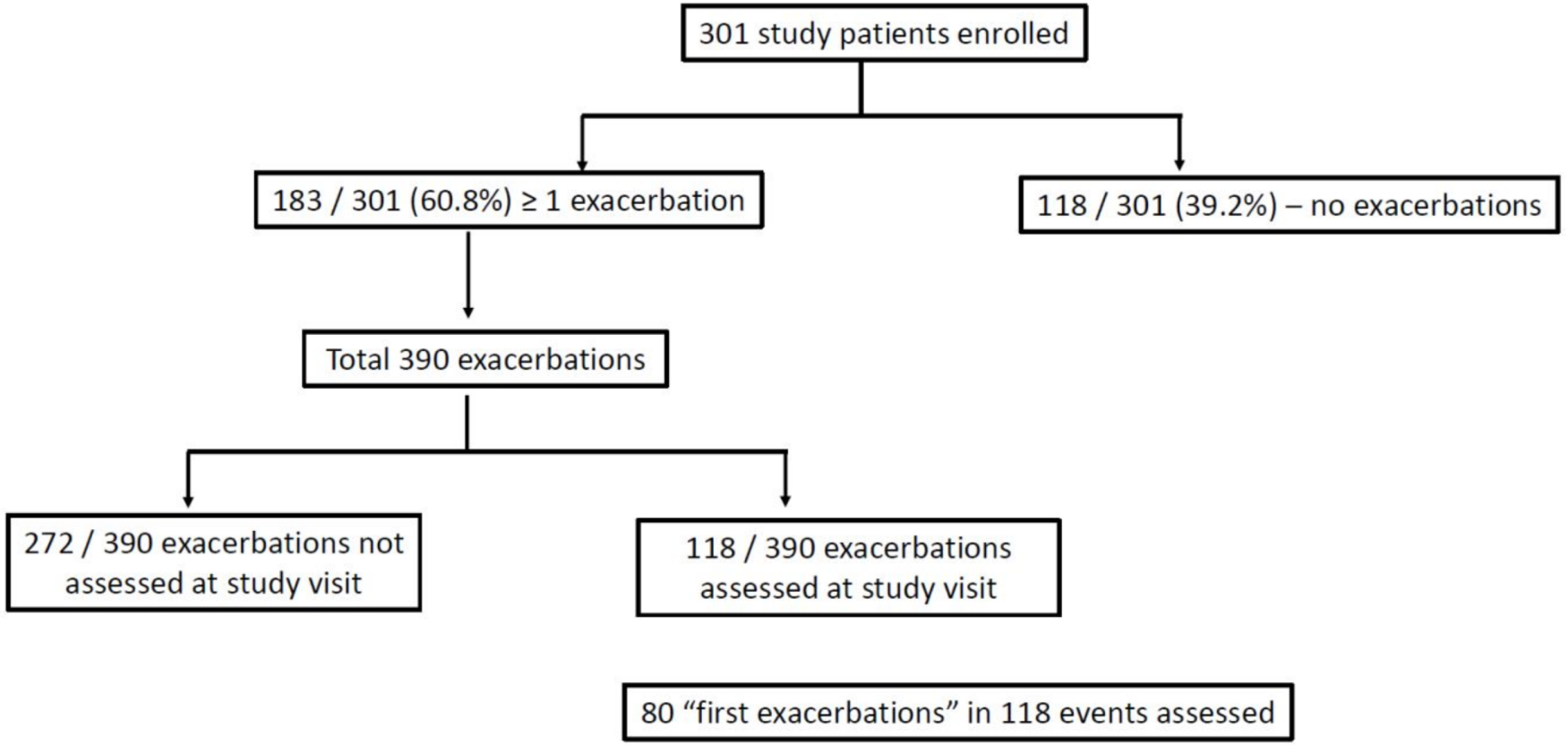
FeNO as a Predictor of Sputum Eosinophilia at Exacerbation



McDowell PJ et al. Lancet Respir Med 2021;9:1174-84 [PMID 33971168]

Exacerbation Profile and Risk Factors in a T2-Low Severe Asthma Population

Figure 1: Cohort flow diagram of all exacerbations during the study. A 'first exacerbation' was the initial exacerbation assessed as a clinical study visit for any individual patient.



McDowell PJ et al. Am J Respir Crit Care Med 2022; [PMID 35549845]

Table 4A. Stability of inflammatory phenotype from baseline study entry to first assessed exacerbation.

	First Exacerbation		
Baseline	**$T2^{LOW}$**	**$T2^{HIGH}$**	**Total**
$T2^{LOW}$	6	11	17
$T2^{HIGH}$	13	45	58
Total	19	56	75
McNemars (P-value) = 0.84, Kappa = 0.12			

Table 4B. Stability of inflammatory phenotype from first to second assessed exacerbation.

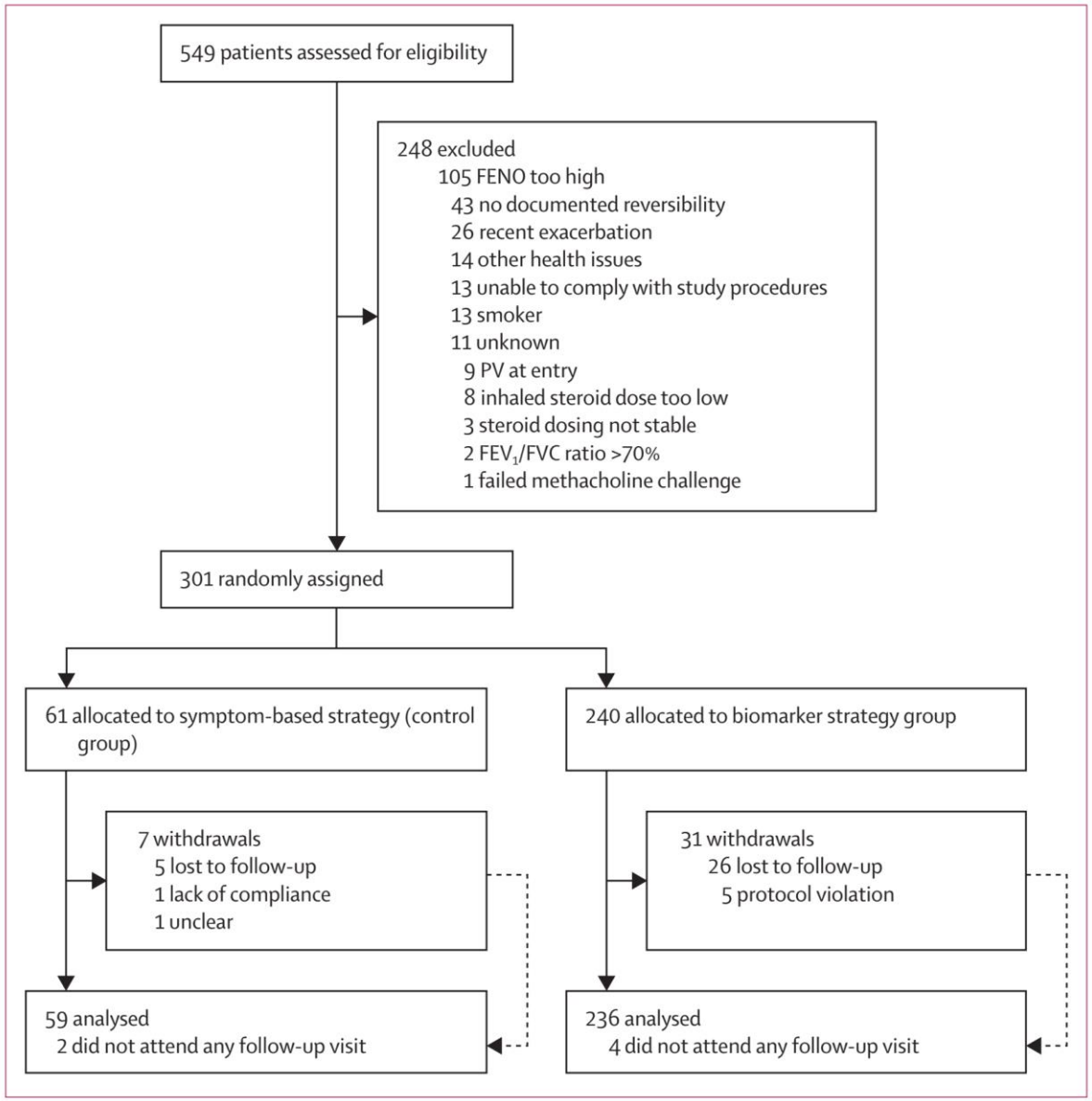
	Second Exacerbation		
First Exacerbation	**$T2^{LOW}$**	**$T2^{HIGH}$**	**Total**
$T2^{LOW}$	2	3	5
$T2^{HIGH}$	4	16	20
Total	6	19	25
McNemars (P-value) = 1.00, Kappa = 0.19			

McDowell PJ et al. Am J Respir Crit Care Med 2022; [PMID 35549845]

Composite type-2 biomarker strategy versus a symptom–risk-based algorithm to adjust corticosteroid dose in patients with severe asthma: a multicentre, single-blind, parallel group, randomised controlled trial

*Liam G Heaney, John Busby, Catherine E Hanratty, Ratko Djukanovic, Ashley Woodcock, Samantha M Walker, Timothy C Hardman, Joseph R Arron, David F Choy, Peter Bradding, Christopher E Brightling, Rekha Chaudhuri, Douglas C Cowan, Adel H Mansur, Stephen J Fowler, Robert M Niven, Peter H Howarth, James L Lordan, Andrew Menzies-Gow, Tim W Harrison, Douglas S Robinson, Cecile T J Holweg, John G Matthews, Ian D Pavord, on behalf of the investigators for the MRC Refractory Asthma Stratification Programme**

- a single-blind, parallel group, randomised controlled trial in adults (18–80 years of age) with severe asthma (at treatment **steps 4 and 5** of the Global Initiative for Asthma) and **FENO of less than 45** parts per billion
- Patients were randomly assigned (4:1) to either the **biomarker strategy group** or **the control group** by an online electronic case-report form, in blocks of ten, stratified by asthma control and use of rescue systemic steroids in the previous year.



Heaney LG et al. Lancet Respir Med 2021;9:57-68 [PMID 32916135]

Table 1 The composite biomarker score is calculated from the individual biomarker scores, and is the mean of all three scores rounded to the nearest integer to give the "composite score" (score of 0, 1 or 2)

Scoring system	0	1	2
Fractional exhaled NO (ppb)	< 15	≥ 15 to < 30	≥ 30
Blood eosinophil count (N/μL)	< 150	≥ 150 to < 300	≥ 300
Periostin (ng/ml)	< 45	≥ 45 to < 55	≥ 55

Table 2 Biomarker-based therapy adjustment

Score	Corticosteroid dose step-wise adjustment	Follow-up
0	Reduce treatment 1 step	If score remains 0 on low-dose corticosteroid – type 2 (T2)-low severe asthma
1	Maintain current treatment	Adjust as necessary based on follow-up scores
2	Increase treatment 1 step	If score remains 2 despite maximal inhaled corticosteroid therapy necessitating systemic steroid therapy – T2-high severe asthma

All therapeutic adjustments will be automatically calculated and advised by the electronic case report form (e-CRF)
Corticosteroid treatment adjustment based on composite biomarker score

Table 4 Symptom-based therapy adjustment (all therapeutic adjustments will be automatically calculated and advised by the e-CRF)

Asthma Control (ACQ7)	Treatment increased according to Table 5
ACQ7 ≥ 1.5 and ≥ 1 change from baseline score *OR* severe exacerbation since last visit (past 8 weeks at baseline randomisation visit)	Increase therapy 1 step
ACQ7 is 1.0 to < 1.5 *OR* ACQ ≥ 1.5 and < 1 change from baseline score *AND* no severe exacerbation since last study visit (past 8 weeks at baseline randomisation visit)	No change
ACQ7 < 1.0 *AND* no severe exacerbation since last study visit (prior 8 weeks at baseline randomisation visit)	Reduce therapy 1 step

All therapeutic adjustments will be automatically calculated and advised by the electronic case report form (e-CRF)
***ACQ7* 7-item Asthma Control Questionnaire**

Hanratty CE et al. Trials 2018;19:5 [PMID 29301585]
Heaney LG et al. Lancet Respir Med 2021;9:57-68 [PMID 32916135]

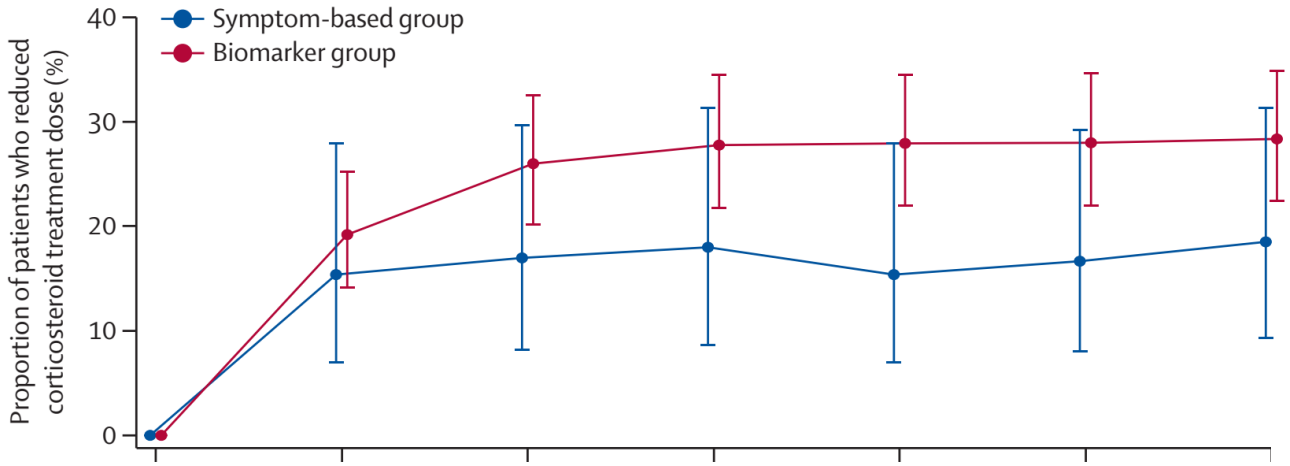
	Biomarker strategy group (n=240)	Control group (n=61)
FENO, ppb	21 (13–29)	19 (12–28)
Blood eosinophil count, 10^9 cells per L	0·20 (0·11–0·32)	0·26 (0·15–0·40)
Periostin, ng/mL	52·8 (15·7)	53·5 (18·2)
Composite biomarker score		
0	55 (23%)	13 (21%)
1	135 (56%)	37 (61%)
2	48 (20%)	10 (16%)

Heaney LG et al. Lancet Respir Med 2021;9:57-68 [PMID 32916135]

Proportion of patients who reduced corticosteroid treatment dose over 48 weeks

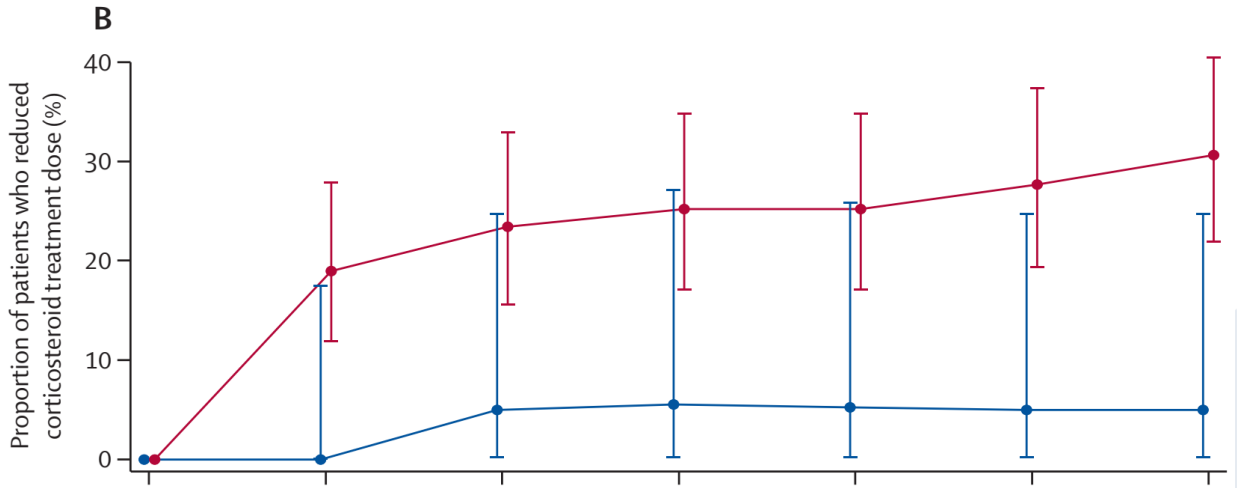
ITT population

p=0·17

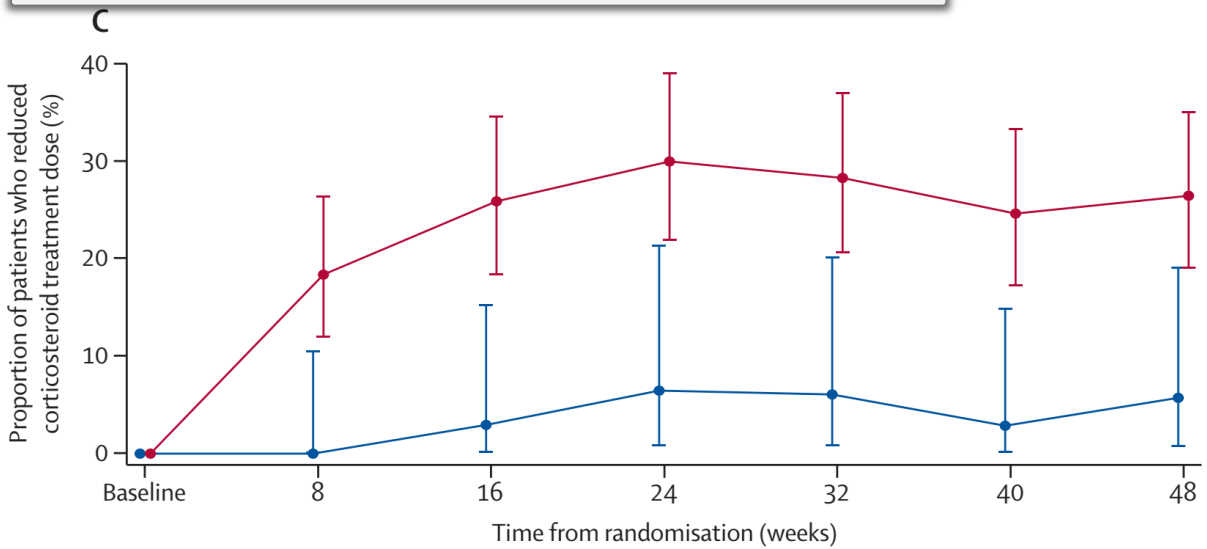


PP population

P=0·026



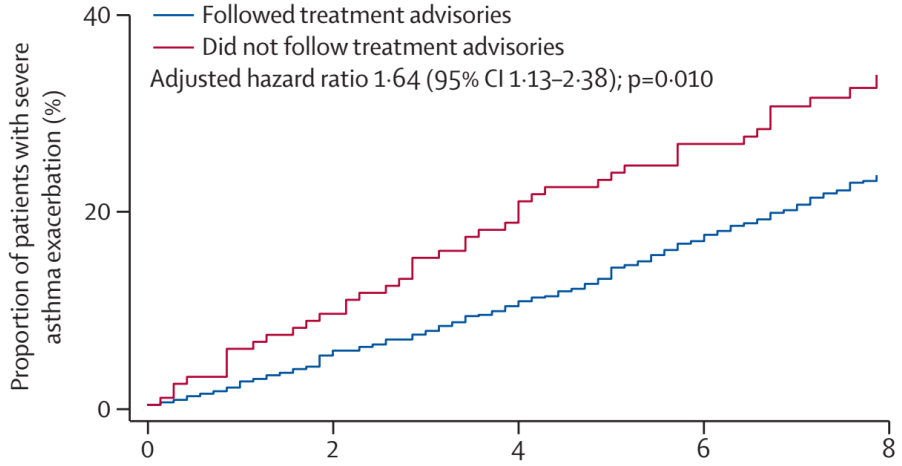
Uncontrolled asthma at baseline



Heaney LG et al. Lancet Respir Med 2021;9:57-68 [PMID 32916135]

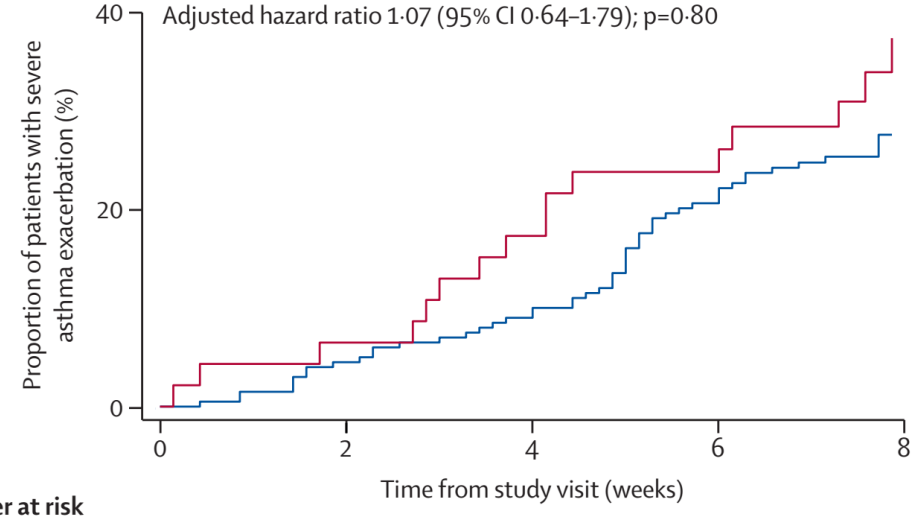
Proportion of patients who did or did not follow treatment advisories and had a severe asthma exacerbation

In the biomarker strategy group



Number at risk (number censored)					
Followed treatment advisories	790	750 (0)	705 (5)	636 (22)	0 (611)
Did not follow treatment advisories	139	126 (0)	111 (2)	97 (5)	0 (94)

In the control group



Number at risk (number censored)					
Followed treatment advisories	199	190 (0)	180 (1)	155 (3)	0 (146)
Did not follow treatment advisories	46	43 (0)	38 (0)	33 (2)	0 (30)

Heaney LG et al. Lancet Respir Med 2021;9:57-68 [PMID 32916135]

Fractional exhaled nitric oxide for the management of asthma in adults: a systematic review

Munira Essat[1], Sue Harnan[1], Tim Gomersall[1], Paul Tappenden[1], Ruth Wong[1], Ian Pavord[2], Rod Lawson[3] and Mark L. Everard[4]

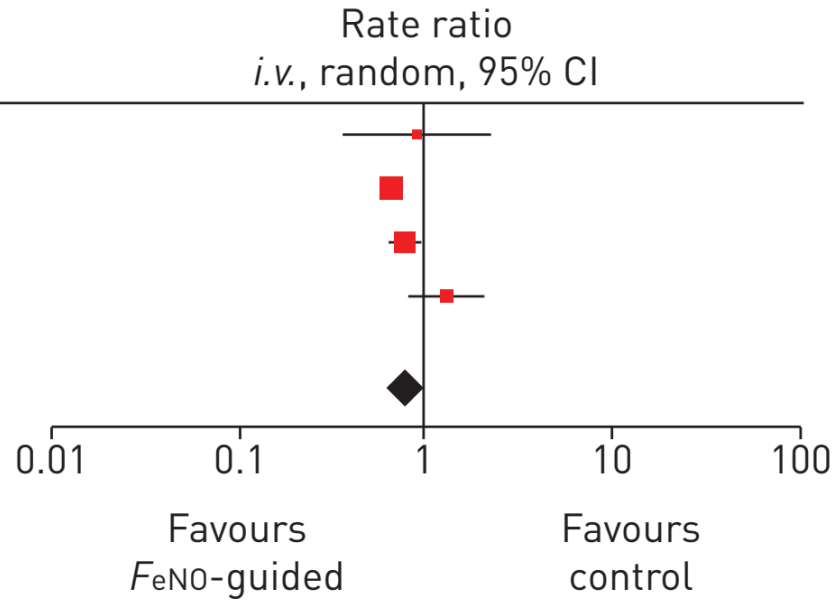
Effects of fractional exhaled nitric oxide (FeNO)-guided asthma management on major/severe exacerbation rates

a)

Study or subgroup	log (rate ratio)	SE	Weight %	Rate ratio *i.v.* random (95% CI)
Calhoun [13]	−0.09097178	0.45116134	6.3	0.91 (0.38–2.21)
Honkoop [16]	−0.41726314	0.0476771	41.1	0.66 (0.60–0.72)
Shaw [25]	−0.24116206	0.0917899	35.2	0.79 (0.66–0.94)
Syk [14]	0.25762178	0.22857143	17.4	1.29 (0.83–2.03)
Total (95% CI)			100.0	0.80 (0.63–1.02)

Heterogeneity, Tau^2=0.03; Chi^2=10.77, df=3 (p=0.01); I^2=72%

Test for overall effect Z=1.77 (p=0.08)



Essat M et al. Eur Respir J 2016;47:751-68 [PMID 26846832]

Fractional exhaled nitric oxide for the management of asthma in adults: a systematic review

Munira Essat[1], Sue Harnan[1], Tim Gomersall[1], Paul Tappenden[1], Ruth Wong[1], Ian Pavord[2], Rod Lawson[3] and Mark L. Everard[4]

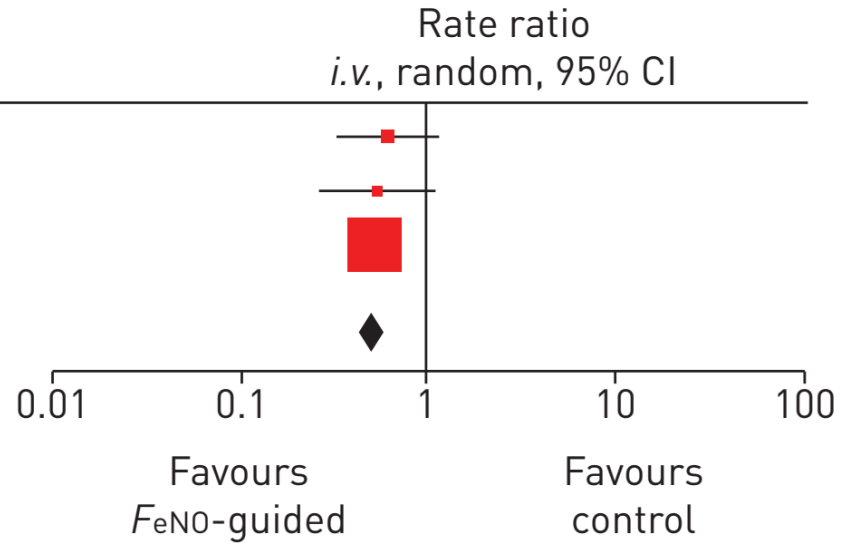
Effects of FeNO-guided asthma management on the composite outcome of all exacerbation and treatment failure rates

c)

Study or subgroup	log (rate ratio)	SE	Weight %	Rate ratio *i.v.* random (95% CI)
Calhoun [13]	−0.46536325	0.2943	6.7	0.63 (0.35–1.12)
Smith [24]	−0.60798937	0.34988064	4.8	0.54 (0.27–1.08)
Syk [14]	−0.65112175	0.0811328	88.5	0.52 (0.44–0.61)
Total (95% CI)			100.0	0.53 (0.46–0.61)

Heterogeneity, $Tau^2=0.00$; $Chi^2=0.38$, df=2 (p=0.83); $I^2=0\%$

Test for overall effect Z=8.34 (p<0.00001)



Essat M et al. Eur Respir J 2016;47:751-68 [PMID 26846832]

Using fractional exhaled nitric oxide to guide step-down treatment decisions in patients with asthma: a systematic review and individual patient data meta-analysis

Kay Wang[1], Jan Y. Verbakel[2], Jason Oke[1], Alexander Fleming-Nouri[3], Josh Brewin[1], Nia Roberts[4], Norihiro Harada[5], Ryo Atsuta[5], Kazuhisa Takahashi[5], Kazutaka Mori[6], Tomoyuki Fujisawa[6], Toshihiro Shirai[7], Tomotaka Kawayama[8], Hiromasa Inoue[9], Stephen Lazarus[10], Stanley Szefler[11], Fernando Martinez[12], Dominick Shaw[13], Ian D. Pavord[14] and Mike Thomas[15]

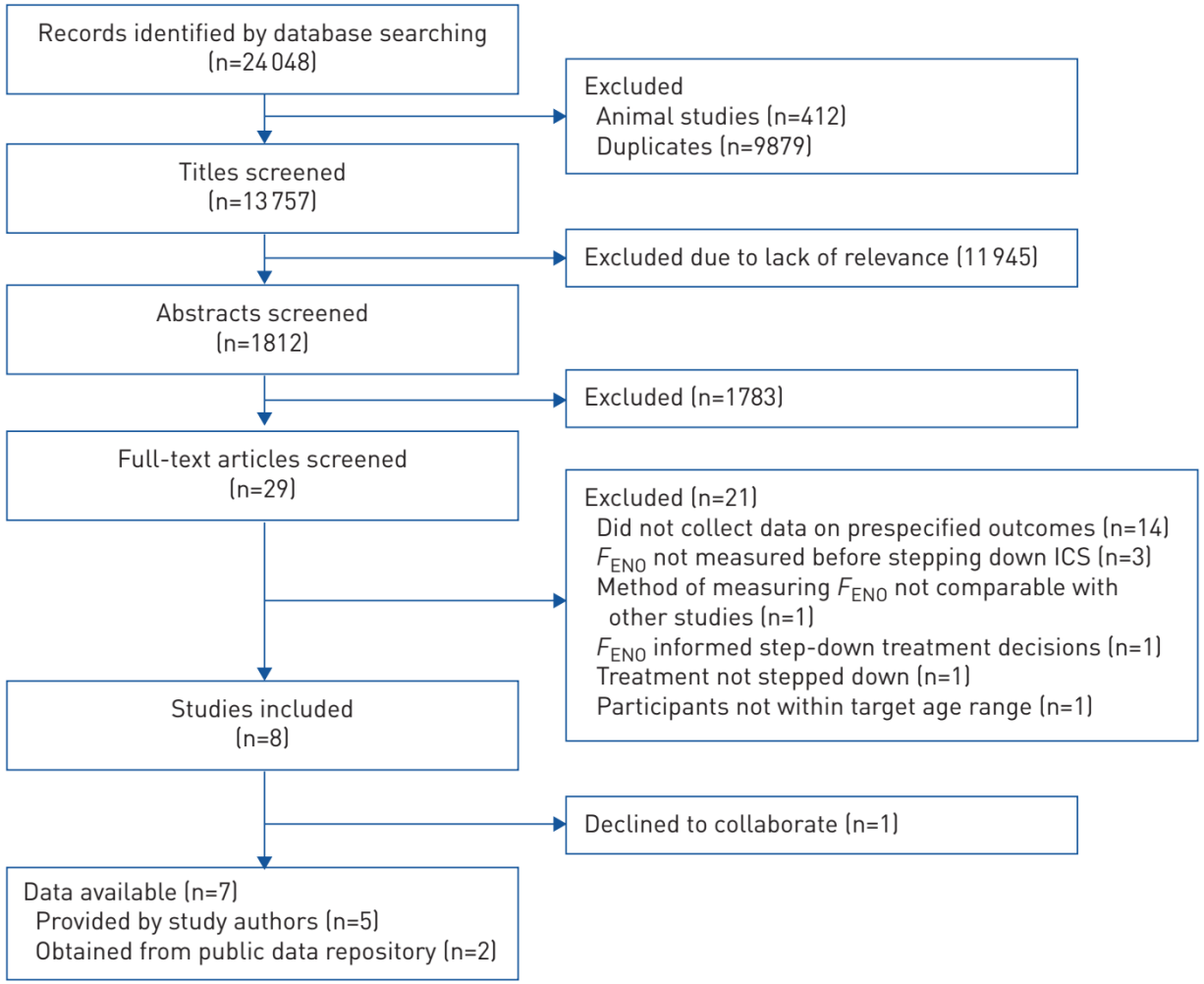


FIGURE 1 Study selection. F_{ENO}: exhaled nitric oxide fraction; ICS: inhaled corticosteroids.

Wang K et al. Eur Respir J 2020;55. [PMID: 32139458]

TABLE 4 Distribution of exhaled nitric oxide fraction (F_{ENO}) measurements according to estimated risk of exacerbation

	F_{ENO} ppb	
	Below decision threshold	**Greater than or equal to decision threshold**
Risk of exacerbation decision threshold %		
10	20.2 (3.1–49.6)	18.4 (3.5–129)
15	18.2 (3.1–49.6)	69.6 (50.4–129)
20	18.9 (31–129)	71.6 (50.4–117.6)

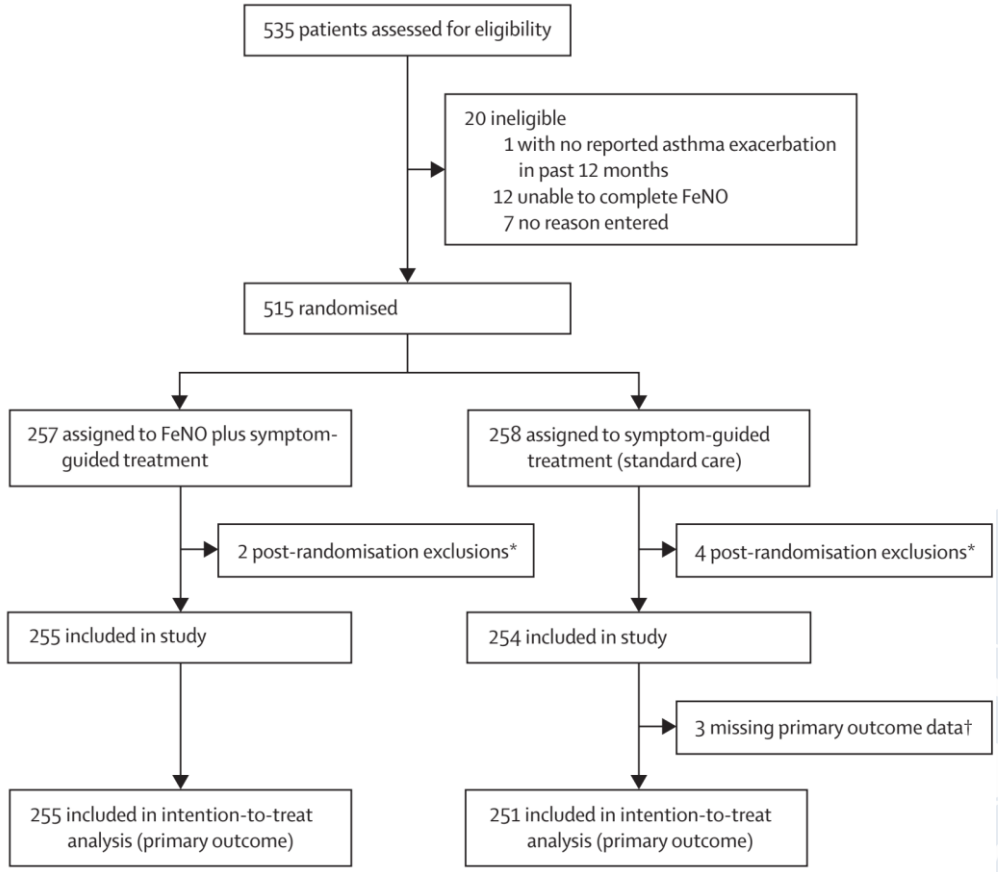
Data are presented as median (range).

Wang K et al. Eur Respir J 2020;55. [PMID: 32139458]

Reducing asthma attacks in children using exhaled nitric oxide (RAACENO) as a biomarker to inform treatment strategy: a multicentre, parallel, randomised, controlled, phase 3 trial

Steve Turner, Seonaidh Cotton, Jessica Wood, Victoria Bell, Edwin-Amalraj Raja, Neil W Scott, Heather Morgan, Louisa Lawrie, David Emele, Charlotte Kennedy, Graham Scotland, Shona Fielding, Graeme MacLennan, John Norrie, Mark Forrest, Erol A Gaillard, Johan de Jongste, Marielle Pijnenburg, Mike Thomas, David Price

- RAACENO was a multicentre, parallel, randomised, controlled, phase 3 trial done in 35 secondary care centres and 17 primary care recruitment sites (only seven primary care sites managed to recruit patients) in the UK.
- Patients with a confirmed **asthma diagnosis, aged 6–15 years, prescribed inhaled corticosteroid**s, and who received a course of oral corticosteroids for **at least one asthma exacerbation** during the 12 months before recruitment were included.
- Participants were randomly assigned to either **FeNO plus symptom-guided treatment** (**intervention**) or symptom-guided treatment alone (**standard** care) using a 24 h in-house, web-based randomisation system.



Turner S et al. Lancet Respir Med 2022;10:584-92 [PMID 35101183]

Reducing asthma attacks in children using exhaled nitric oxide (RAACENO) as a biomarker to inform treatment strategy: a multicentre, parallel, randomised, controlled, phase 3 trial

Steve Turner, Seonaidh Cotton, Jessica Wood, Victoria Bell, Edwin-Amalraj Raja, Neil W Scott, Heather Morgan, Louisa Lawrie, David Emele, Charlotte Kennedy, Graham Scotland, Shona Fielding, Graeme MacLennan, John Norrie, Mark Forrest, Erol A Gaillard, Johan de Jongste, Marielle Pijnenburg, Mike Thomas, David Price

	Intervention group	Standard care group	Adjusted OR* (95% CI)	p value	Unadjusted OR (95% CI)	p value
Intention-to-treat analysis						
Children with at least one exacerbation	123/255 (48·2%)	129/251 (51·4%)	0·88 (0·61–1·27)	0·49	0·88 (0·62–1·25)	0·48
Per-protocol analysis						
Children with at least one exacerbation	84/165 (50·9%)	79/153 (51·6%)	0·98 (0·61–1·55)	0·92	0·97 (0·62–1·51)	0·90

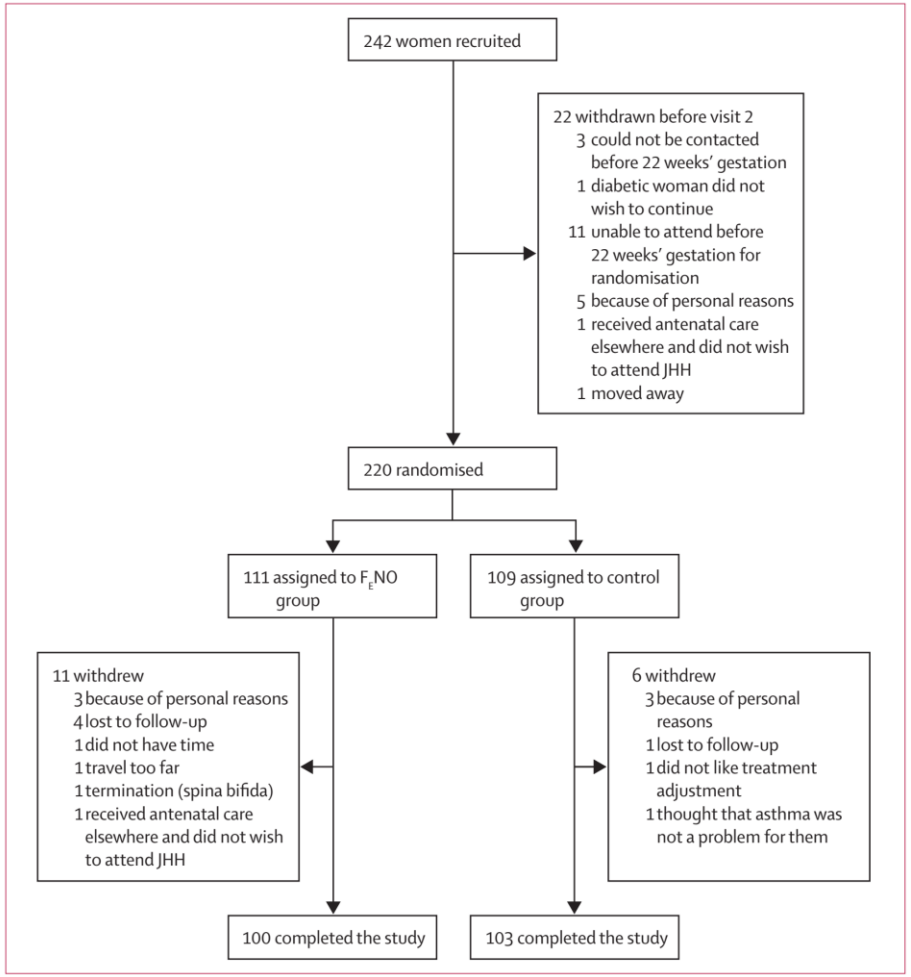
The per-protocol analysis included only those compliant with the algorithm—ie, the algorithm recommended treatment was followed on three or four scheduled visits between baseline and 9 months. OR=odds ratio. *Adjusted for age, sex, asthma severity, and centre.

Table 2: **Analysis of asthma exacerbation requiring oral corticosteroids over 12 months post-randomisation (primary outcome)**

Turner S et al. Lancet Respir Med 2022;10:584-92 [PMID 35101183]

Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial

Heather Powell, Vanessa E Murphy, D Robin Taylor, Michael J Hensley, Kirsten McCaffery, Warwick Giles, Vicki L Clifton, Peter G Gibson



- a double-blind, parallel-group, controlled trial in two antenatal clinics in Australia.
- 220 pregnant, non-smoking women with asthma, before 22 weeks' gestation
- treatment adjustment at monthly visits by an algorithm using
  - clinical **symptoms** (**control** group) or
  - **FENO** concentrations (active **intervention** group) used to uptitrate (FENO >29 ppb) or downtitrate (FENO <16 ppb) inhaled corticosteroid dose.
- Long-acting β2 agonist and minimum dose inhaled corticosteroid were used to treat symptoms when FENO was not increased.
- The primary **outcome**: **total asthma exacerbations** (moderate and severe).

Powell H et al. Lancet 2011;378:983-90 [PMID 21907861]

In the biomarker strategy group

	F_ENO concentration (ppb)	Symptoms (ACQ score)	ICS dose change	β2-agonist dose change
Level 1	>29	NA	↑ ICS × 1 step	No change
Level 2	16–29	≤1·5	No change	No change
Level 3	16–29	>1·5	No change	↑ LABA × 1 step
Level 4	<16	≤1·5	↓ ICS × 1 step	No change
Level 5	<16	>1·5	↓ ICS × 1 step	↑ LABA × 1 step

F_ENO=fraction of exhaled nitric oxide. ACQ=asthma control questionnaire. ICS=inhaled corticosteroid. NA=not part of the assessment at this F_ENO level. LABA=longacting β2 agonist.

Table 1: **Dose changes based on F_ENO and ACQ results for the F_ENO intervention algorithm**

	ICS step	β2 step
Step 1	0	Salbutamol as required
Step 2	Budesonide 100 μg twice per day	Formoterol 6 μg twice per day
Step 3	Budesonide 200 μg twice per day	Formoterol 12 μg twice per day
Step 4	Budesonide 400 μg twice per day	Formoterol 2 × 12 μg twice per day
Step 5	Budesonide 800 μg twice per day	Formoterol 2 × 12 μg twice per day

F_ENO=fraction of exhaled nitric oxide. ICS=inhaled corticosteroid.

Table 2: **F_ENO algorithm treatment steps**

In the control group

	ACQ score	Treatment adjustment
Level 1	>1·5	↑ 1 step
Level 2	0·75–1·5	No change
Level 3	<0·75	↓ 1 step

ACQ=asthma control questionnaire.

Table 3: **Dose changes based on clinical assessment for the clinical algorithm (control)**

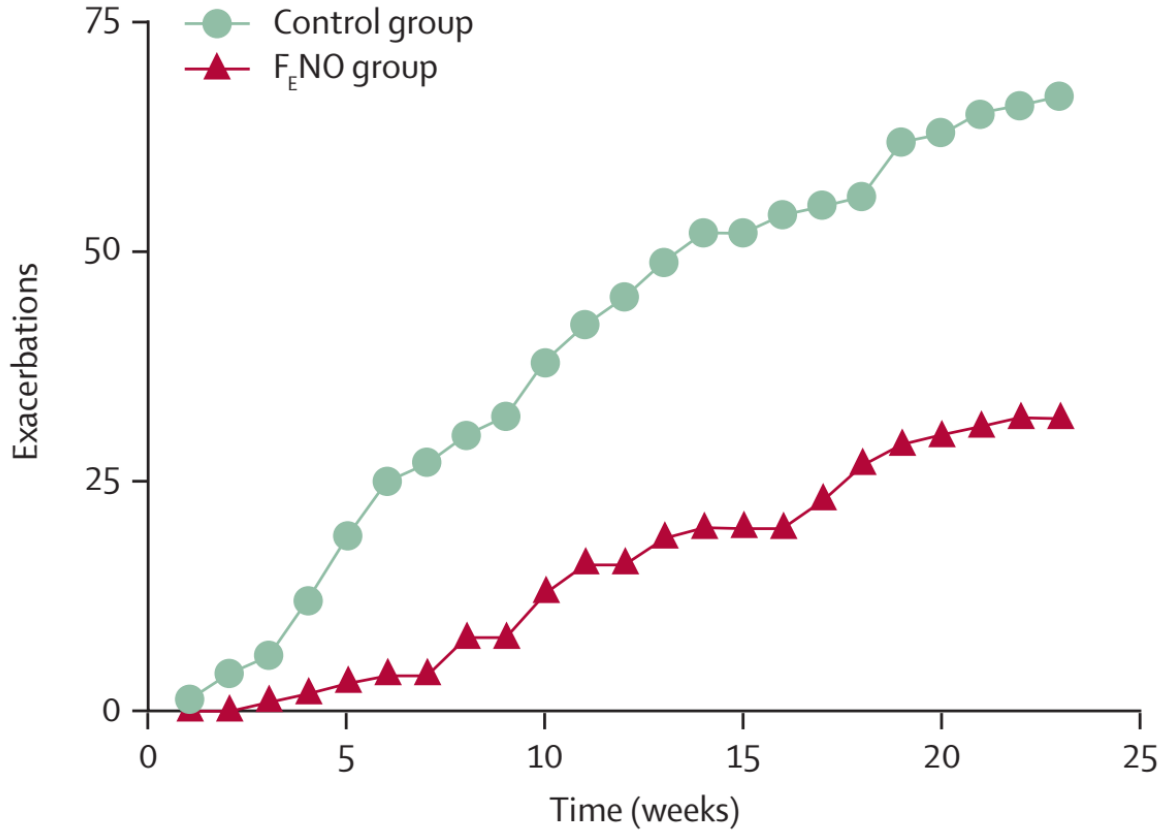
	Treatment
Step 1	Salbutamol as required
Step 2	Budesonide 200 μg twice per day
Step 3	Budesonide 400 μg twice per day
Step 4	Budesonide 400 μg and formoterol 12 μg twice per day
Step 5	Budesonide 800 μg and formoterol 24 μg twice per day

Table 4: **Clinical algorithm treatment steps**

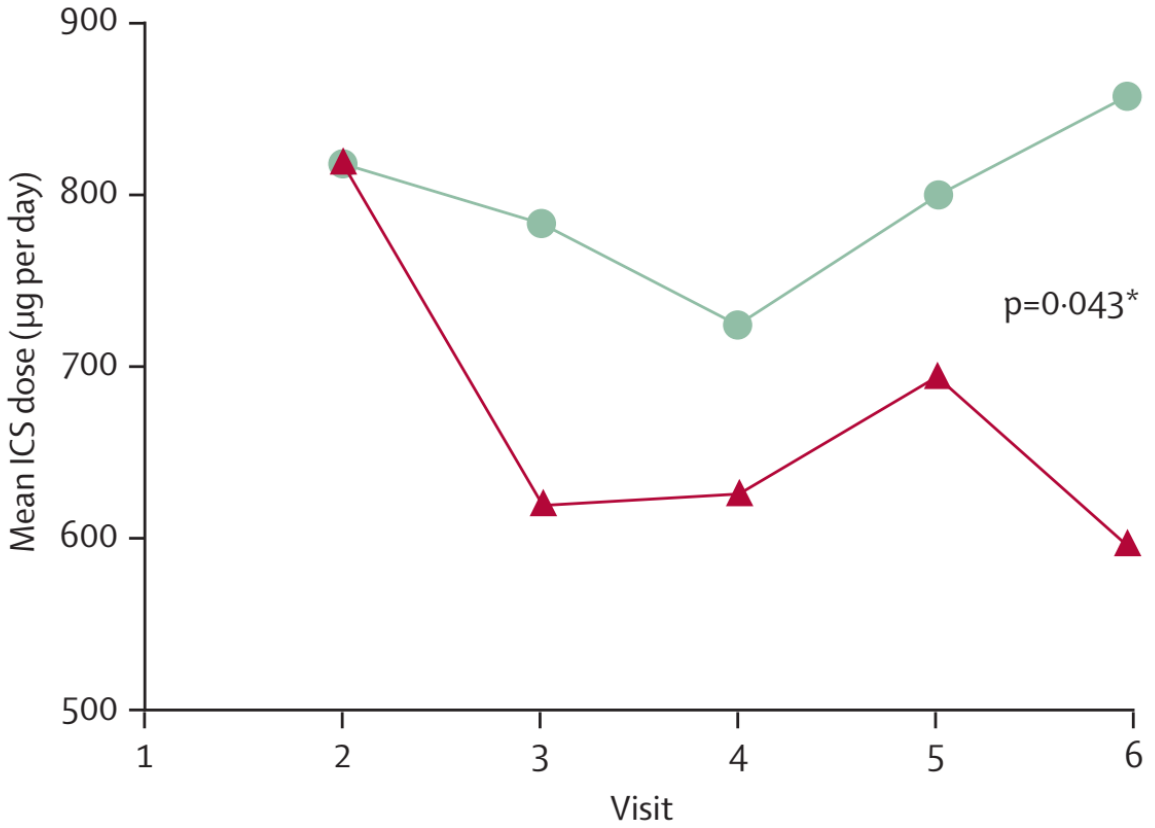
Powell H et al. Lancet 2011;378:983-90 [PMID 21907861]

Effect of FENO-guided asthma management during pregnancy

number of asthma exacerbations



maintenance mean daily ICS dose

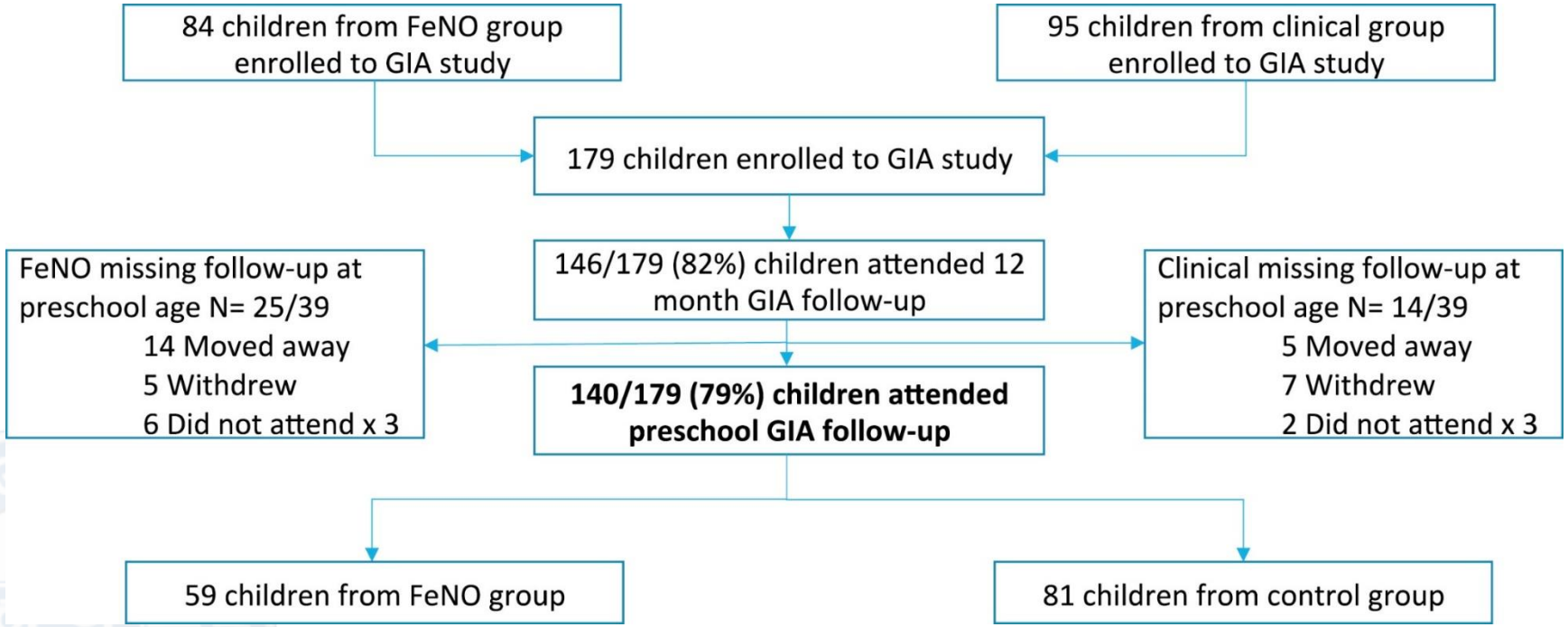


Powell H et al. Lancet 2011;378:983-90 [PMID 21907861]

Managing Asthma in Pregnancy (MAP) trial: FENO levels and childhood asthma

Matthew Morten, PhD,[a,b,c] Adam Collison, PhD,[a,b,c] Vanessa E. Murphy, PhD,[a,b,c] Daniel Barker, PhD,[b,c] Christopher Oldmeadow, PhD,[b,c] John Attia, PhD,[b,c] Joseph Meredith, BMed,[a,e] Heather Powell, MMedSci,[b,c,d] Paul D. Robinson, BMed, PhD,[f] Peter D. Sly, MD, DSc,[g] Peter G. Gibson, MBBS,[b,c,d,h] and Joerg Mattes, MD, PhD[a,b,c,e]

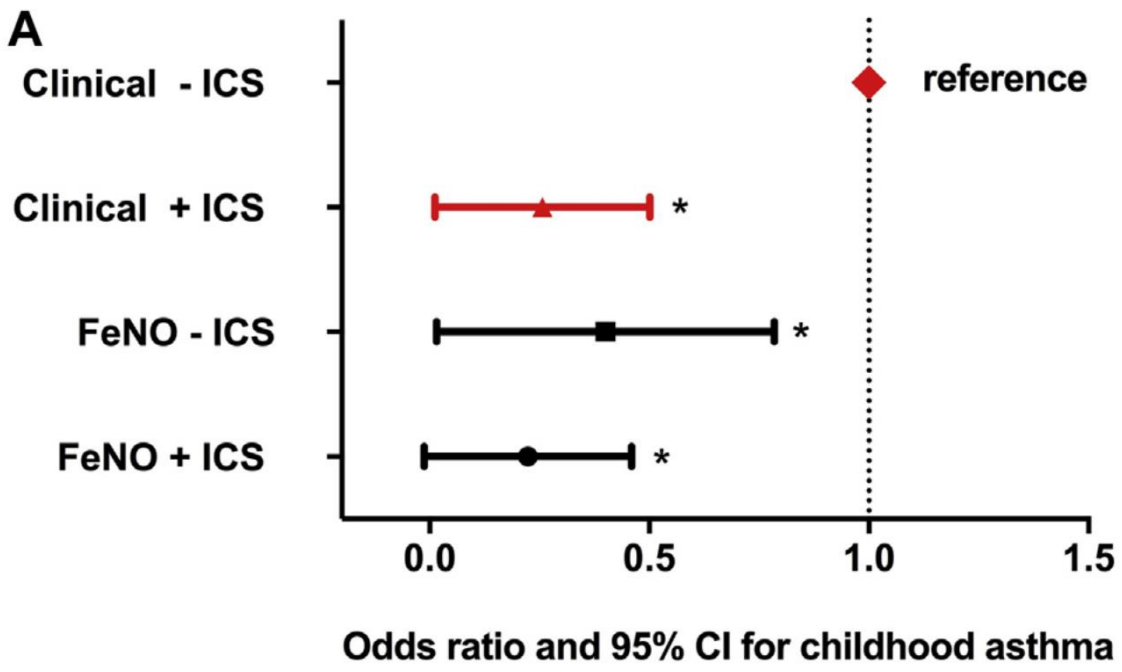
Newcastle, Sydney, and South Brisbane, Australia

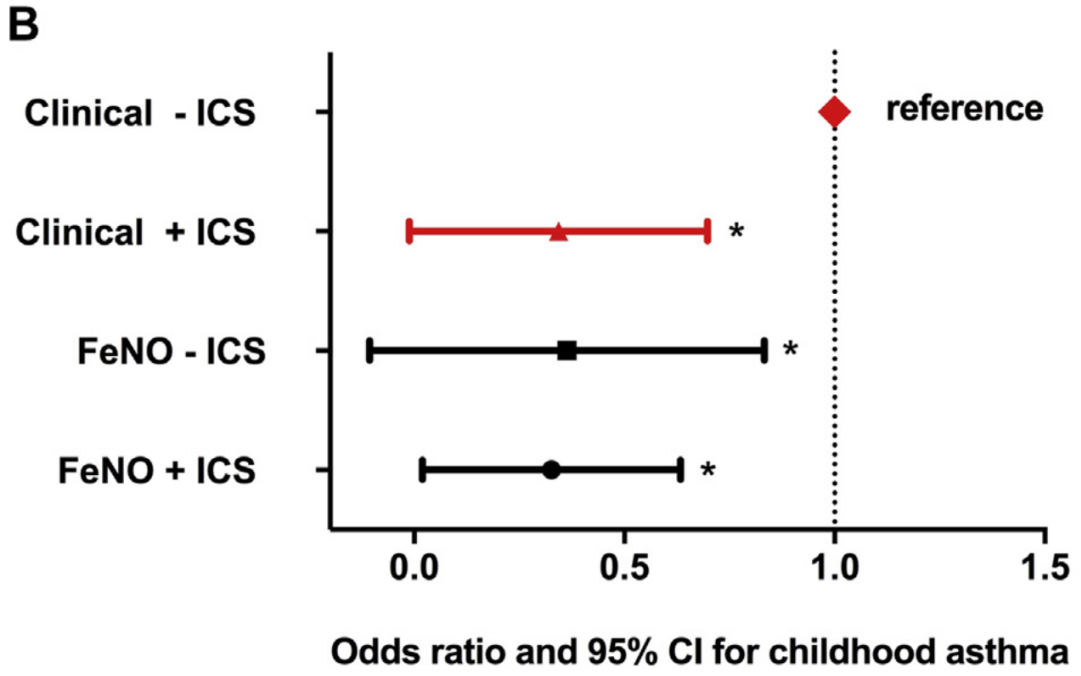


- a treatment algorithm using the fraction of exhaled nitric oxide (FENO) in combination with asthma symptoms (**FENO group**) vs.
  a treatment algorithm using clinical symptoms only (**clinical group**) in pregnant asthmatic women
- The primary outcome was a **50% reduction** in asthma exacerbations during pregnancy in the FENO group
- the effect of FENO-guided management on the **development of asthma in the offspring**
- **Growing into Asthma (GIA)**

Morten M et al. J Allergy Clin Immunol 2018;142:1765-72 e4 [PMID 29524536]

Adjusted ORs and 95% CI for childhood asthma stratified for double-blind asthma management intervention during pregnancy and (A) ICS use (yes [1] or no [-]) at randomization and (B) ICS at last RCT visit.





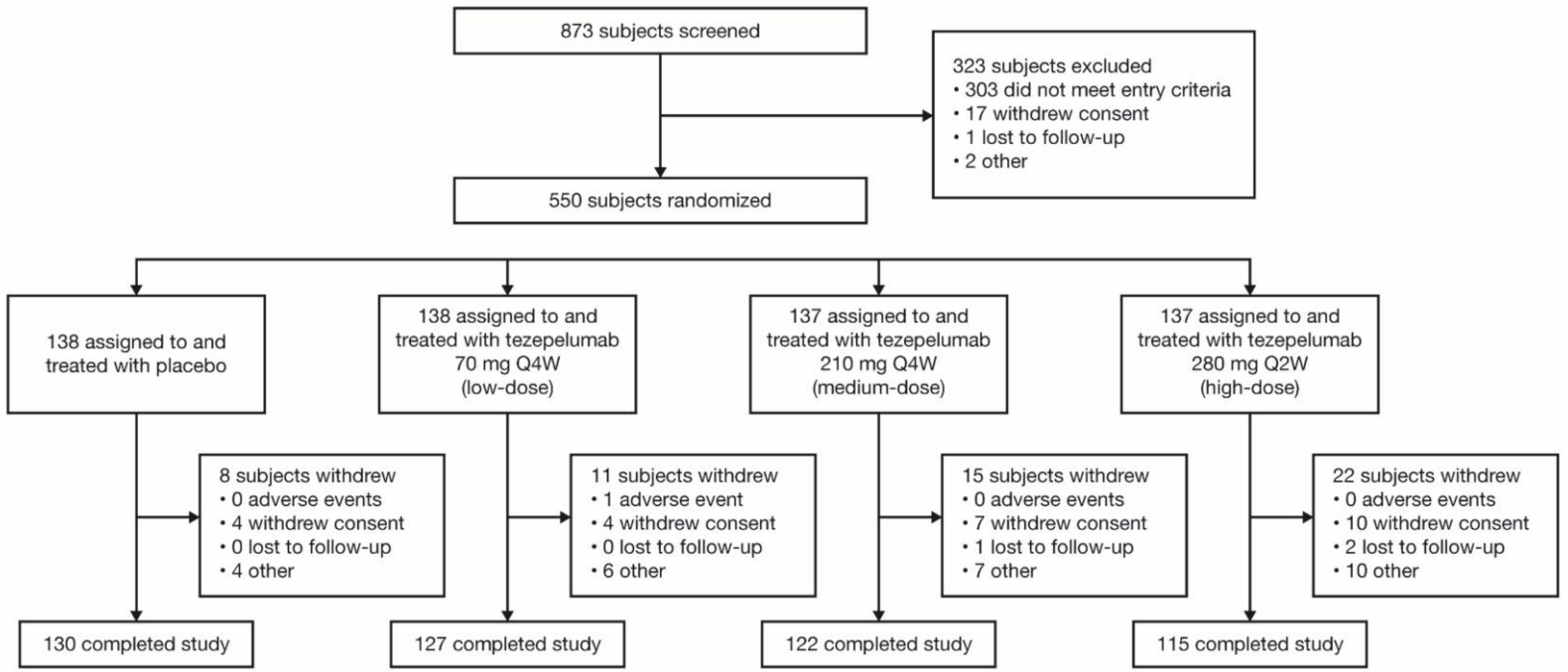
- FENO-guided asthma management during pregnancy prevented **doctor-diagnosed asthma in the offspring** at preschool age

Morten M et al. J Allergy Clin Immunol 2018;142:1765-72 e4 [PMID 29524536]

- PATHWAY -

Tezepelumab in Adults with Uncontrolled Asthma

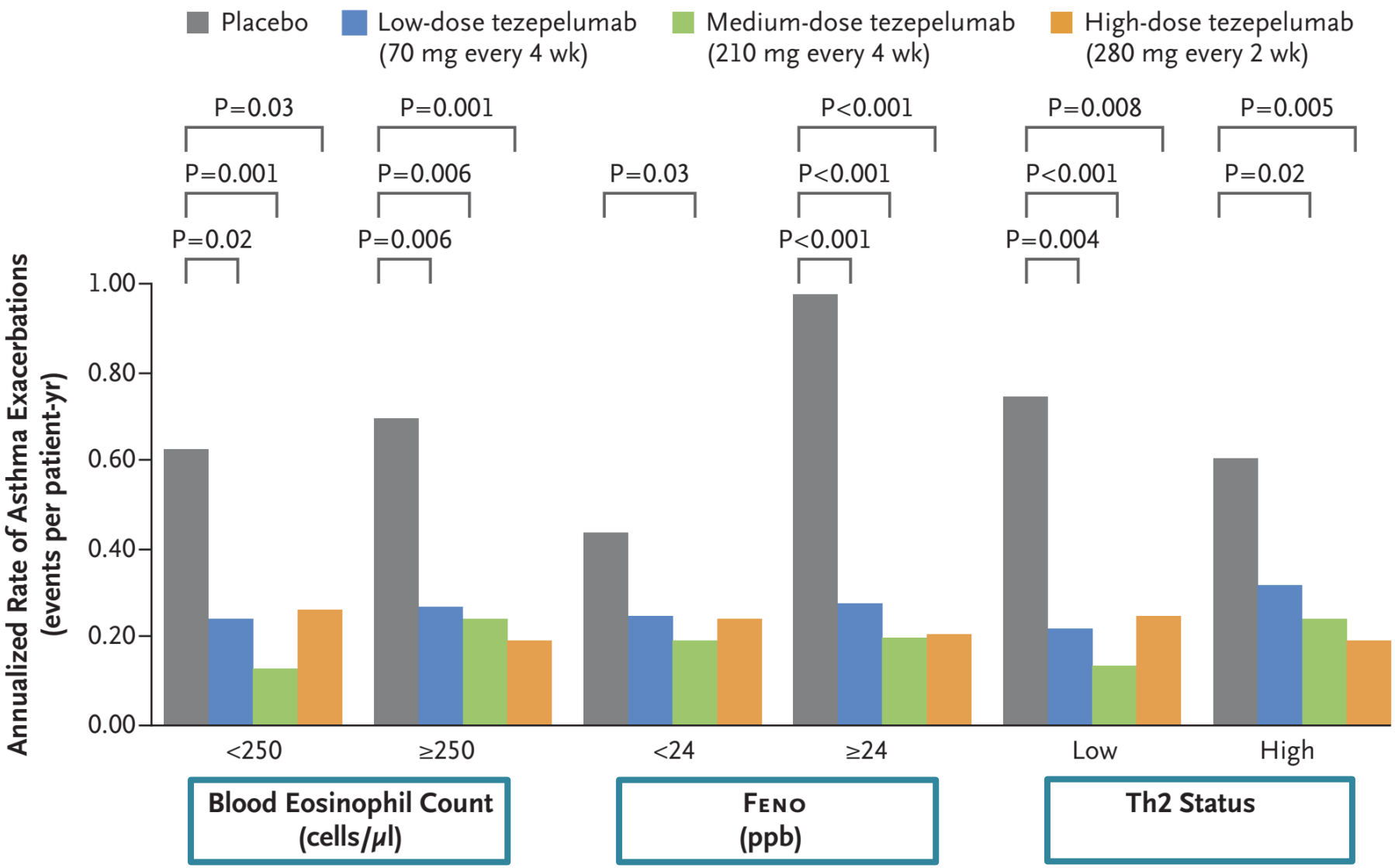
- phase 2b, dose-ranging, randomized, double-blind, placebo-controlled trial
- subcutaneous tezepelumab at three dose levels with placebo over a 52-week



- The primary end point was the annualized rate of asthma exacerbations (events per patient-year) at week 52

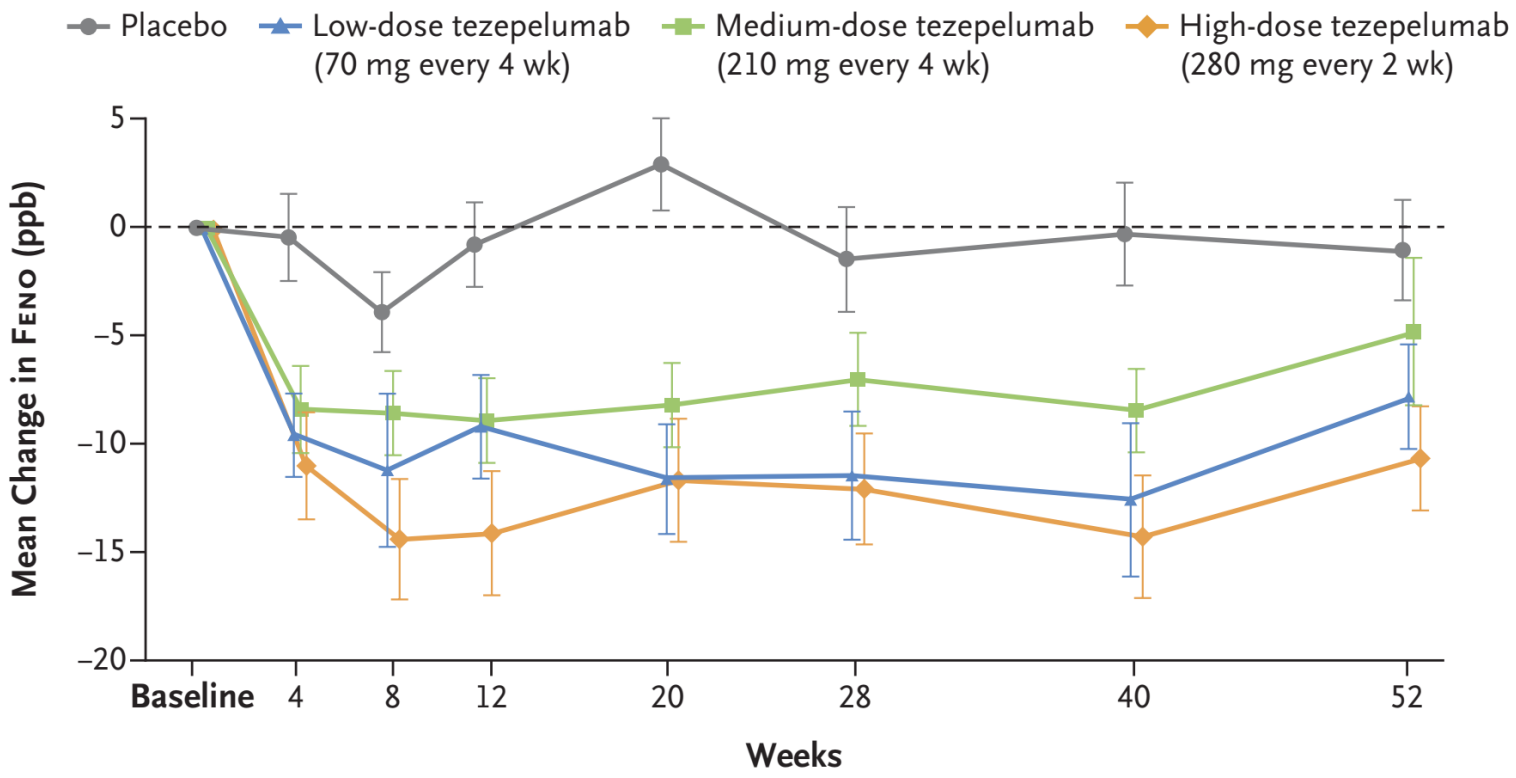
Corren J, N Engl J Med 2017;377:936-46.

Annualized Rate of Asthma Exacerbations (events per patient-yr) According to Baseline Biomarker Status



Corren J, N Engl J Med 2017;377:936-46.

Change in FENO



No. at Risk

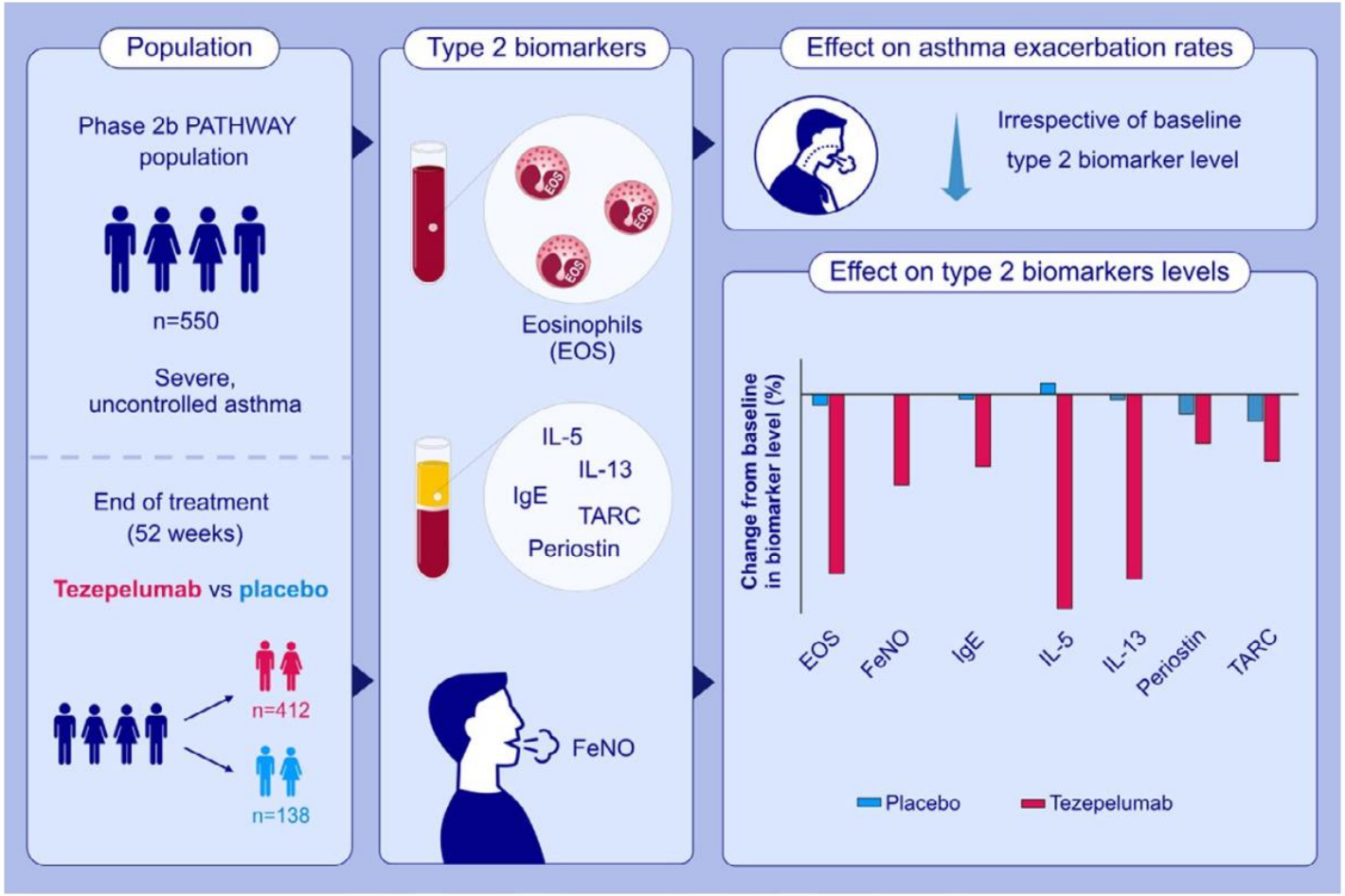
Placebo	146	119	119	121	118	114	116	113
Low-dose tezepelumab	144	111	107	114	106	118	106	109
Medium-dose tezepelumab	143	112	110	111	102	94	102	101
High-dose tezepelumab	141	110	108	112	92	104	103	103

Corren J, N Engl J Med 2017;377:936-46.

Baseline type 2 biomarker levels and response to tezepelumab in severe asthma

Jonathan Corren[1] | Tuyet-Hang Pham[2] | Esther Garcia Gil[3] | Kinga Sałapa[4] | Pin Ren[5] | Jane R. Parnes[6] | Gene Colice[7] | Janet M. Griffiths[2]

PATHWAY



Corren J et al, Allergy 2021; [PMID 34913186]

Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma

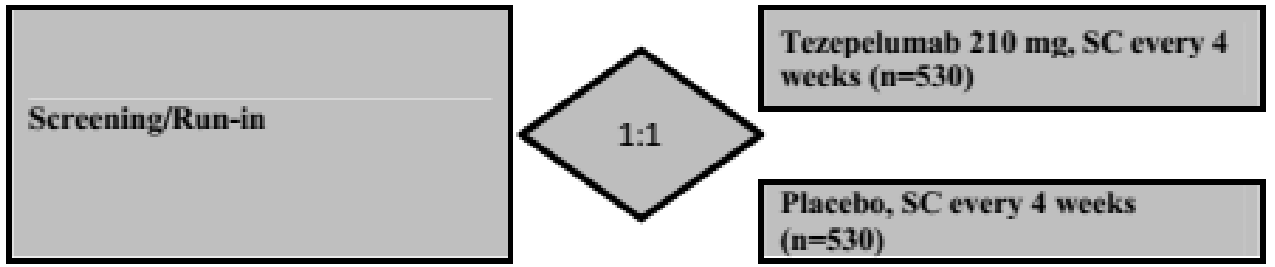
Andrew Menzies-Gow, M.D., Jonathan Corren, M.D., Arnaud Bourdin, M.D., Geoffrey Chupp, M.D., Elliot Israel, M.D., Michael E. Wechsler, M.D., Christopher E. Brightling, F.Med.Sci., Janet M. Griffiths, Ph.D., Åsa Hellqvist, M.Sc., Karin Bowen, M.Sc., Primal Kaur, M.D., Gun Almqvist, M.Sc., Sandhia Ponnarambil, M.D., and Gene Colice, M.D.

- conducted **a phase 3**, multicenter, randomized, double-blind, placebo-controlled trial.
- **MD to HD ICS + ≥ 1 controllers + ≥ 2 AE**
- Patients (12 to 80 years of age) were randomly assigned to receive Tezepelumab (**210** mg) or placebo subcutaneously every 4 weeks **for 52 weeks.**
- The primary end point was the **annualized rate of asthma exacerbations** over a period of 52 weeks.

NAVIGATOR

Figure 1 **Study design**

V1	V2-V2a	V3	V4-V16	V17	V18, V19
Day -42 to -35	Day -28 to -25	Week 0	Week 0 to 48	Week 52	Week 58, 64
Screening	**Run-in**	**Randomization**	**Treatment Phase**	**End of Treatment**	**Follow-up**



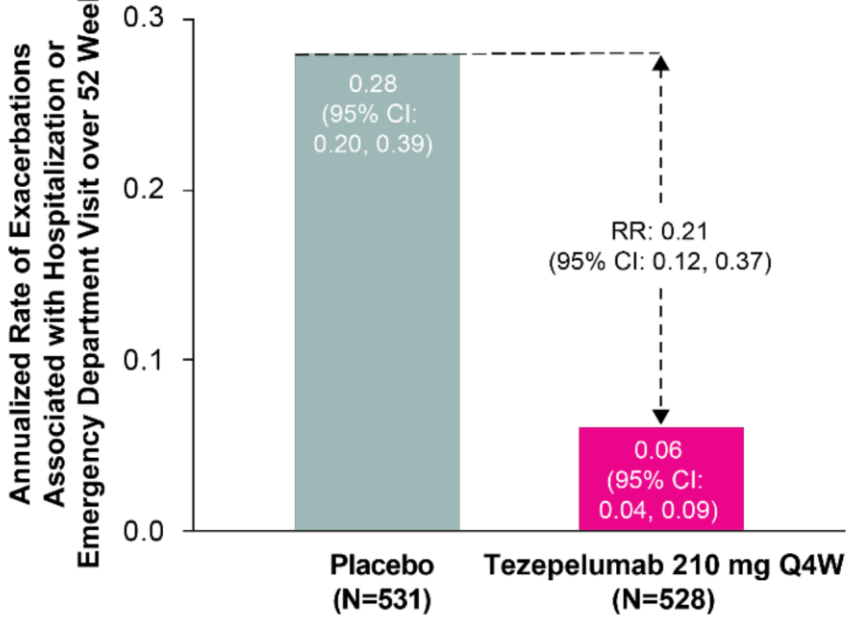
Menzies-Gow A et al, N Engl J Med 2021;384:1800-9 [PMID 33979488]

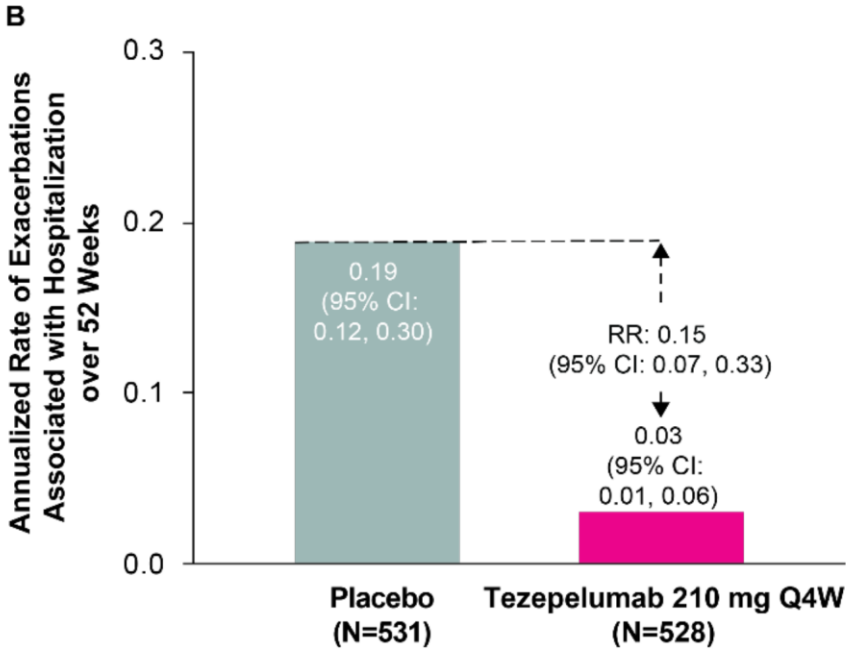
Baseline Characteristics

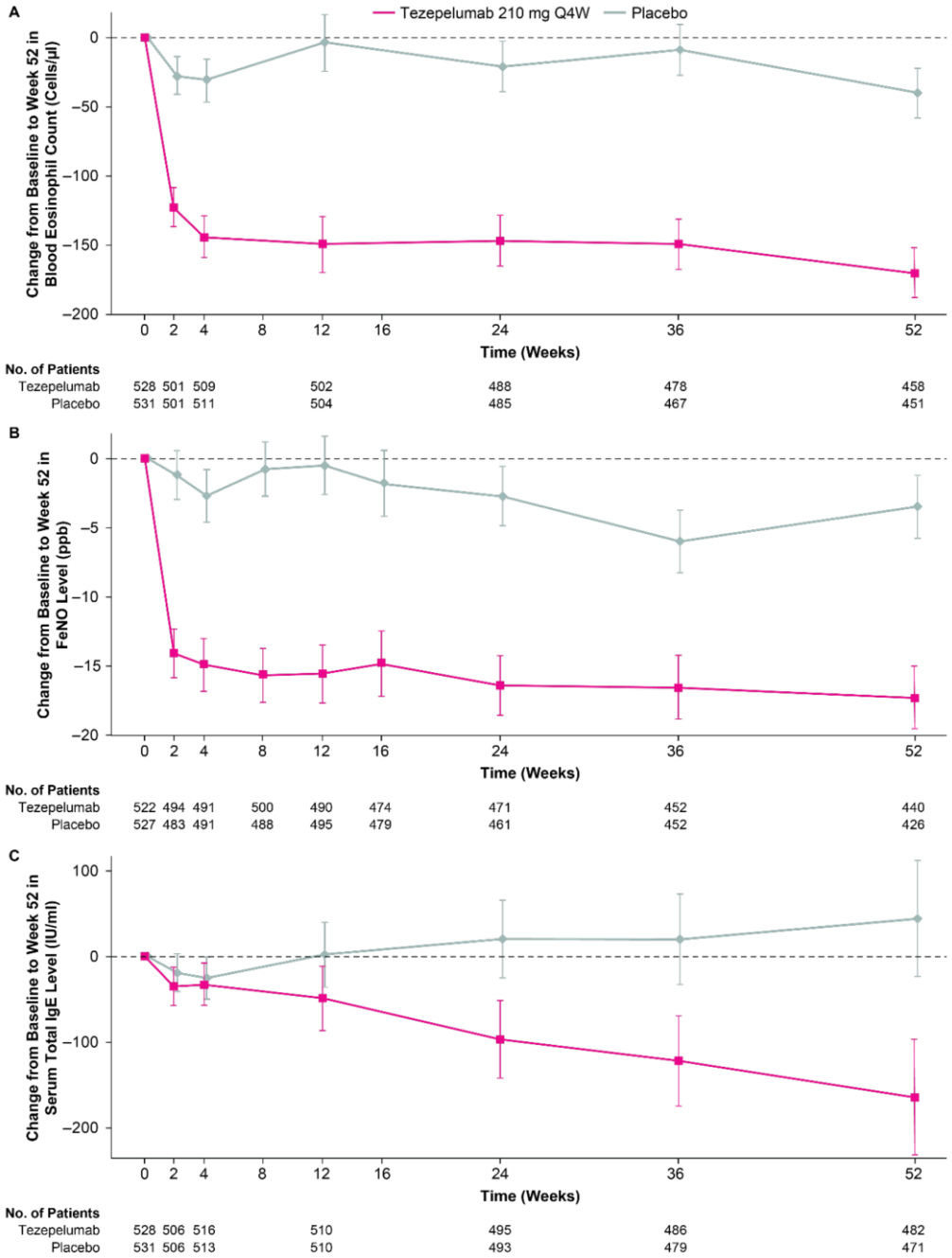
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Tezepelumab (N=528)	Placebo (N=531)	Total (N=1059)
Age — yr	49.9±16.3	49.0±15.9	49.5±16.1
Male sex — no. (%)	193 (36.6)	194 (36.5)	387 (36.5)
White race — no. (%)†	332 (62.9)	327 (61.6)	659 (62.2)
Body-mass index‡	28.7±7.1	28.3±6.9	28.5±7.0
Dose of inhaled glucocorticoids — no. (%)			
Low	0	1 (0.2)	1 (0.1)
Medium	131 (24.8)	132 (24.9)	263 (24.8)
High	397 (75.2)	398 (75.0)	795 (75.1)
Use of oral glucocorticoids — no. (%)			
Yes	49 (9.3)	51 (9.6)	100 (9.4)
No	479 (90.7)	480 (90.4)	959 (90.6)
Prebronchodilator FEV_1 — % of predicted normal value	62.8±18.0	62.7±18.0	62.7±18.0
ACQ-6 score§	2.8±0.8	2.8±0.8	2.8±0.8
AQLQ(S)+12 overall score¶			
No. of patients evaluated	527	529	1056
Mean	3.9±1.0	3.9±1.0	3.9±1.0
F_{ENO} level			
No. of patients evaluated	522	527	1049
Mean — ppb	41.4±36.3	46.3±44.7	43.8±40.8
Median (range) — ppb	31.0 (5.0–235.0)	30.0 (5.0–265.0)	30.0 (5.0–265.0)
<25 ppb — no. (%)	213 (40.8)	220 (41.7)	433 (41.3)
≥25 ppb — no. (%)	309 (59.2)	307 (58.3)	616 (58.7)
Blood eosinophil count			
Mean — cells/μl	327±293	353±488	340±403
Median (range) — cells/μl	250 (0–3650)	250 (0–8170)	250 (0–8170)
<300 cells/μl — no. (%)	309 (58.5)	309 (58.2)	618 (58.4)
≥300 cells/μl — no. (%)	219 (41.5)	222 (41.8)	441 (41.6)
Serum total IgE — IU/ml			
Mean	515.7±959.8	614.1±1159.5	565.0±1065.2
Median (range)	194.9 (1.5–12,823.2)	196.7 (1.5–9740.9)	195.6 (1.5–12,823.2)

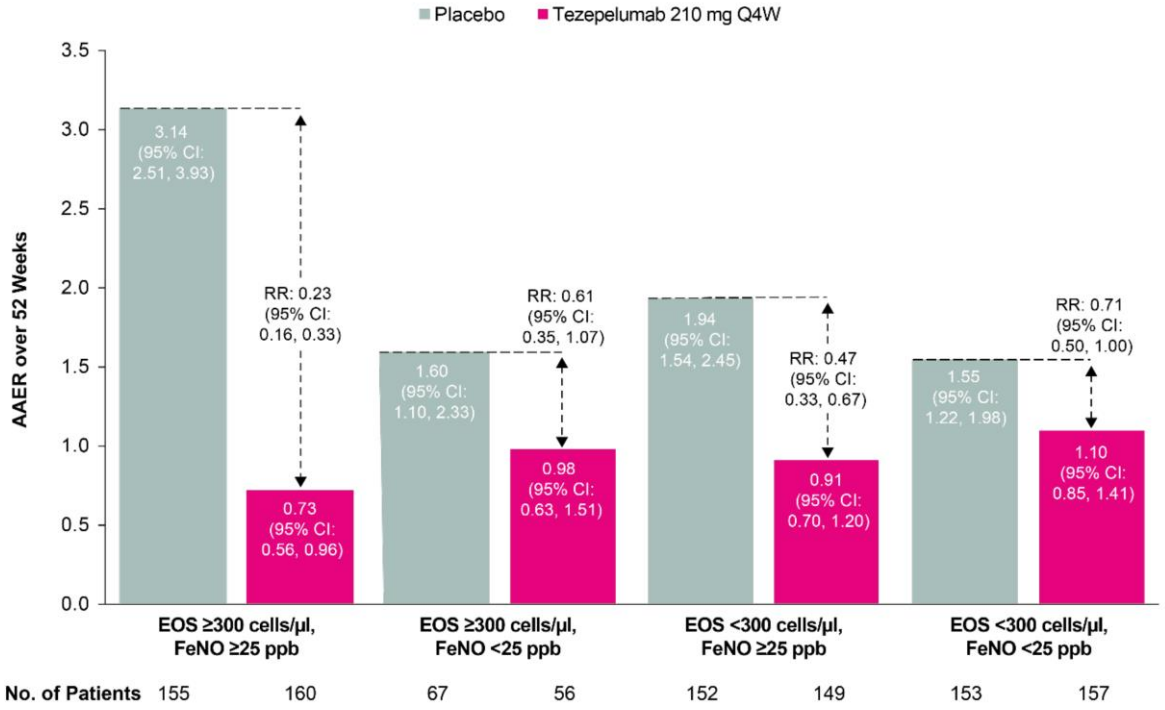
Menzies-Gow A et al, N Engl J Med 2021;384:1800-9 [PMID 33979488]

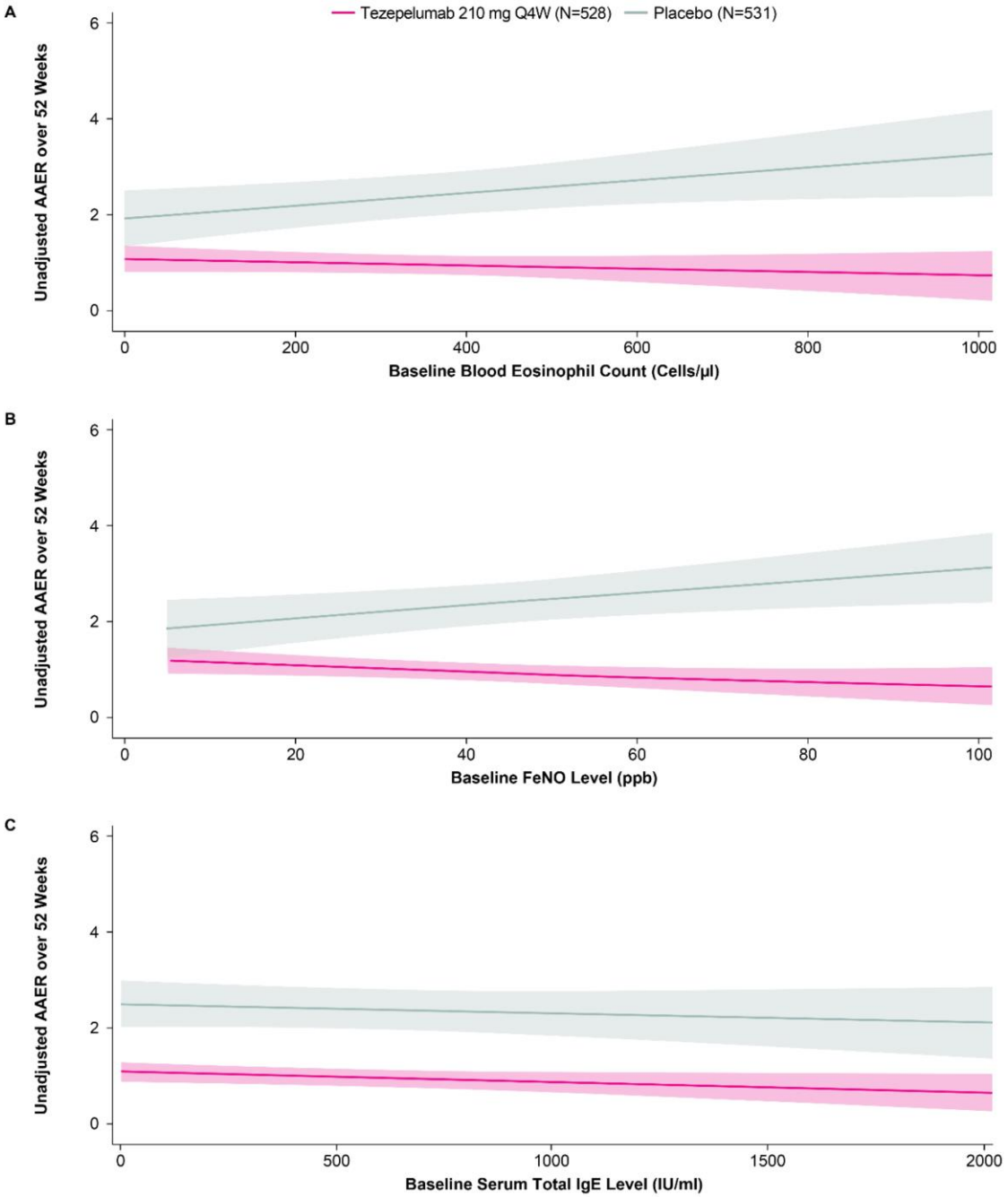






Menzies-Gow A et al, N Engl J Med 2021;384:1800-9 [PMID 33979488]





Menzies-Gow A et al, N Engl J Med 2021;384:1800-9 [PMID 33979488]

TABLE 1 Measures of adherence

Method of assessment	Examples	Parameter measure	Advantages	Disadvantages
Physician assessment	Questions asked during clinic visit	Indication of non-adherence	• Easy to gather information • Quick • Inexpensive	• Subjective • Not standardised • Risk of recall bias
Self-reported questionnaire	Medication Adherence Report Scale for asthma [11], Morisky Medication Adherence Scale [12], Test of Adherence to Inhalers [13]	Pre-established cut-off point determines whether patient is adherent or non-adherent	• Easy to use • Inexpensive	• Subjective • Risk of recall and reporting bias leading to overestimation of adherence • Usually only available in English
Prescription database	Medication possession ratio, proportion of days covered	Percentage calculated	• Objective • Easy to use • Inexpensive • Adherence can be measured over a long period • Non-adherent patients can be easily identified	• Prescription may not be redeemed • Evidence of dispensed medication does not equate to medication being correctly administered
Dispensing records	Medication possession ratio, proportion of days covered	Percentage calculated	• Objective • Easy to use • Inexpensive • Adherence can be measured over a long period • Non-adherent patients can be easily identified • More accurate than a prescription database	• Evidence of dispensed medication does not equate to medication correctly being administered • Prescription may not be redeemed from the same pharmacy each time

TABLE 1 Measures of adherence

Dose counter	Dose counter on inhaler	Comparison of expected to actual dose counter reading	• Quick • Easy to use • Inexpensive	• Not on all devices have a dose counter • "Dose dumping" will conceal non-adherence
Type 2 biomarker	F_{ENO} suppression test	Change in F_{ENO}	• Objective • Identifies non-adherence when used with DOT • Identifies patients with ICS-resistant Type 2 inflammation who may benefit from biologic therapy	• Cost • Time and resource dependent for patient and HCP • Not widely used
Serum drug level	Serum ICS concentration	Serum concentration	• Objective	• Invasive • Cost • Provides short-term recent adherence data only
Electronic monitoring devices	INCA, Propeller, Hailie, Turbu+, Respiro, Herotracker, CapMedic, Digihaler	Frequency of inhaler use	• Objective • Some can distinguish between intentional and non-intentional (*e.g.* error in inhaler technique) non-adherence • Patterns of non-adherence can be identified	• Usually requires the patient to own a smartphone device and be technologically literate • Cost

DOT: directly observed treatment; F_{ENO}: exhaled nitric oxide fraction; HCP: healthcare professional; ICS: inhaled corticosteroids; INCA: Inhaler Compliance Assessment.

Dhruve H et al. Eur Respir Rev 2022;31 [PMID 35613744]

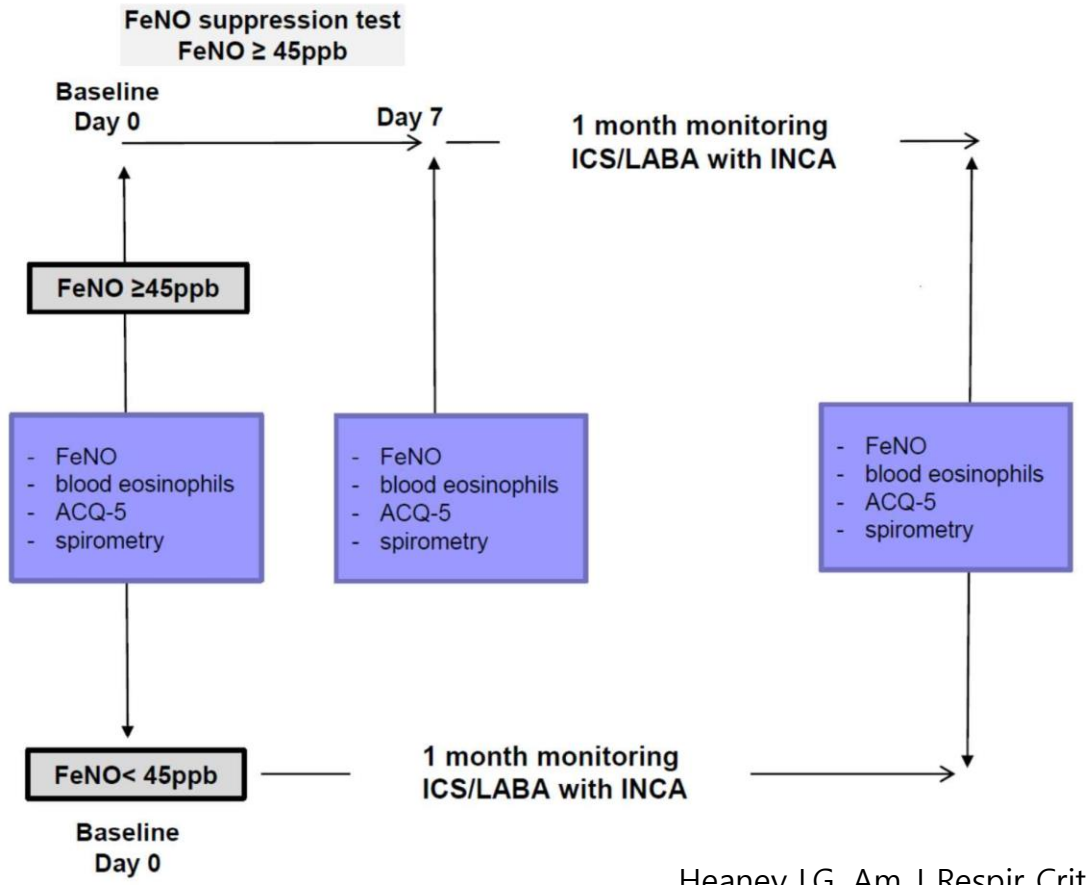
Remotely Monitored Therapy and Nitric Oxide Suppression Identifies Nonadherence in Severe Asthma

Liam G. Heaney[1], John Busby[1], Peter Bradding[2], Rekha Chaudhuri[3], Adel H. Mansur[4], Robert Niven[5], Ian D. Pavord[6], John T. Lindsay[7], and Richard W. Costello[8]; on behalf of the Medical Research Council UK Refractory Asthma Stratification Programme (RASP-UK)

◆ To **distinguishing** patients with **difficult-to-control asthma** who respond to ICS from **refractory asthma**

Study population

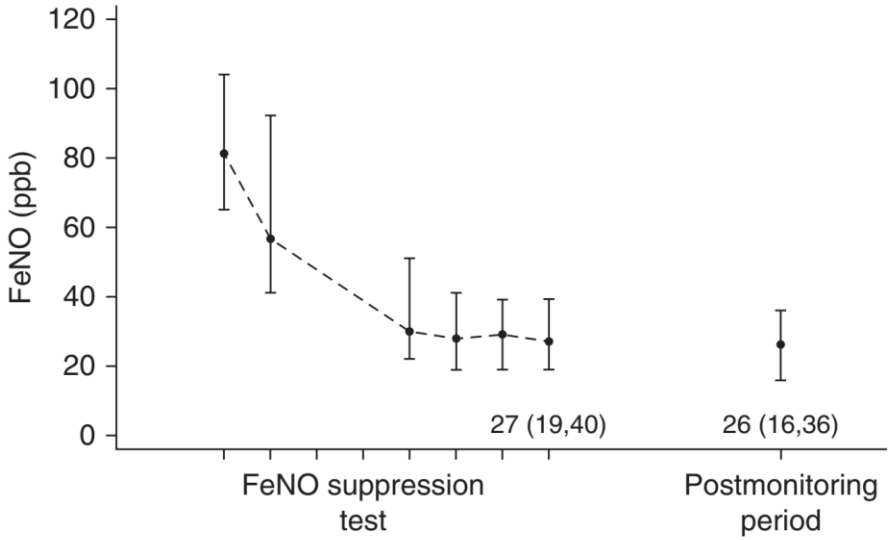
- GINA Step 4/5 severe asthma
- attending UK Specialist Severe Asthma Service
- clinical and demographic details
- serum prednisolone / cortisol (subjects on maintenance prednisolone)
- instructed in use of INCA enabled Accuhaler



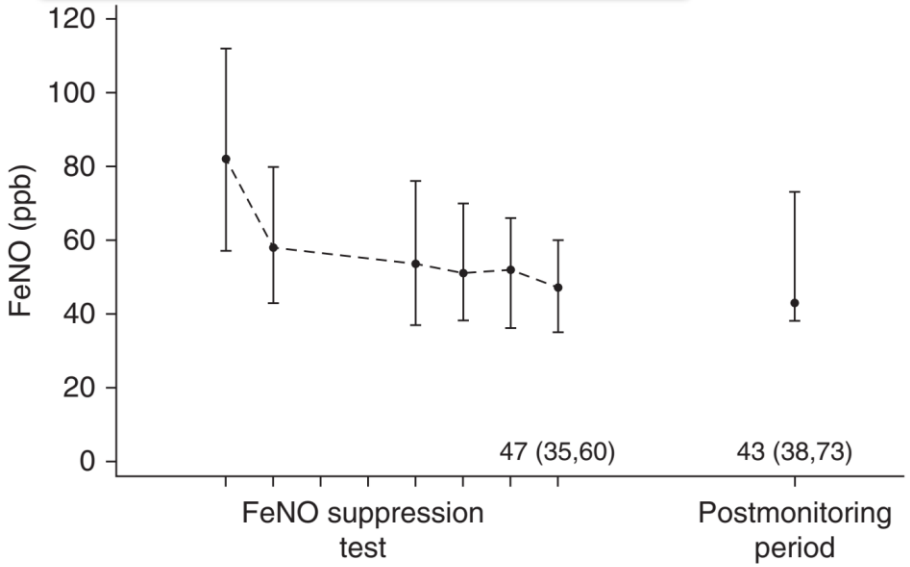
Heaney LG, Am J Respir Crit Care Med 2019;199:454-64.

Relationship Between FENO after 7-day Suppression Testing and FEBO after 1-month Monitoring for Subject with Good Adherence

Positive suppression test



Negative suppression test



- Remote FENO suppression testing is an effective means of identifying nonadherence to ICS in subjects with difficult-to-control asthma

Heaney LG, Am J Respir Crit Care Med 2019;199:454-64.

호기산화질소(FeNO) in NAEPPCC

- In individuals aged 5 y and older for whom **the diagnosis of asthma is uncertain (천식 진단이 불확실할 때)** using history, clinical findings, clinical course, and spirometry, including bronchodilator responsiveness testing, or in whom spirometry cannot be performed, the Expert Panel **conditionally recommends the addition of FENO measurement** as an adjunct to the evaluation process. (Conditional, Moderate)

- In individuals aged 5 y and older with persistent allergic asthma, for whom there is **uncertainty (조절 정도가 불분명할 때)** in choosing, monitoring, or adjusting anti-inflammatory therapies based on history, clinical findings, and spirometry, the Expert Panel conditionally recommends **the addition of FENO measurement as part of an ongoing asthma monitoring and management strategy** that includes frequent assessments. (Conditional Low)

Expert Panel Working Group of the National Heart L, J Allergy Clin Immunol 2020;146:1217-70 [PMID 33280709]

호기산화질소(FeNO) in NAEPPCC

- In individuals aged 5 y and older with asthma, the Expert Panel recommends **against** the use of FENO **measurements in isolation to assess (단독으로 평가)** asthma control, predict future exacerbations, or assess exacerbation severity. If used, it should be as part of an ongoing monitoring and management strategy. (Strong Low)

- In **children** aged 0-4 y with recurrent wheezing, the Expert Panel recommends **against** FENO measurement to predict the future development of asthma (**소아의 천식 발명 예측**). (Strong Low)

Expert Panel Working Group of the National Heart L, J Allergy Clin Immunol 2020;146:1217-70 [PMID 33280709]

AMERICAN THORACIC SOCIETY DOCUMENTS

Use of Fractional Exhaled Nitric Oxide to Guide the Treatment of Asthma

An Official American Thoracic Society Clinical Practice Guideline

Sumita B. Khatri, Jonathan M. Iaccarino, Amisha Barochia, Israa Soghier, Praveen Akuthota, Anna Brady, Ronina A. Covar, Jason S. Debley, Zuzana Diamant, Anne M. Fitzpatrick, David A. Kaminsky, Nicholas J. Kenyon, Sandhya Khurana, Brian J. Lipworth, Kevin McCarthy, Michael Peters, Loretta G. Que, Kristie R. Ross, Elena K. Schneider-Futschik, Christine A. Sorkness, and Teal S. Hallstrand; on behalf of the American Thoracic Society Assembly on Allergy, Immunology, and Inflammation

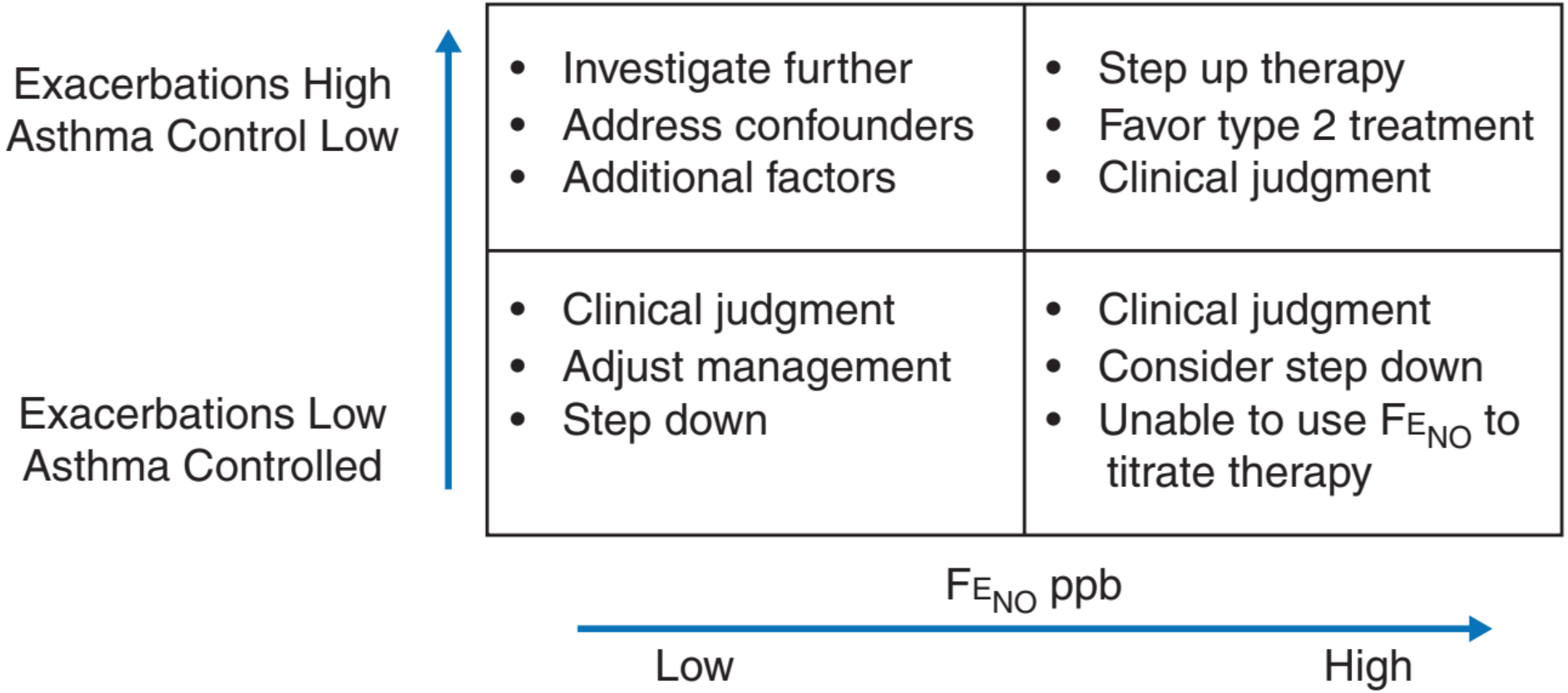
THIS OFFICIAL CLINICAL PRACTICE GUIDELINE OF THE AMERICAN THORACIC SOCIETY WAS APPROVED SEPTEMBER 2021

- An international, multidisciplinary panel of experts was convened to form a consensus document regarding a single question relevant to the use of FENO

- In patients with asthma in whom treatment is being considered, we suggest that FENO is beneficial and should be used in addition to usual care.

Khatri SB et al. Am J Respir Crit Care Med 2021;204:e97-e109 [PMID 34779751]

Conceptual framework for the use of fractional exhaled nitric oxide (FENO) testing to guide treatment decisions for individuals with asthma

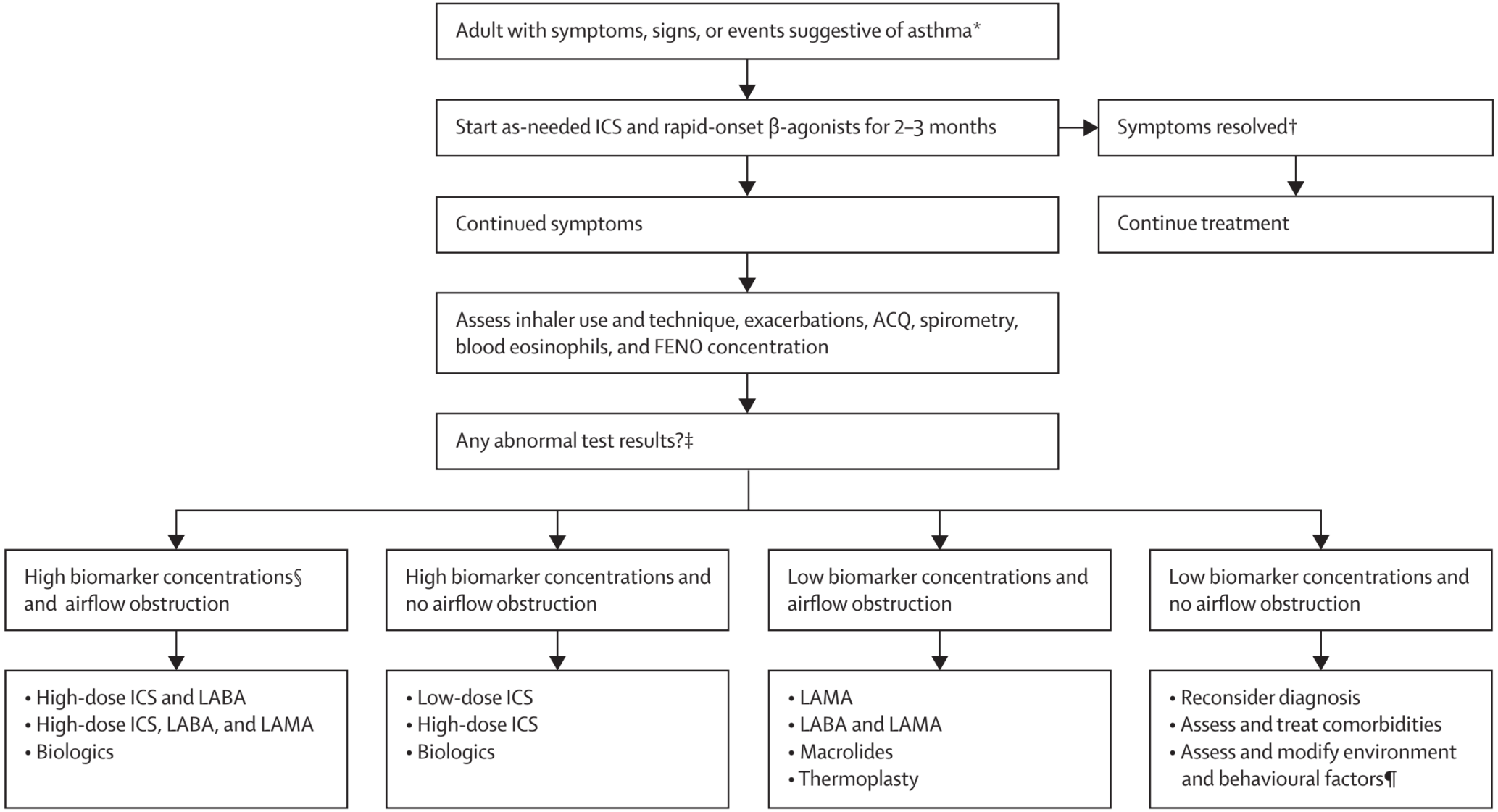


Khatri SB et al. Am J Respir Crit Care Med 2021;204:e97-e109 [PMID 34779751]

GINA 2022

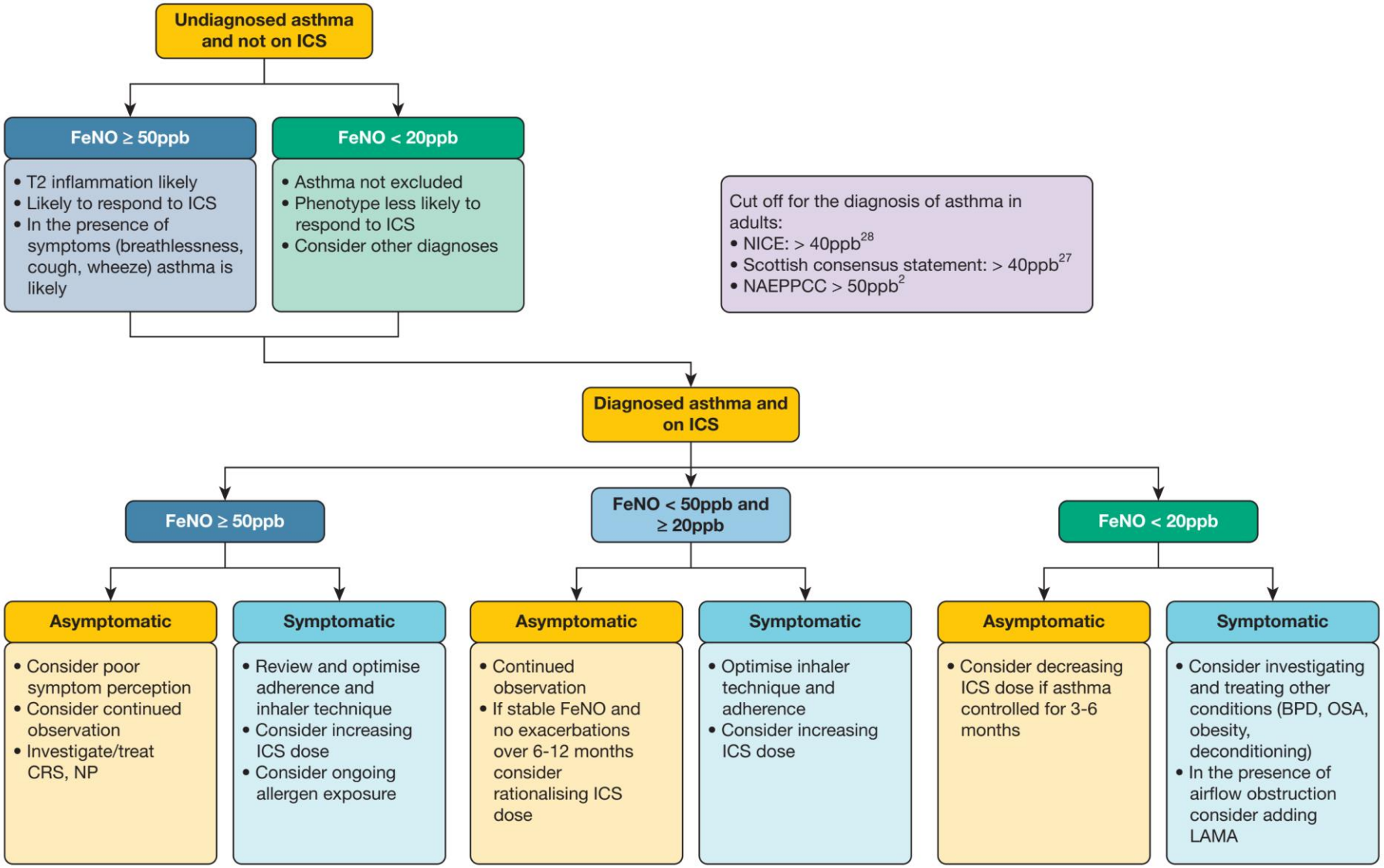
- **There is a need for evidence-based corticosteroid de-escalation strategies in patients with asthma**. In a randomized controlled trial (RCT) of patients taking high dose ICS-LABA, a strategy based on a composite of Type 2 biomarkers only vs. an algorithm based on ACQ-7 and history of recent exacerbation was inconclusive because a substantial proportion of patients did not follow recommendations for treatment change.(200) **Until more definitive evidence for a specific strategy is available, GINA continues to recommend a clinical evaluation** that includes patient-reported symptoms as well as modifiable risk factors, comorbidities and patient preferences when making treatment decisions. Further evidence on the role of biomarkers in such decisions in Steps 1–4 is needed.

New approach for the initial management of suspected asthma



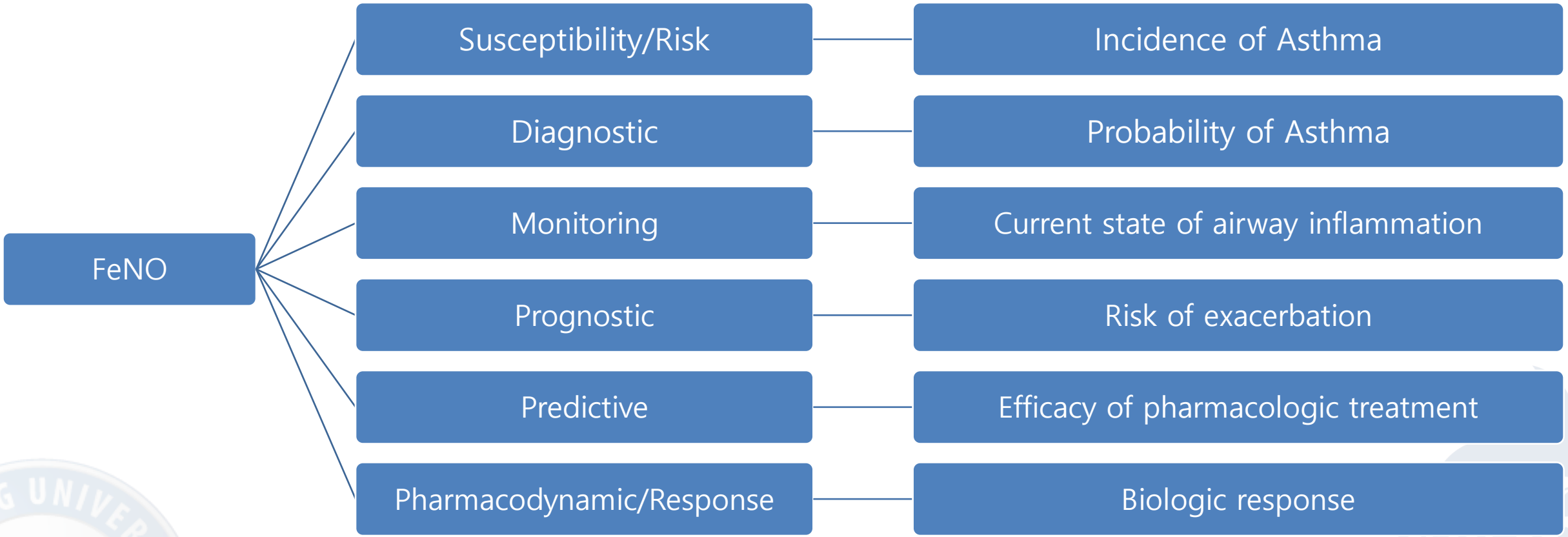
Shaw DE et al. Lancet Respir Med 2021;9:786-94. [PMID: 33639099]

Algorithm highlighting the usefulness of FENO



Rupani H et al. Chest 2022;161:906-17 [PMID 34673021]

Summary


FeNO
Susceptibility/Risk
Incidence of Asthma
Diagnostic
Probability of Asthma
Monitoring
Current state of airway inflammation
Prognostic
Risk of exacerbation
Predictive
Efficacy of pharmacologic treatment
Pharmacodynamic/Response
Biologic response