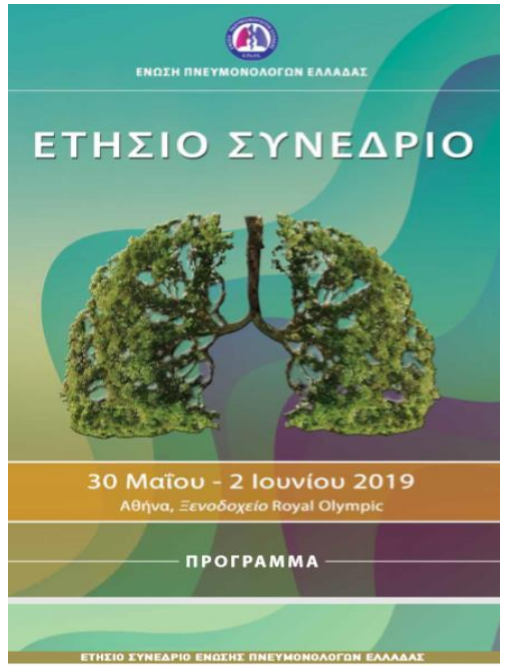

Biomarker-driven asthma management: ready for clinical practice?

Konstantinos (Kostas) Kostikas MD, PhD, FCCP
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Conflict of Interest Statement

I was an employee of Novartis Pharma AG (Basel Switzerland - 01.01.2015 to 31.10.2018)

I have received honoraria for presentations and/or consulting services from AstraZeneca, Boehringer Ingelheim, Chiesi, ELPEN, GSK, and Novartis

I am a member of the GOLD Assembly

Letter from Greece

"This may sound overly optimistic, but this time of crisis and austerity may be the greatest opportunity for change of mindset, brave reforms, electronic governance and investment in research and development of new technologies."

Kostikas K, Respirology 2019 (Photo courtesy of Patty K)

Biomarker-driven asthma management: ready for clinical practice?

- The hype around biomarkers
- Blood vs. sputum vs. exhaled air
- Biomarkers and biologics
- Management of DTT asthma
- The way forward

Biomarker-driven asthma management: ready for clinical practice?

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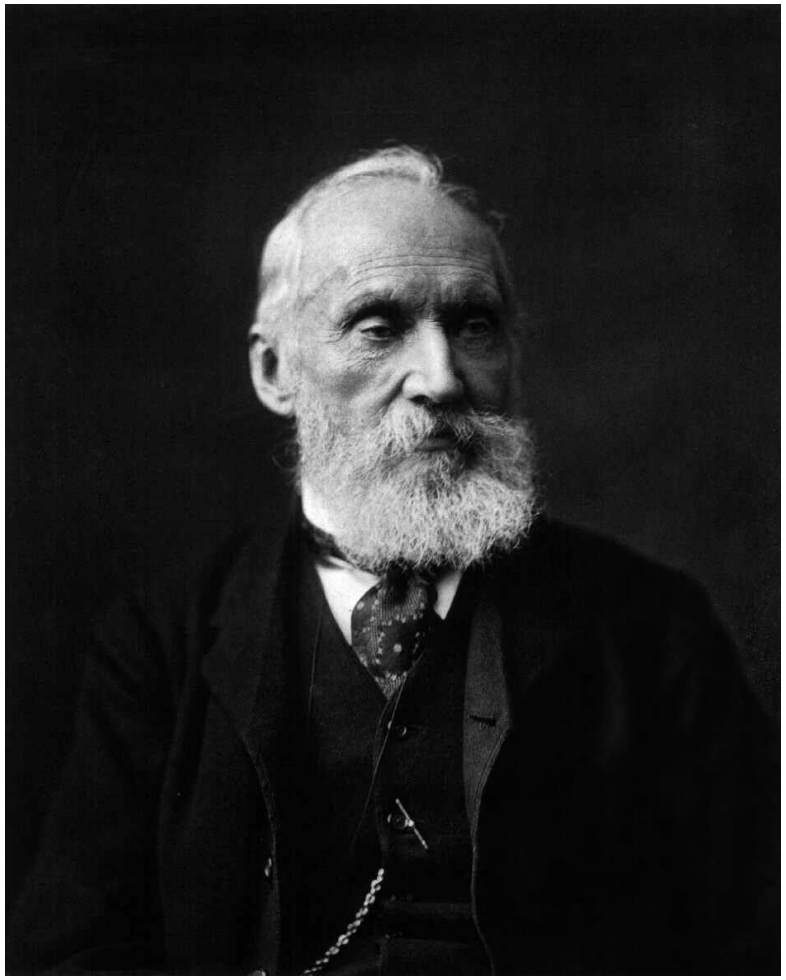
Why should we measure biomarkers?



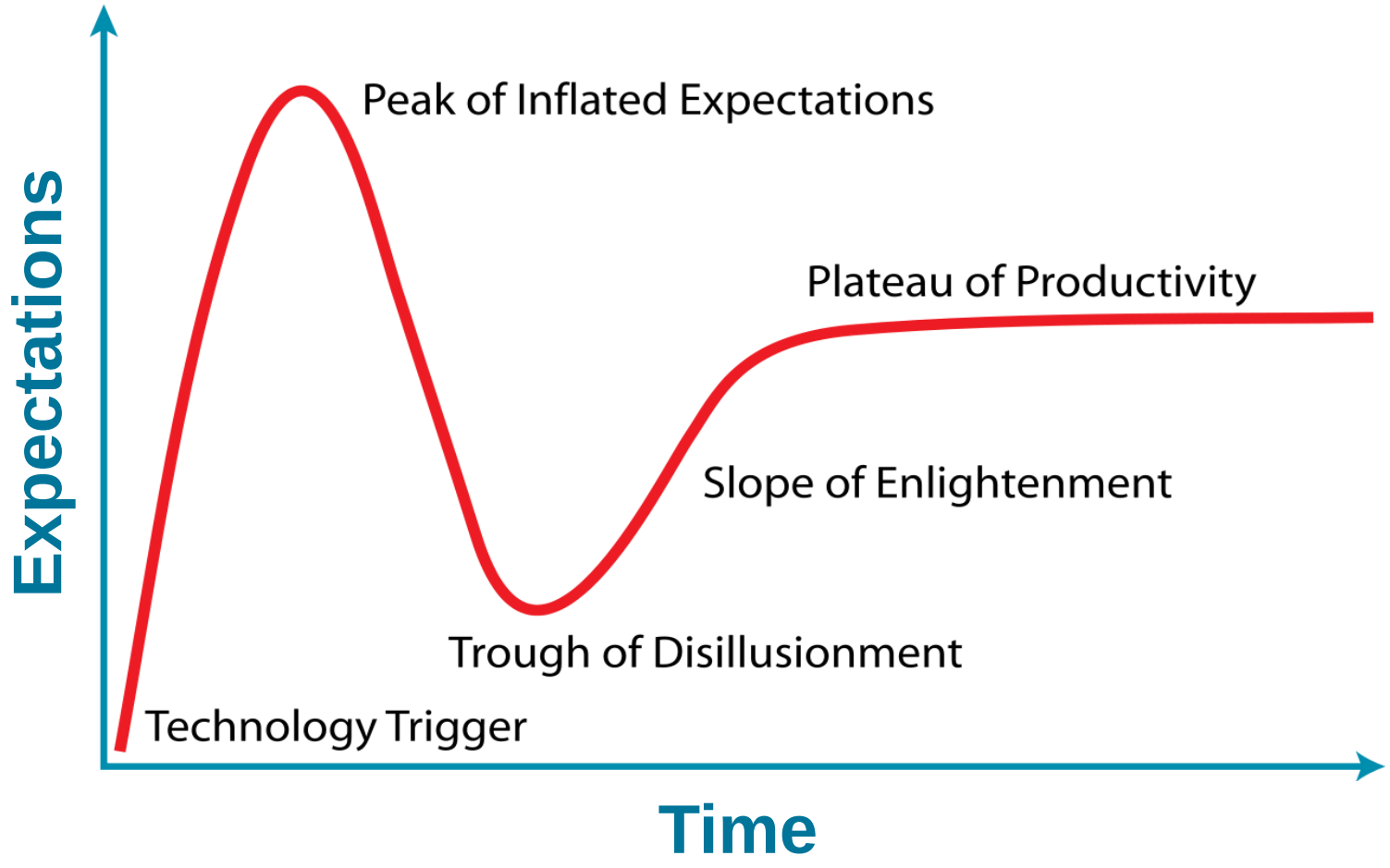
“To measure is to know

If you cannot measure it
you cannot improve it”

Lord Kelvin

https://en.wikipedia.org/wiki/William_Thomson,_1st_Baron_Kelvin

The Gartner Hype Cycle



http://www.gartner.com/technology/research/methodologies/hype-cycle.jsp

Definitions

FDA

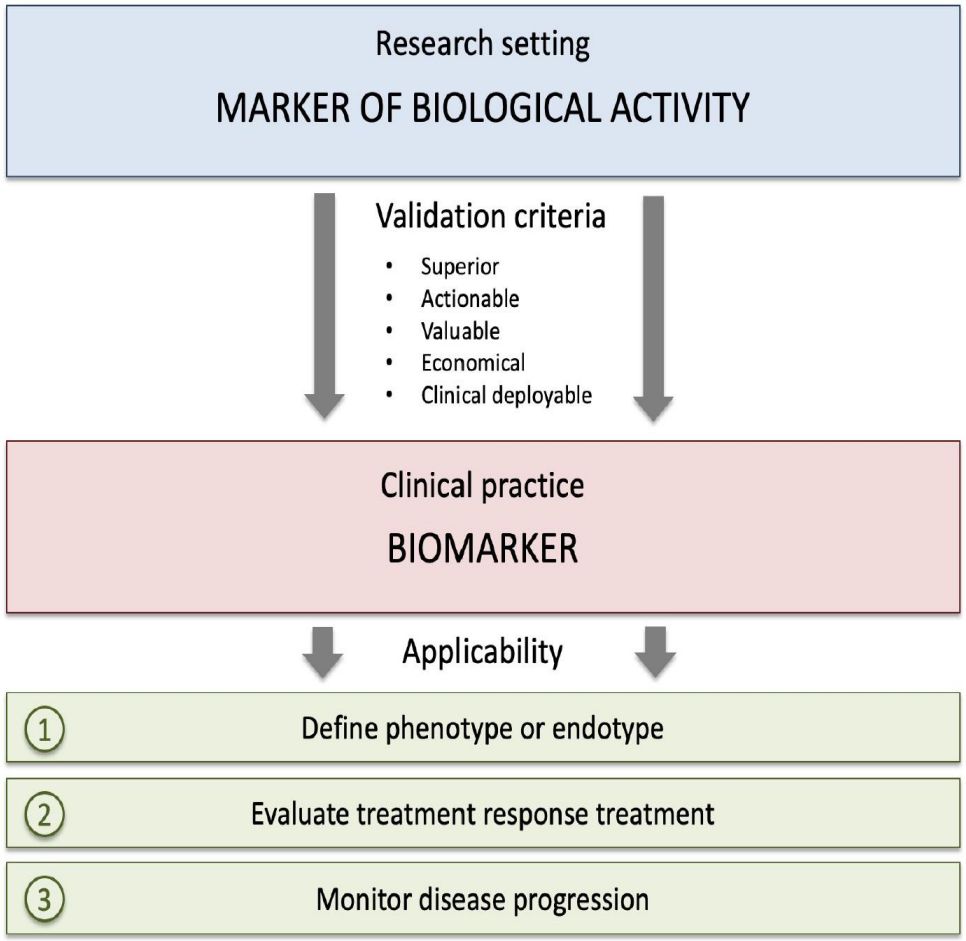
A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or biological responses to a therapeutic intervention.

EMA

Biomarkers are tests that can be used to follow body processes and diseases in humans and animals. They can be used to **predict how a patient will respond to a medicine *or* whether they have, or are likely to develop, a certain disease**.

https://www.fda.gov/Drugs/NewsEvents/ucm424545.htm;
http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000349.jsp

Clinical applicability of biomarkers in asthma management



Superior (outperform current practice)

Actionable (change patient management)

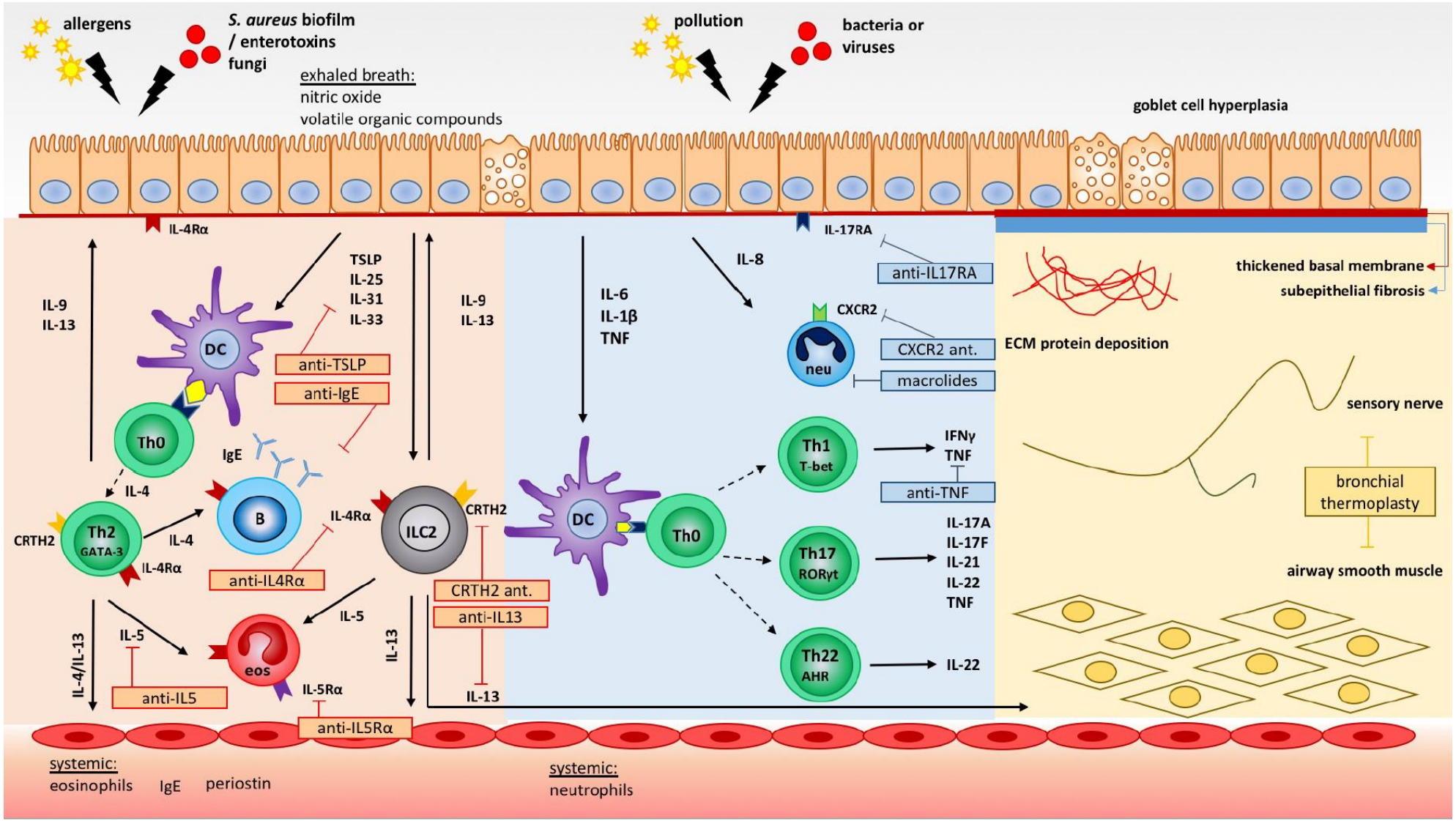
Valuable (improve patient outcomes)

Economical (cost-saving or cost-effective) and

Deployable (technology available in clinical laboratory)

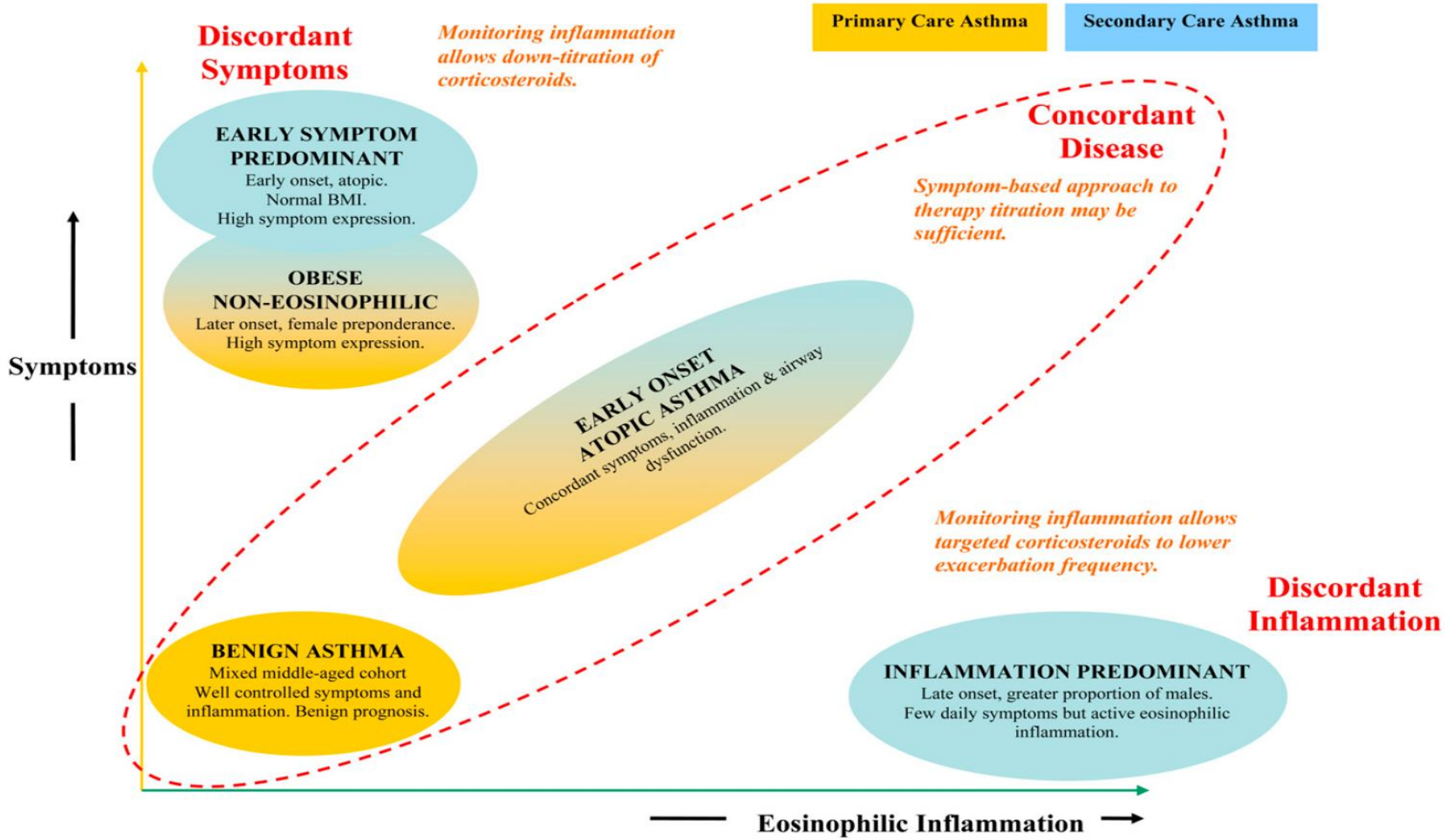
Diamant Z et al, Allergy 2019 (in press, EAACI Position Paper); FDA CDER Biomarker Qualification Program [Internet]. Available from: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/default.htm

Asthma endotypes and targeted treatment approaches



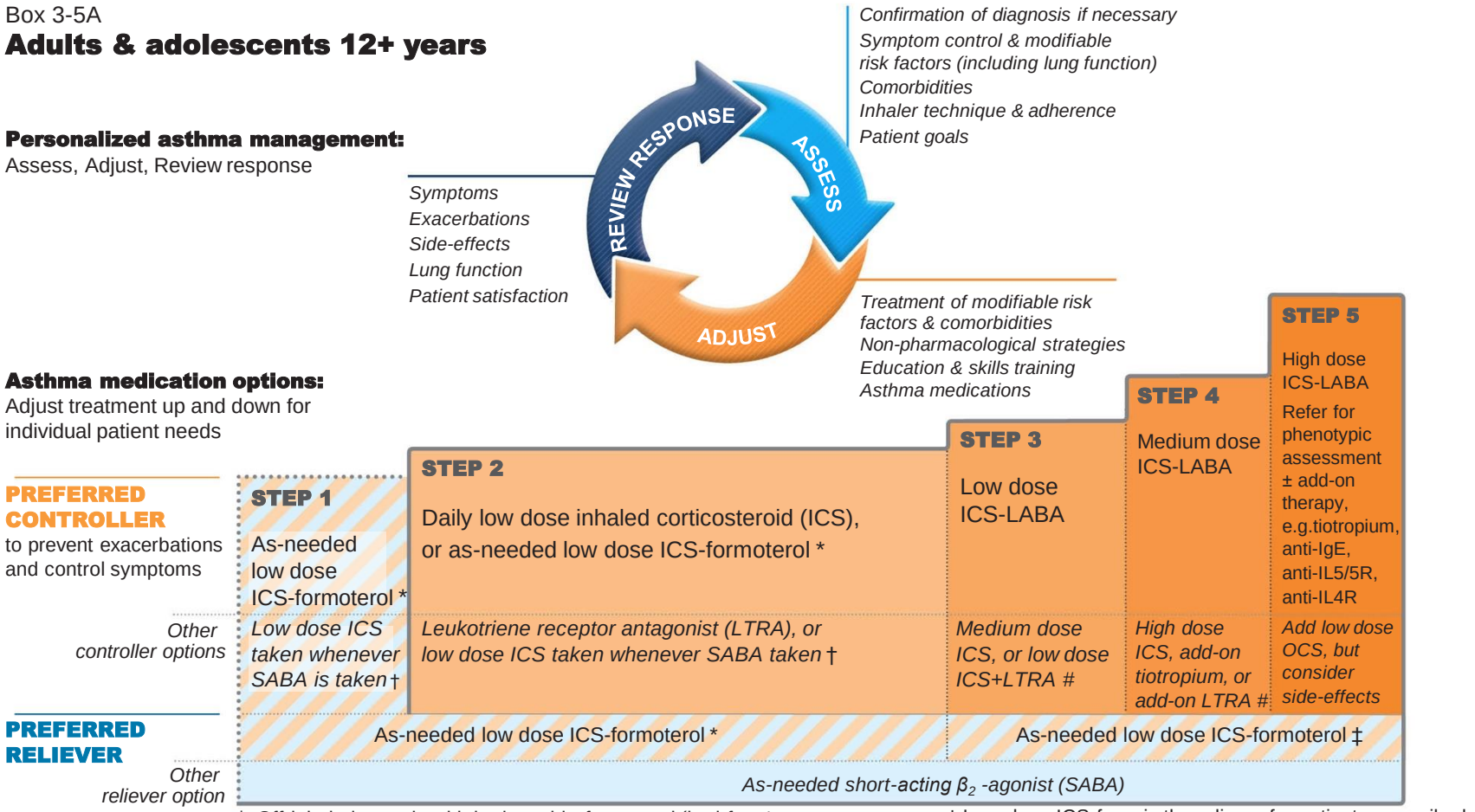
Diamant Z et al, Allergy 2019 (in press, EAACI Position Paper)

The clinical problem: discordance between symptoms and inflammation in severe/DTT asthma

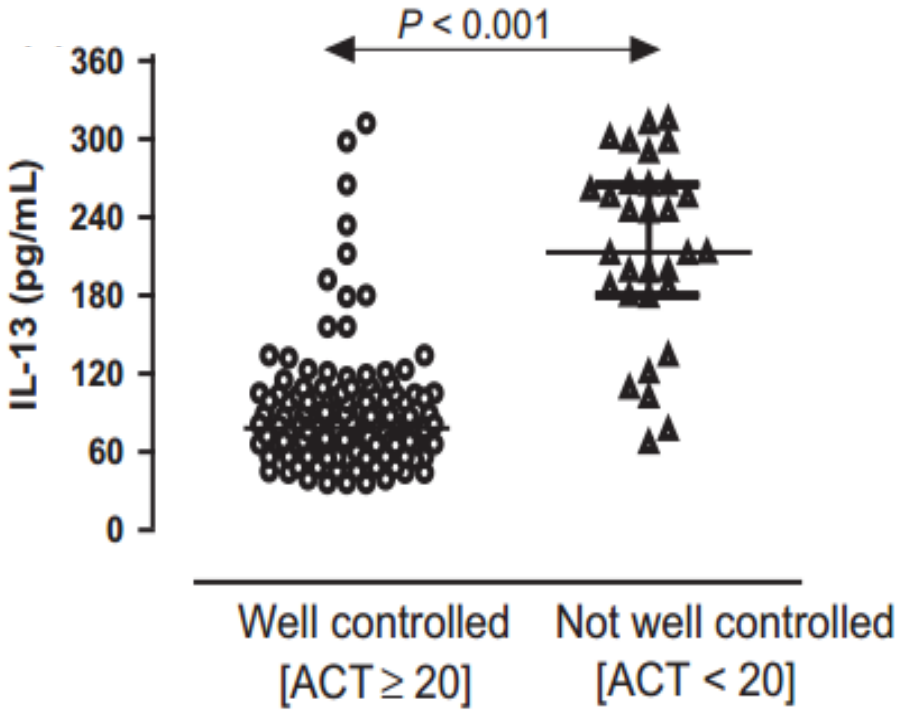


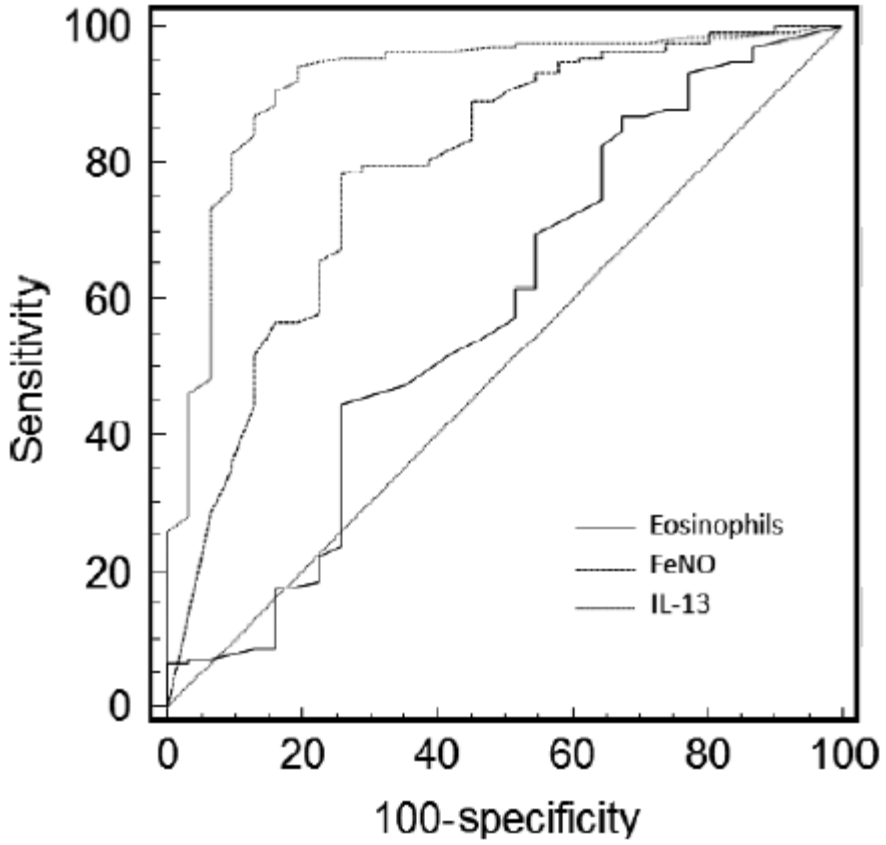
Haldar P, Am J Respir Crit Care Med 2008; 178: 218–224

Stepwise management - pharmacotherapy



Complicated Biomarkers: Sputum IL-13 and Asthma Control

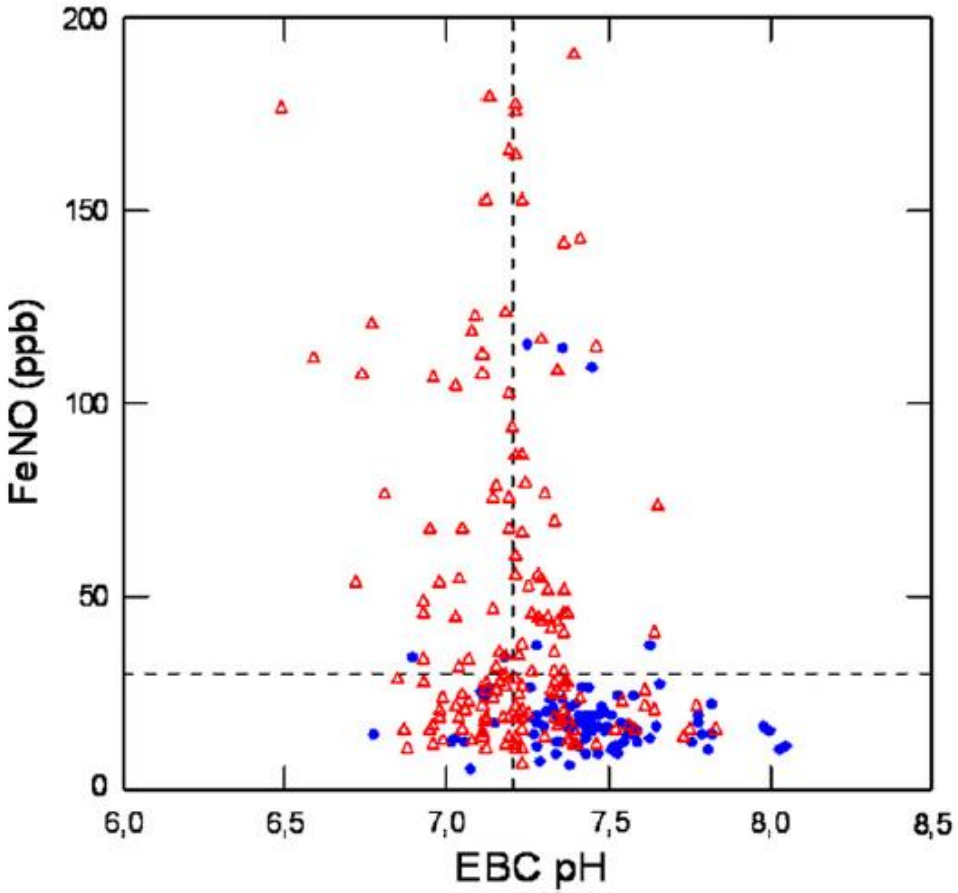


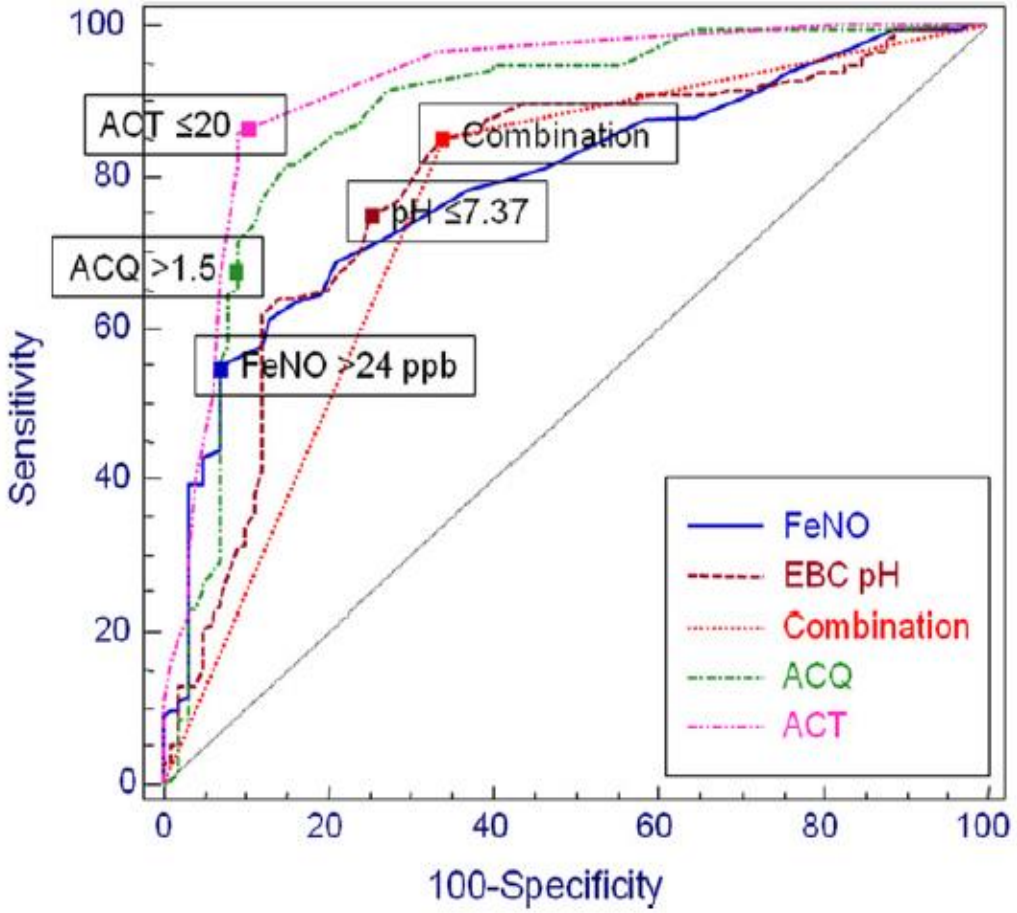


AUC	
Sputum IL-13	0.92
FeNO	0.71
Sputum EOS	0.65

Tsilogianni Z,… and Kostikas K, Clin Exp Allergy 2016; 46: 923-931

Complicated Concepts: FeNO and EBC in Asthma Control

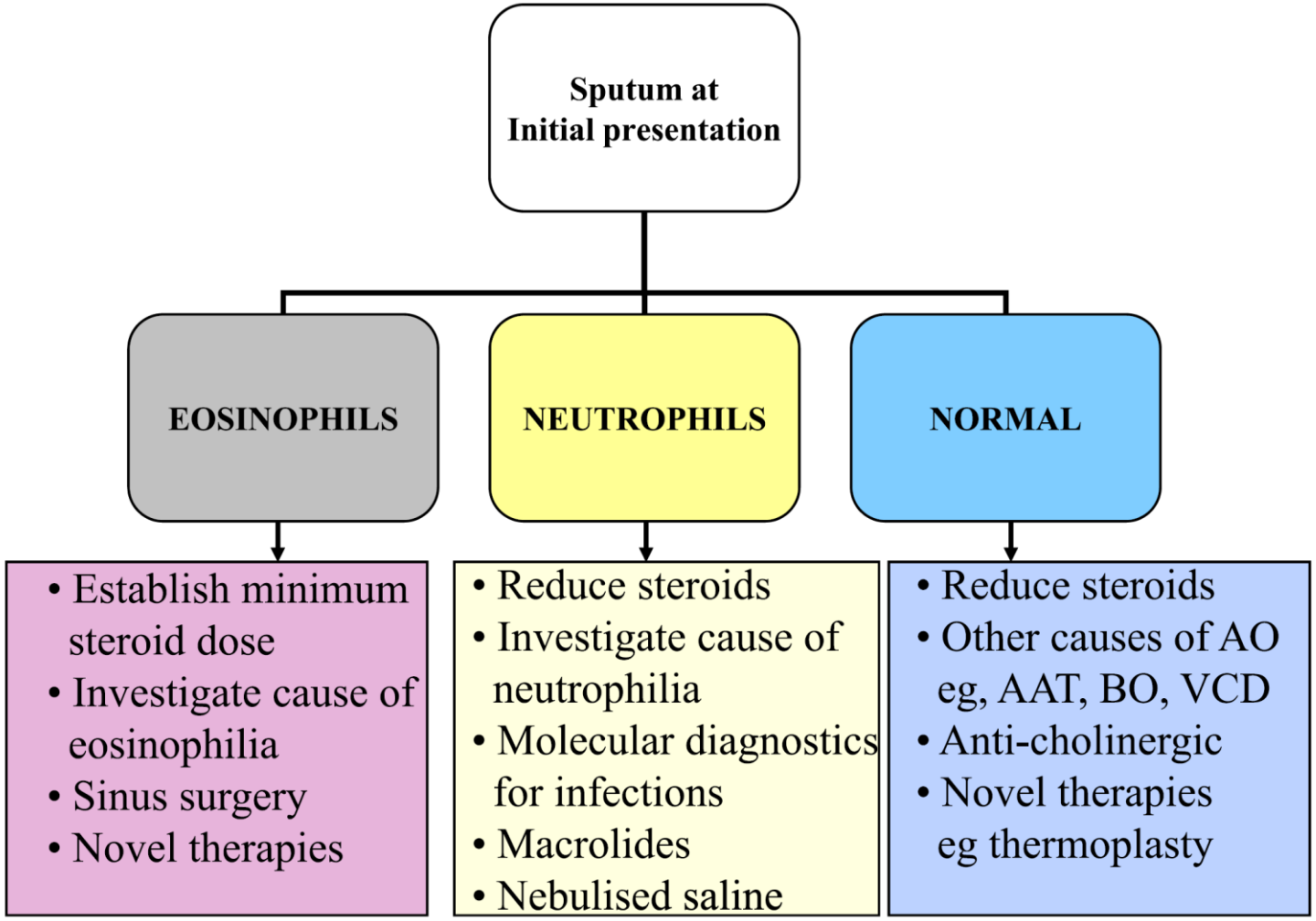




FeNO >30 and/or EBC pH <7.20 identified
88.3% of not-well controlled patients

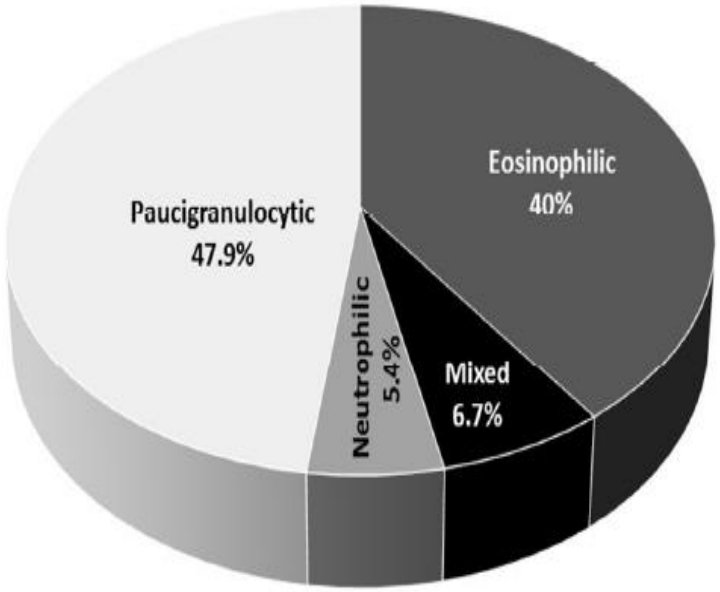
Kostikas K et al., Respir Med 2011; 105: 526-532

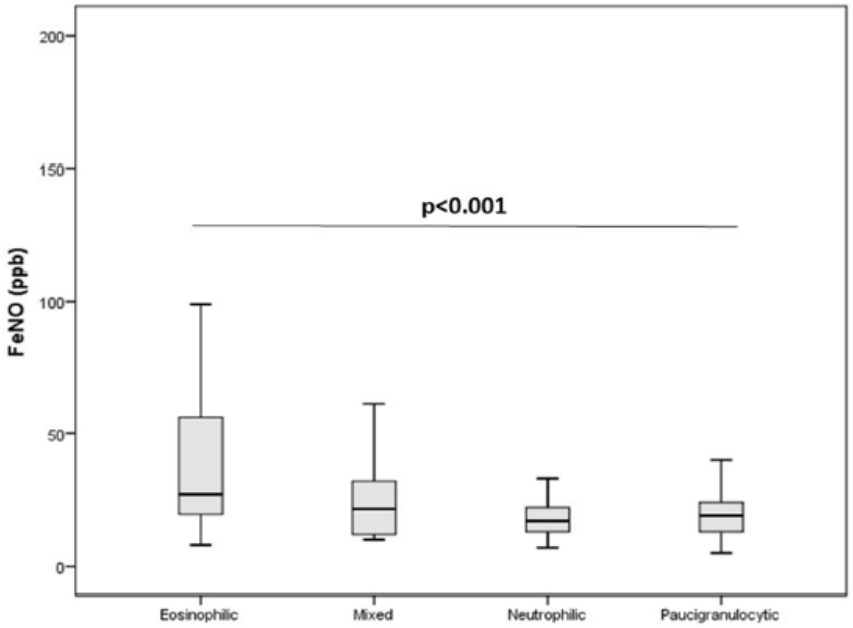
Strategy for asthma management based on sputum cell counts

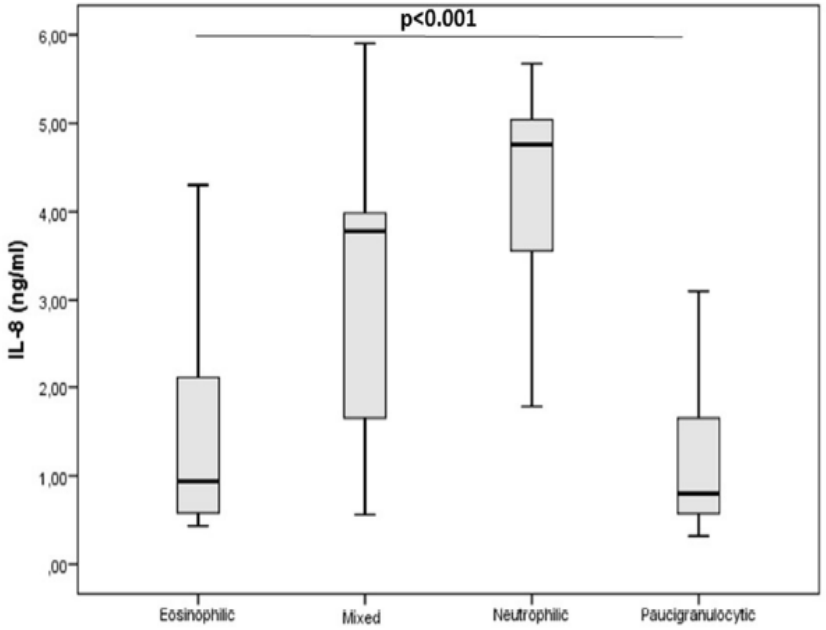


Hargreave FE & Nair P, Chest 2011; 139(6): 1270-3

Sputum Biomarkers in Paucigranulocytic Optimally Treated Asthma







14.8% of patients with paucigranulocytic asthma had poor asthma control

Neutrophilic: ≥60% neutrophils and <3% eosinophils
Eosinophilic: ≥3% eosinophils and <60% neutrophils
Mixed: ≥3% eosinophils and ≥60% neutrophils
Paucigranulocytic: <3% eosinophils and <60% neutrophils

Ntontsi P, Kostikas K, et al., Allergy. 2017 Nov;72(11):1761-1767

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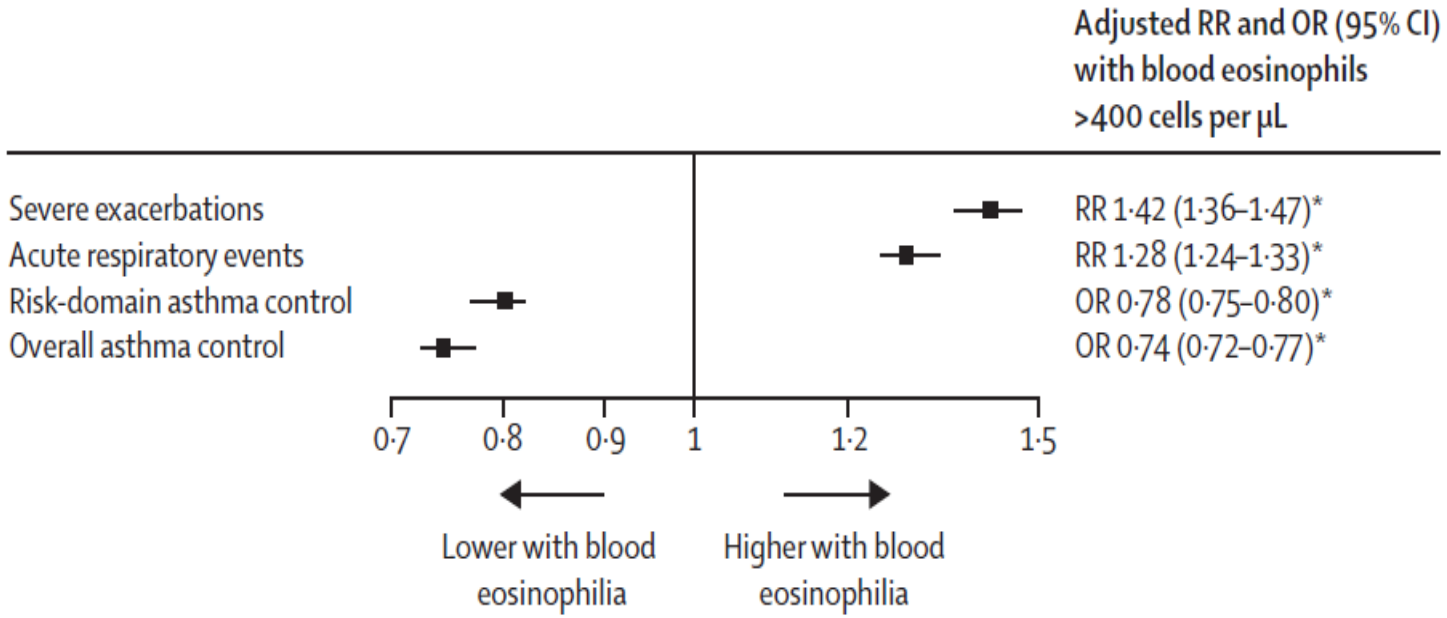
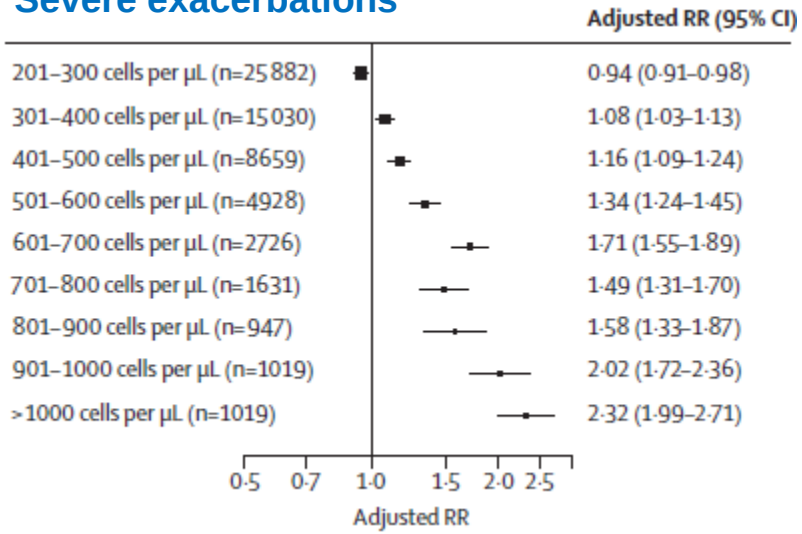
Blood Eosinophils and Asthma Disease Burden

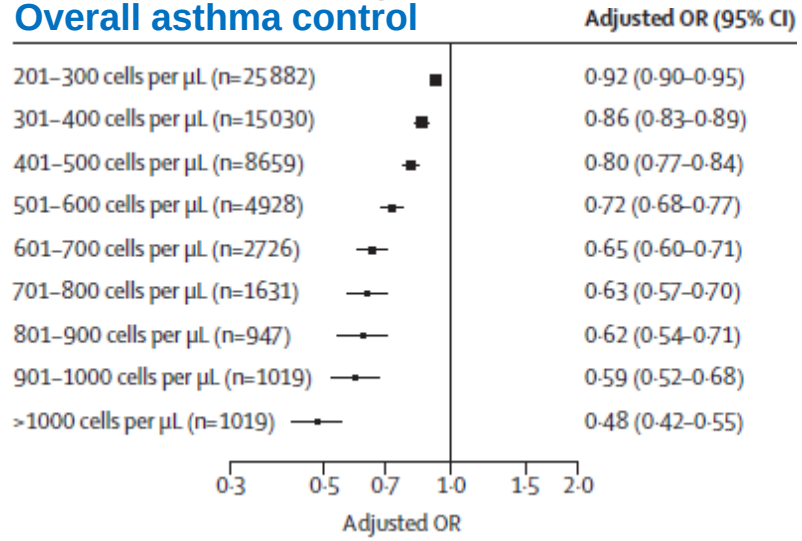


130,547 asthma patients in the UK OPCRD and CPRD (1990–2013)
RR: adjusted rate ratios for severe exacerbations and acute respiratory events
OR: adjusted odds ratios (ORs) for asthma control

Severe exacerbations



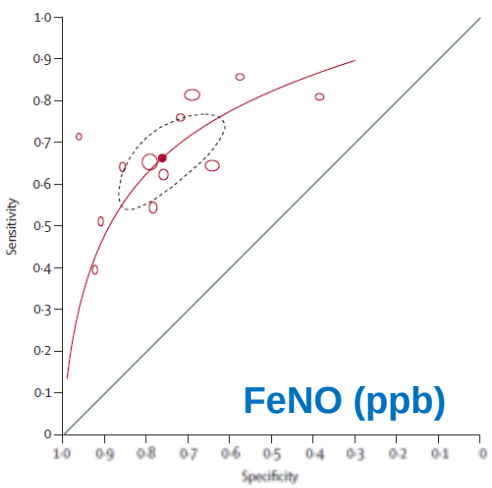
Overall asthma control

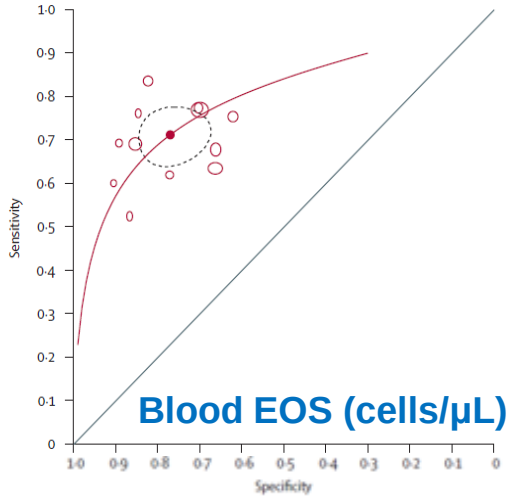


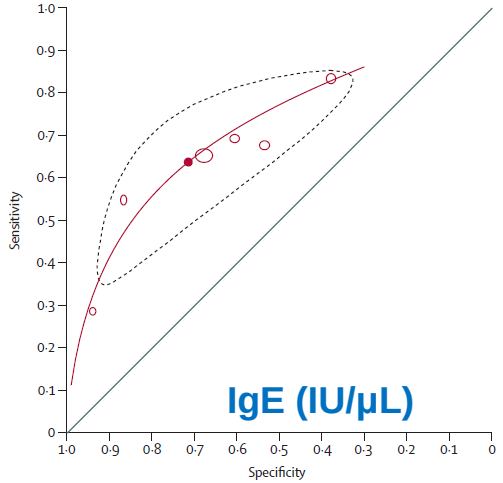
Price DB et al., Lancet Respir Med 2015; 3(11): 849-858

Minimally Invasive Markers for Airway Eosinophilia:
Systematic Review and Meta-Analysis

	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)
Exhaled VOCs	1	1	18	0·98‡
EBC model	1	1	53	0·69‡
Nasal lavage eosinophils	1	1	130	0·88‡

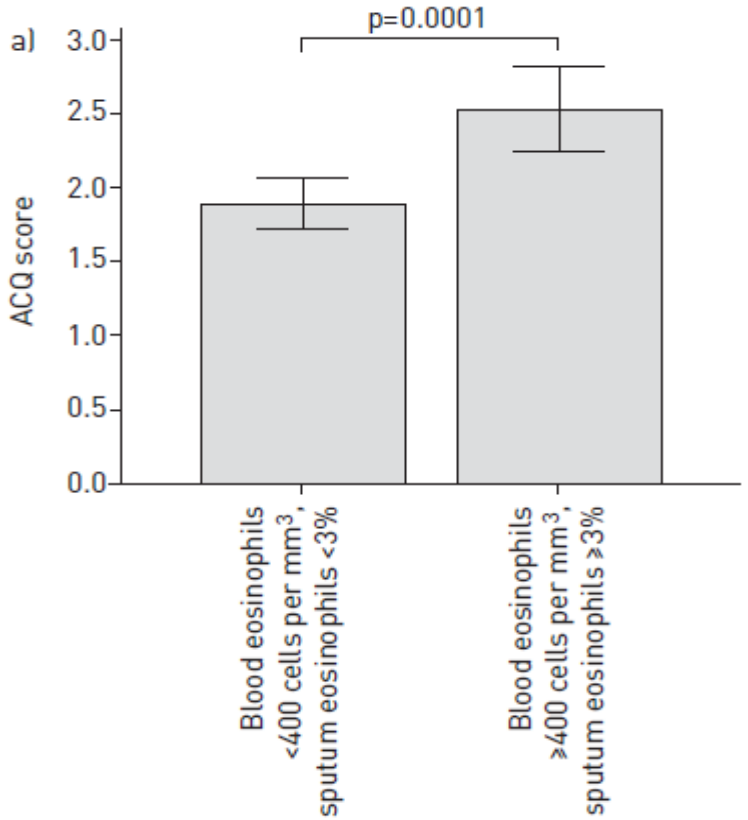


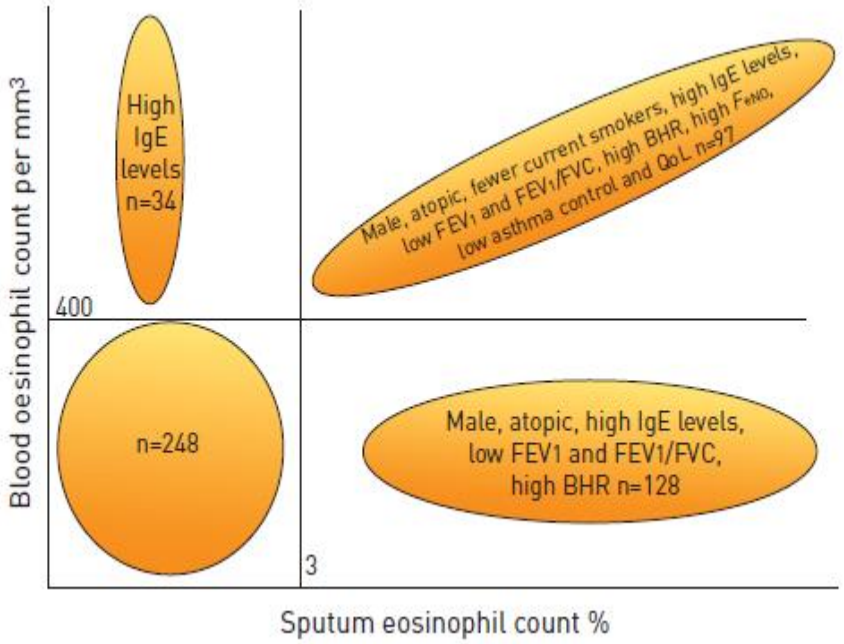




Korevaar DA et al., Lancet Respir Med 2015; 3: 290-300

Local and systemic eosinophilia in uncontrolled asthma





EDITORIAL
ASTHMA

Airway and systemic eosinophilia in asthma: does site matter?

Konstantinos Kostikas, Eleftherios Zervas and Mina Gaga

Schleich FN, Eur Respir J 2014; 44: 97–108; Kostikas K, Eur Respir J 2014; 44: 14–16

Biomarker-driven asthma management: ready for clinical practice?

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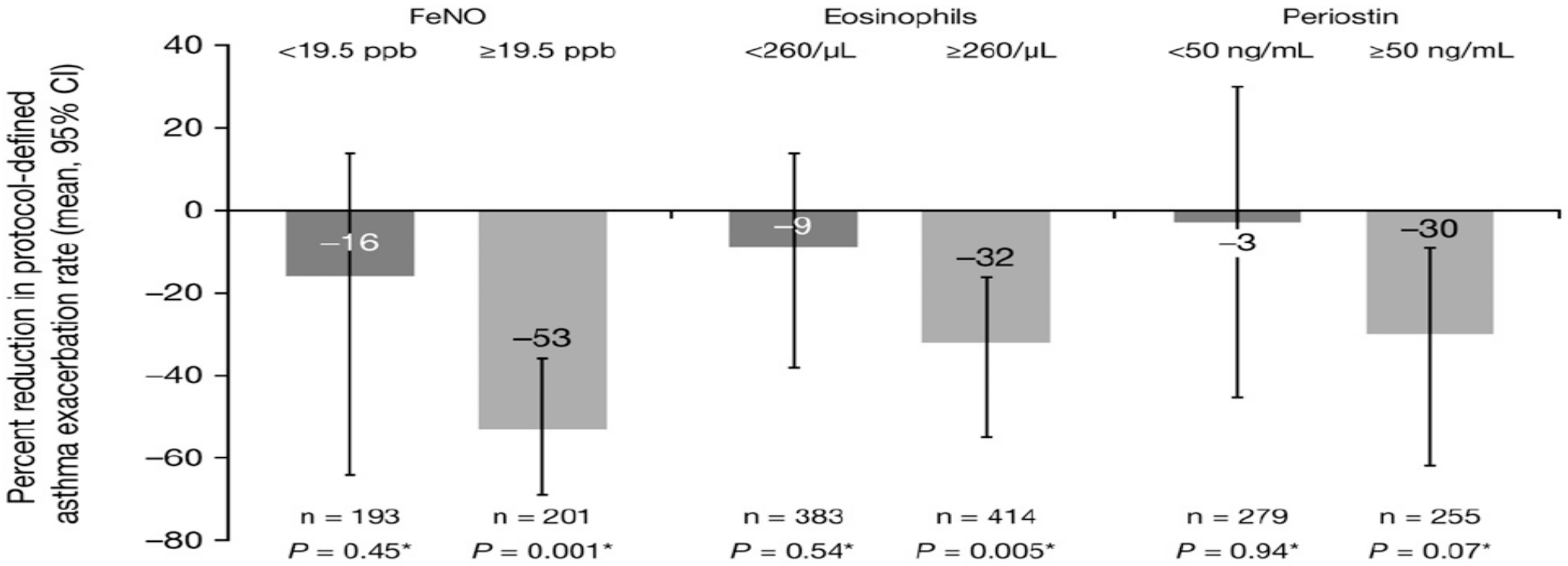
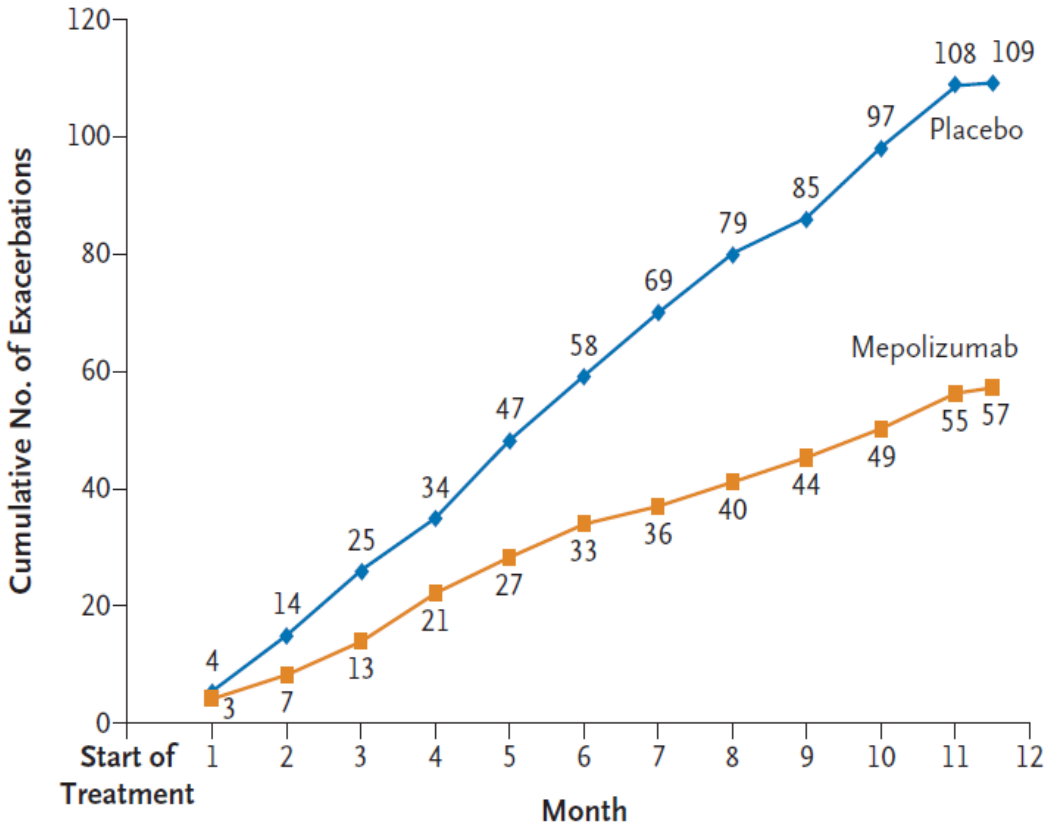
T2 high biomarkers and response to omalizumab (EXTRA)

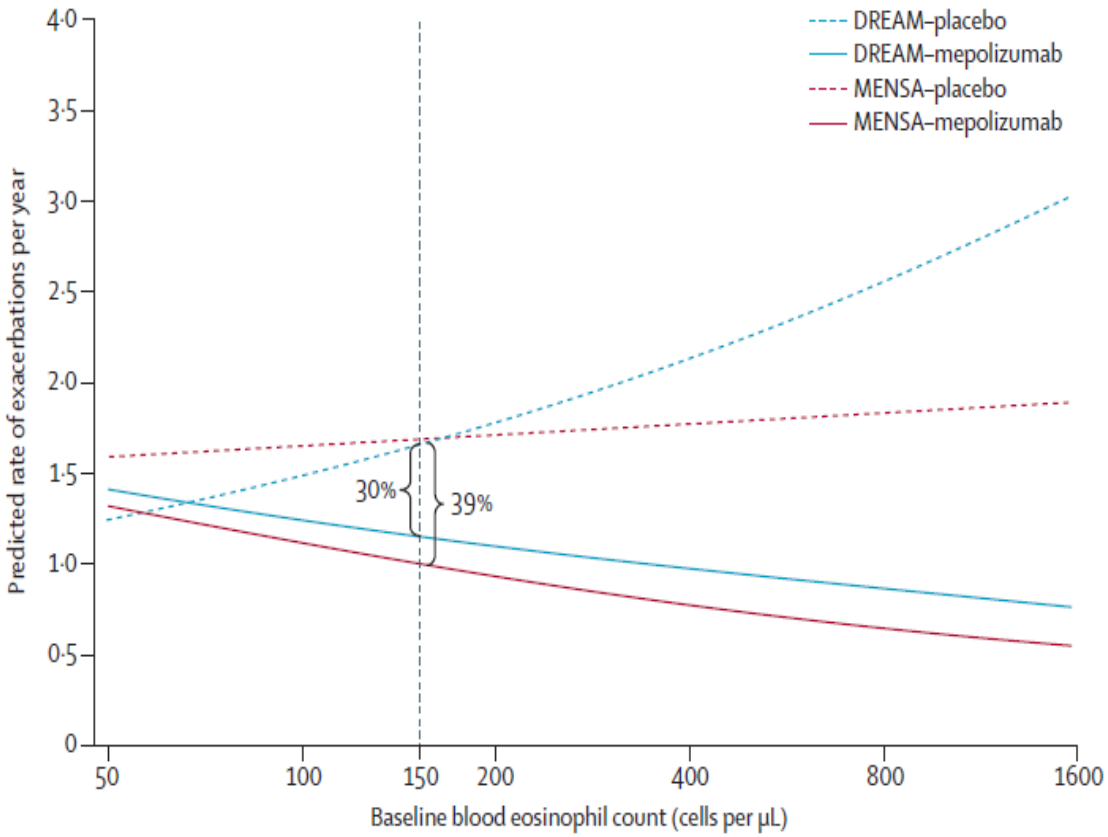


Exacerbation rates						
	Low FeNO at baseline	High FeNO at baseline	Low eosinophils at baseline	High eosinophils at baseline	Low periostin at baseline	High periostin at baseline
Omalizumab	0.60	0.50	0.65	0.70	0.73	0.66
Placebo	0.71	1.07	0.72	1.03	0.72	0.93

Hanania N, AJRCCM 2013; 187(8): 804-11

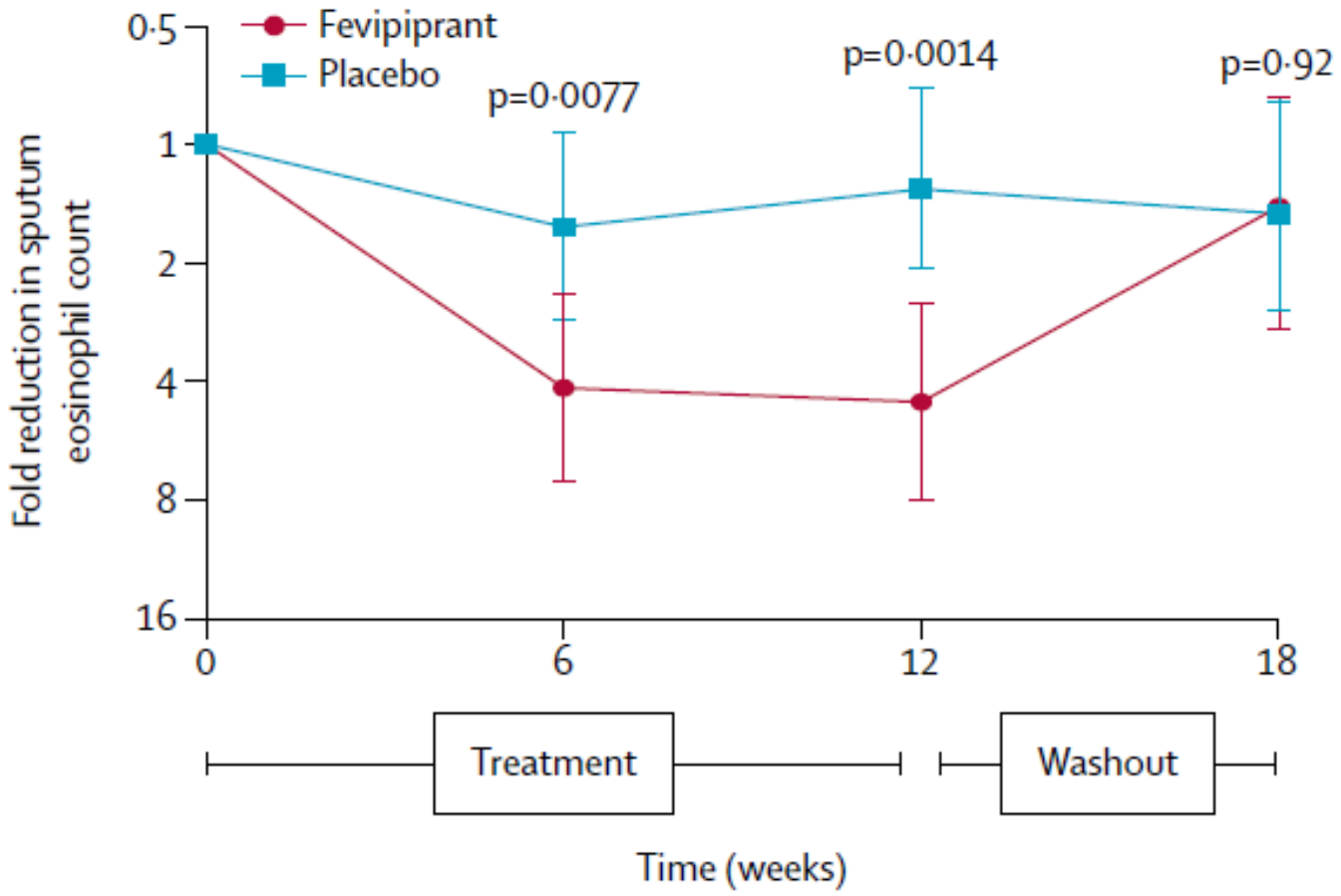
Sputum and blood eosinophils and anti-IL5 response





Haldar P, et al., N Engl J Med 2009;360:973-84; Ortega H et al., Lancet Respir Med 2016; 4: 549–56

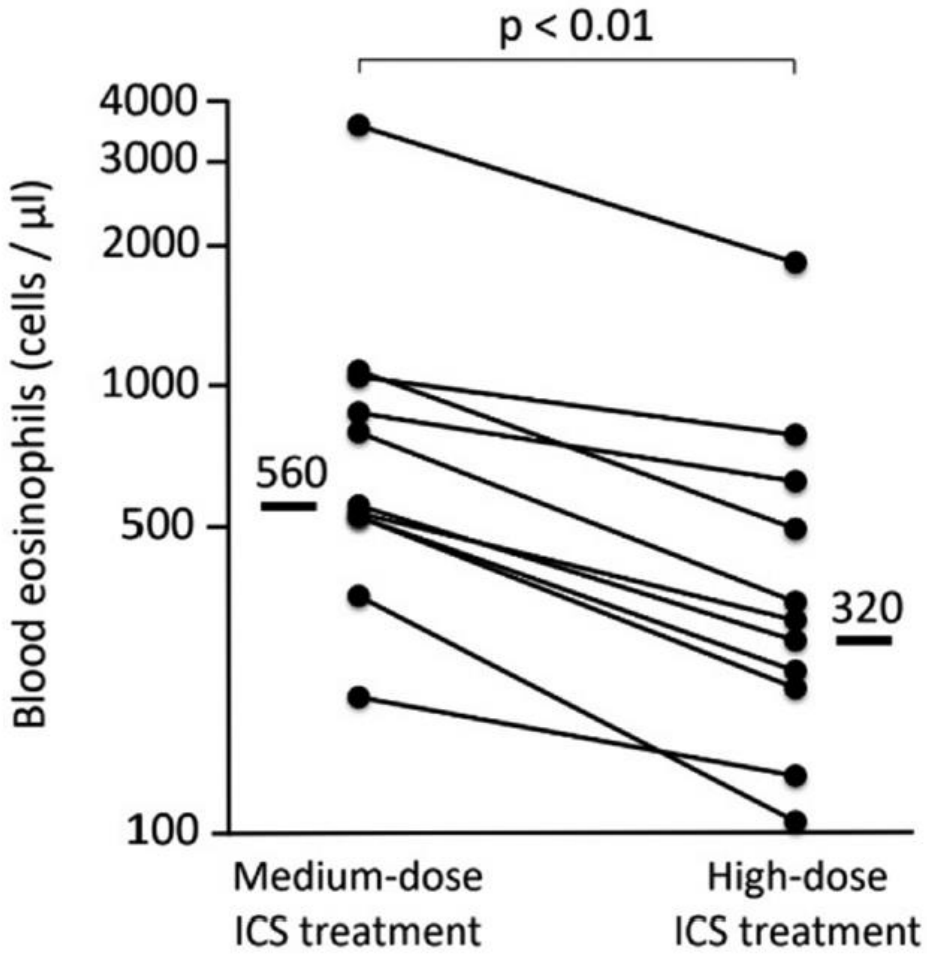
DP2 antagonism and eosinophilic airway inflammation



Fevipiprant is a DP_2 (prostaglandin D2 receptor 2) antagonist under development for severe asthma

Gonem S et al., Lancet Respir Med 2016; 4: 699-707

Impact of increasing ICS dose on blood eosinophils



Lommatzsch M, et al., Thorax 2019;74:417-418.

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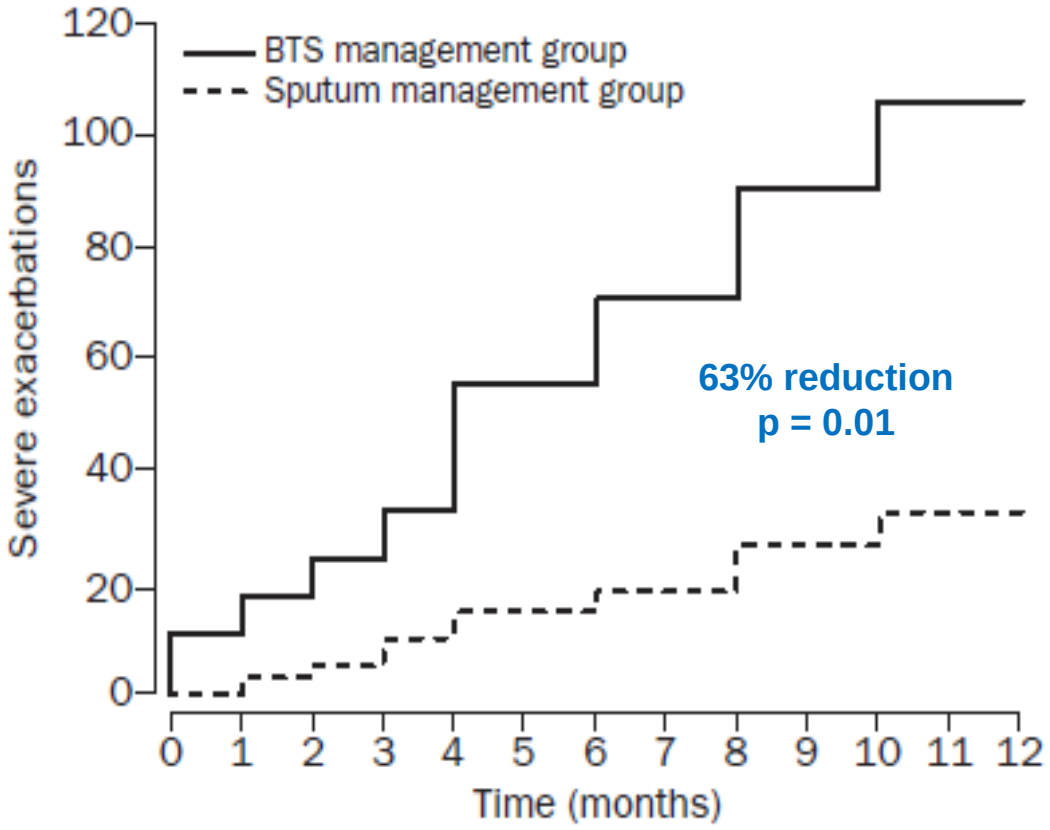
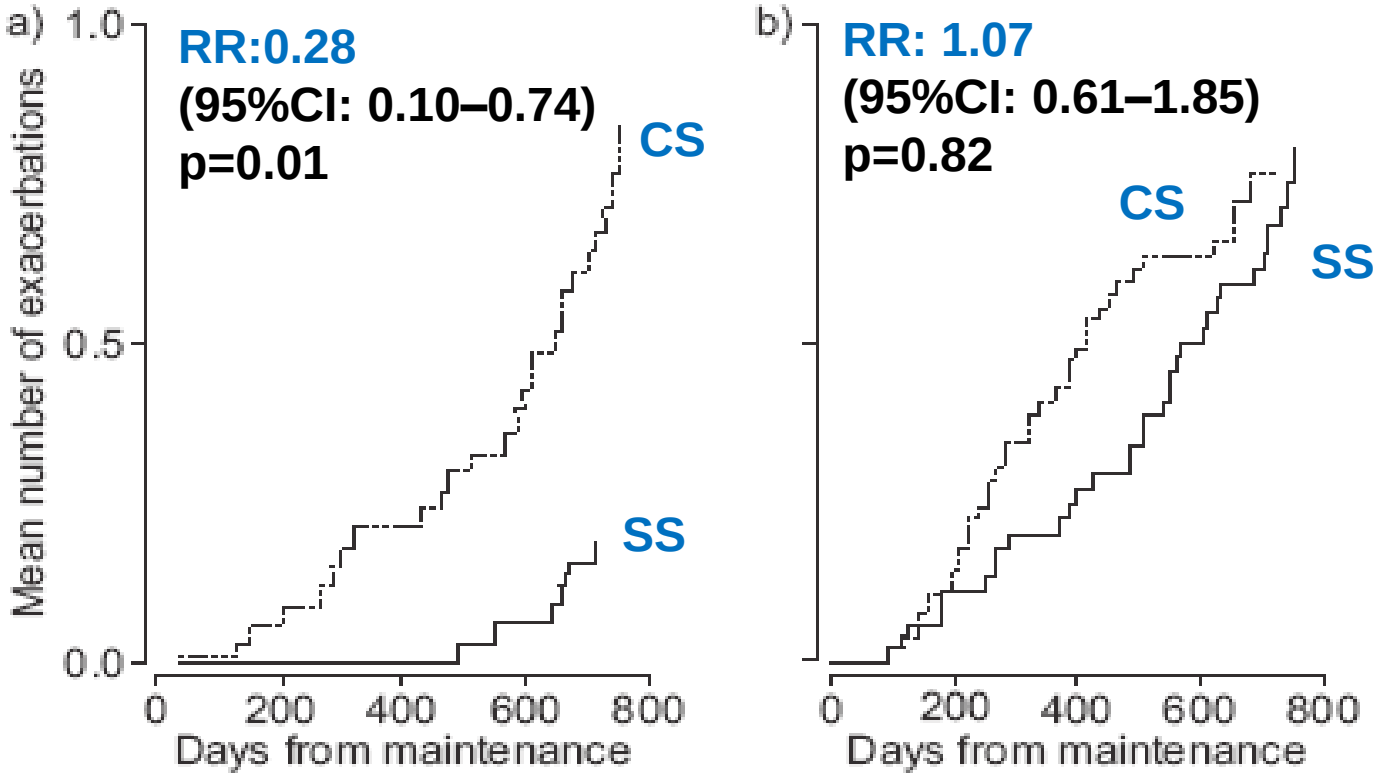
Sputum eosinophils for asthma management



n=74 patients with moderate to severe asthma from hospital clinics
Average daily dose of ICS or oral CS did not differ between the two groups



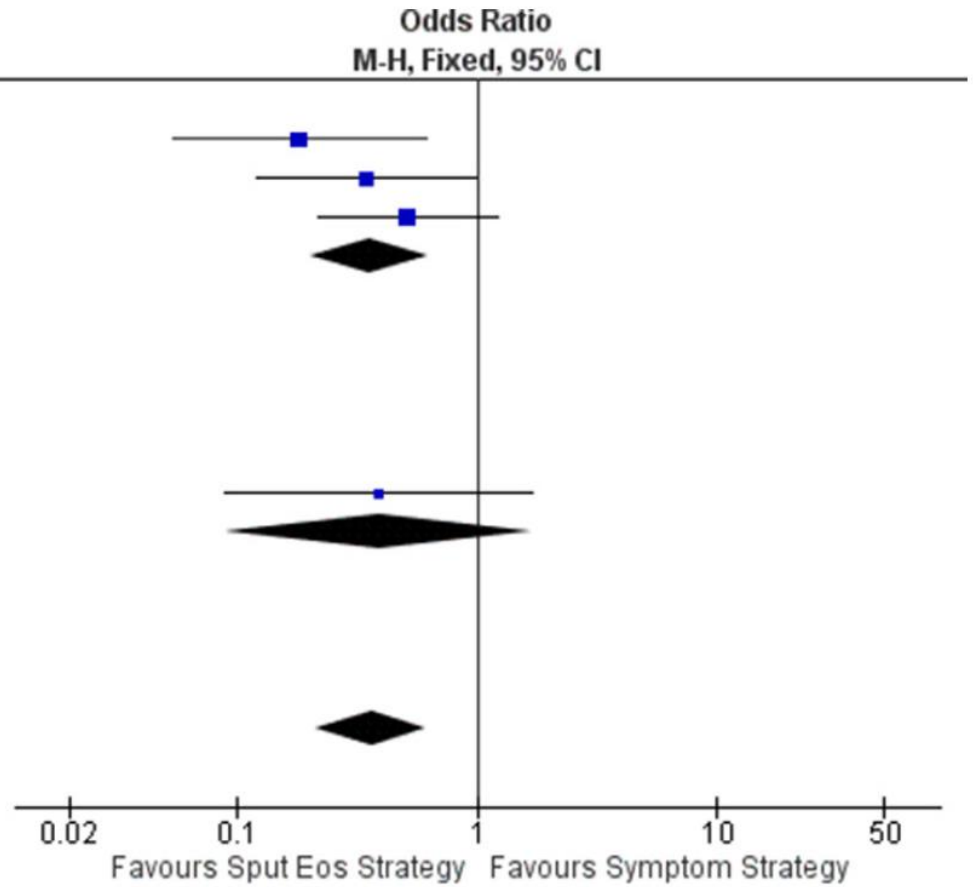
Eosinophilic | **Non-eosinophilic**

n=117 patients with mild to severe asthma
CS: Clinical Strategy, SS: Sputum Strategy (CS + sputum eosinophils ≤2%)

Green RH, Lancet 2002; 360: 1715–21; Jarayam L, Eur Respir J 2006; 27: 483–494

Sputum eosinophils for asthma management

Study or Subgroup	Sputum Eos Strategy Events	Total	Symptom Strategy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Adult						
Chlumsky 2006	8	30	14	21	26.9%	0.18 [0.05, 0.61]
Green 2002 (1)	18	34	26	34	27.2%	0.35 [0.12, 0.98]
Jayaram 2006	26	45	37	51	32.6%	0.52 [0.22, 1.22]
Subtotal (95% CI)		**109**		**106**	**86.7%**	**0.36 [0.20, 0.64]**
Total events	52		77			
Heterogeneity: Chi² = 1.92, df = 2 (P = 0.38); I² = 0%						
Test for overall effect: Z = 3.49 (P = 0.0005)						
1.2.2 Children						
Fleming 2012	21	28	23	26	13.3%	0.39 [0.09, 1.71]
Subtotal (95% CI)		**28**		**26**	**13.3%**	**0.39 [0.09, 1.71]**
Total events	21		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.25 (P = 0.21)						
Total (95% CI)		**137**		**132**	**100.0%**	**0.36 [0.21, 0.62]**
Total events	73		100			
Heterogeneity: Chi² = 1.93, df = 3 (P = 0.59); I² = 0%						
Test for overall effect: Z = 3.70 (P = 0.0002)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%						

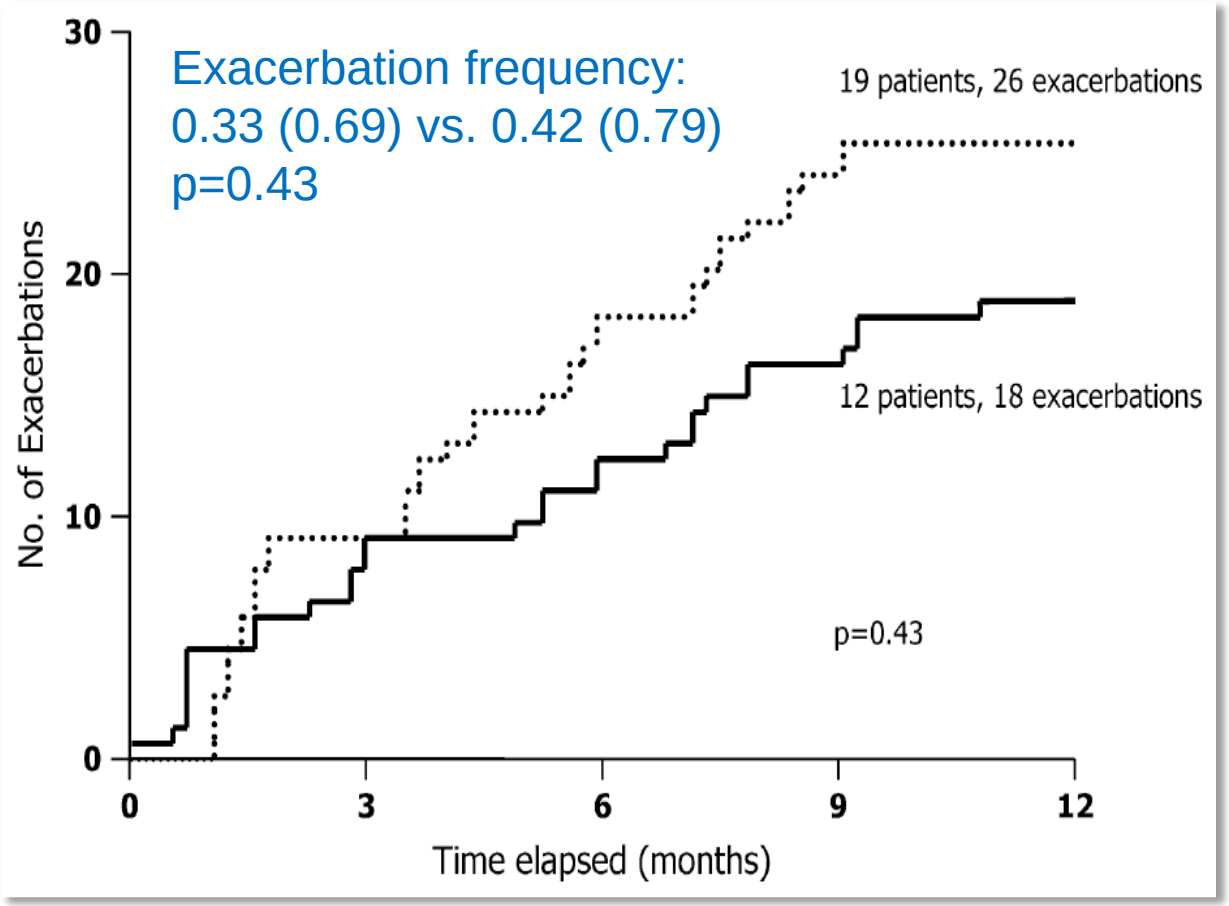


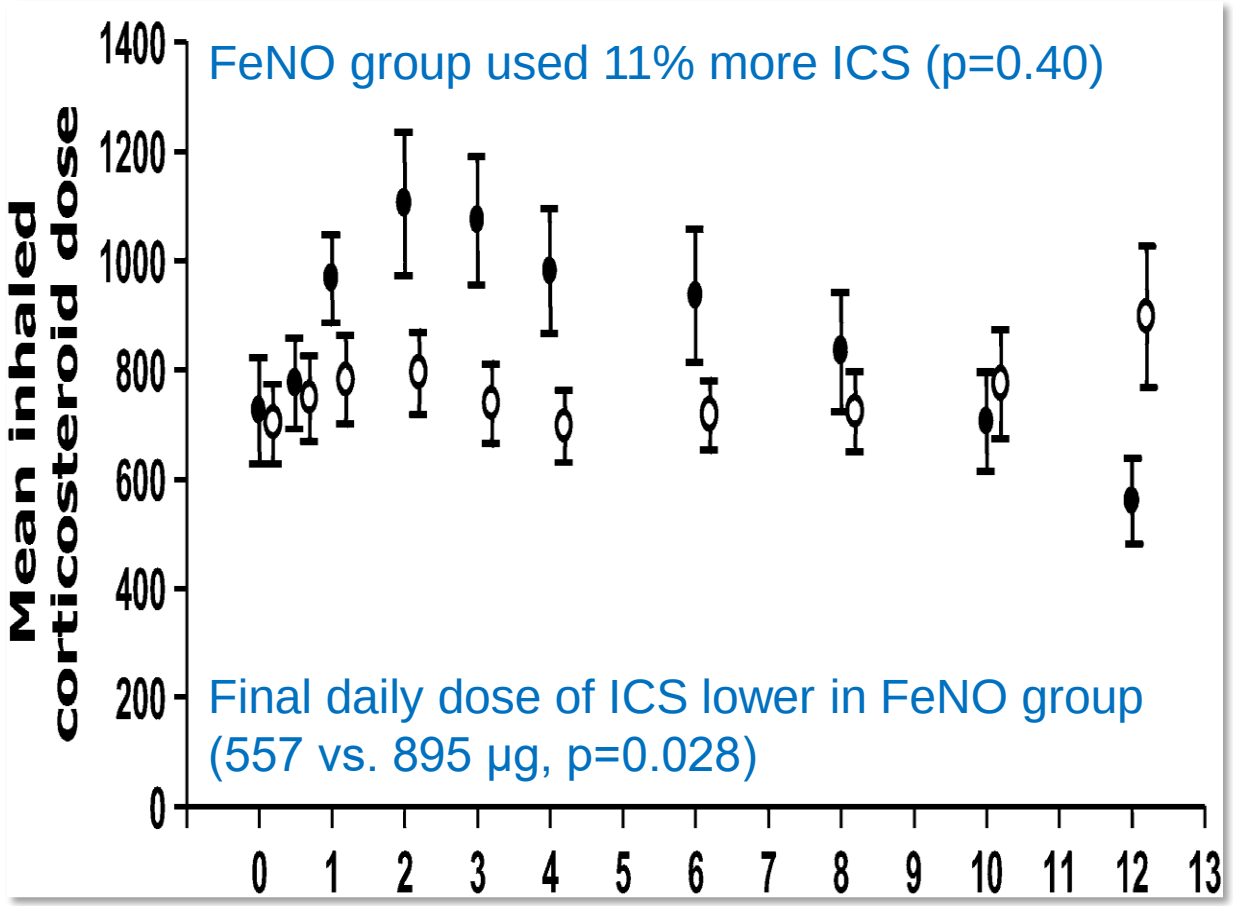
Footnotes

(1) p=0.058

Petsky HL et al., Thorax 2018;0:1–10. doi:10.1136/thoraxjnl-2018-211540

FeNO to Guide Asthma Management





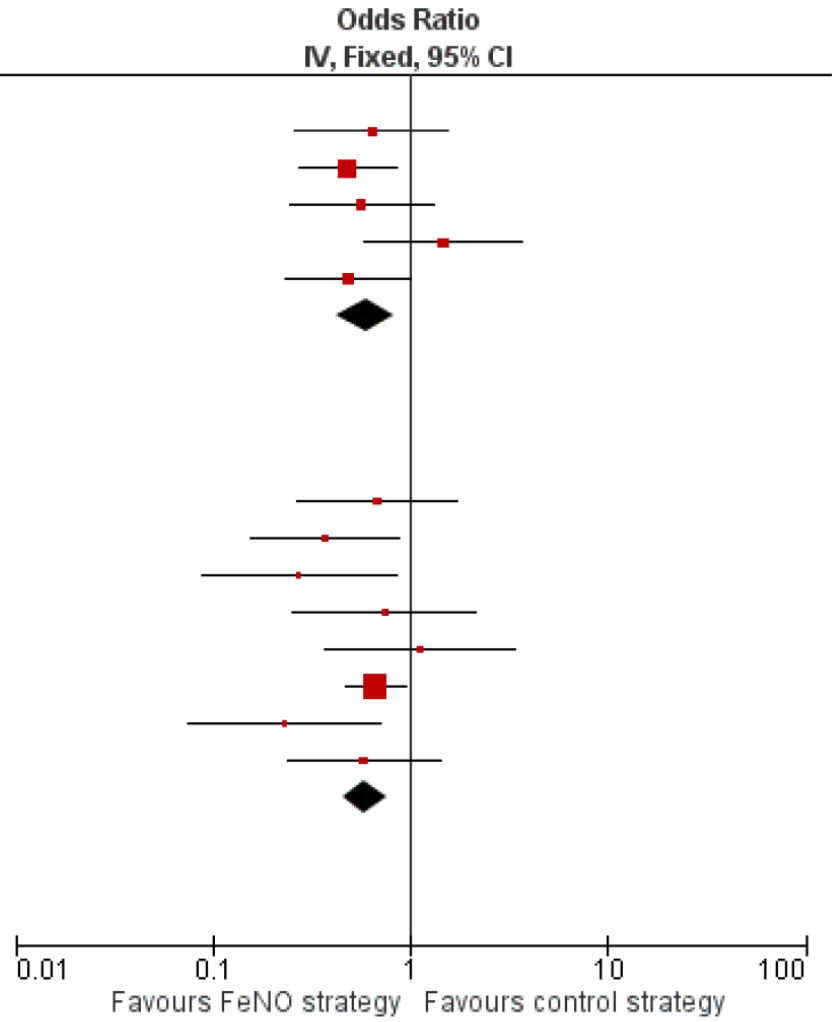
118 pts. mild-to-moderate asthma - FeNO-guided vs. BTS management

Shaw DE et al., Am J Respir Crit Care Med Vol 176. pp 231–237, 2007

FeNO for asthma management

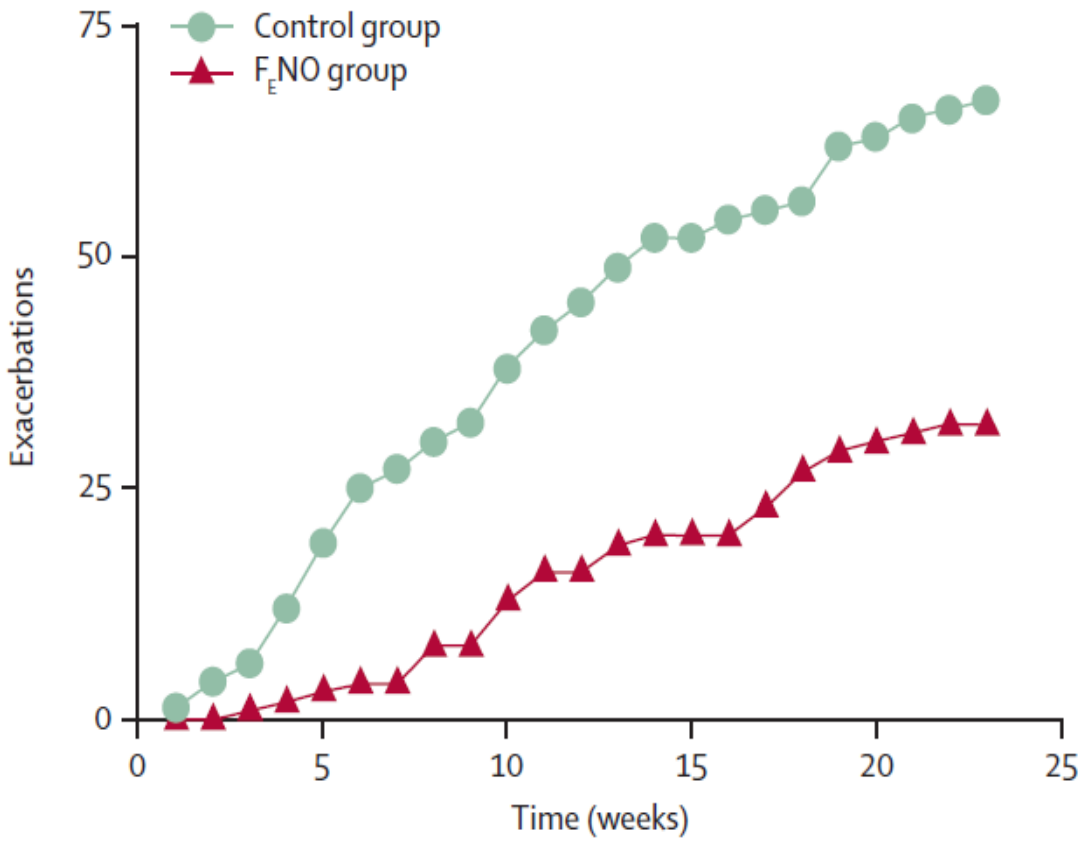
Study or Subgroup	log[Odds Ratio]	SE	FeNO strategy Total	Control strategy Total	Weight	Odds Ratio IV, Fixed, 95% CI
1.1.1 Adults						
Honkoop 2014	-0.4463	0.4546	189	203	14.3%	0.64 [0.26, 1.56]
Powell 2011	-0.7344	0.2926	111	109	34.4%	0.48 [0.27, 0.85]
Shaw 2007	-0.5746	0.4267	58	60	16.2%	0.56 [0.24, 1.30]
Smith 2005	0.3863	0.4697	46	48	13.4%	1.47 [0.59, 3.69]
Syk 2013	-0.7244	0.3679	93	88	21.8%	0.48 [0.24, 1.00]
Subtotal (95% CI)			**497**	**508**	**100.0%**	**0.60 [0.43, 0.84]**
Heterogeneity: Chi² = 4.61, df = 4 (P = 0.33); I² = 13%						
Test for overall effect: Z = 3.00 (P = 0.003)						
1.1.2 Children						
de Jongste 2008	-0.383	0.4757	75	72	7.6%	0.68 [0.27, 1.73]
Peirsman 2014a	-0.9985	0.4454	49	50	8.6%	0.37 [0.15, 0.88]
Petsky 2015	-1.302	0.5763	31	32	5.1%	0.27 [0.09, 0.84]
Pijnenburg 2005a	-0.3011	0.5463	42	47	5.7%	0.74 [0.25, 2.16]
Pike 2013a	0.1069	0.5667	44	46	5.3%	1.11 [0.37, 3.38]
Szefler 2008a	-0.411	0.1776	276	270	54.2%	0.66 [0.47, 0.94]
Verini 2010a	-1.4663	0.5746	32	32	5.2%	0.23 [0.07, 0.71]
Voorend-van Bergen 2015	-0.5432	0.456	92	89	8.2%	0.58 [0.24, 1.42]
Subtotal (95% CI)			**641**	**638**	**100.0%**	**0.58 [0.45, 0.76]**
Heterogeneity: Chi² = 7.54, df = 7 (P = 0.38); I² = 7%						
Test for overall effect: Z = 4.11 (P < 0.0001)						

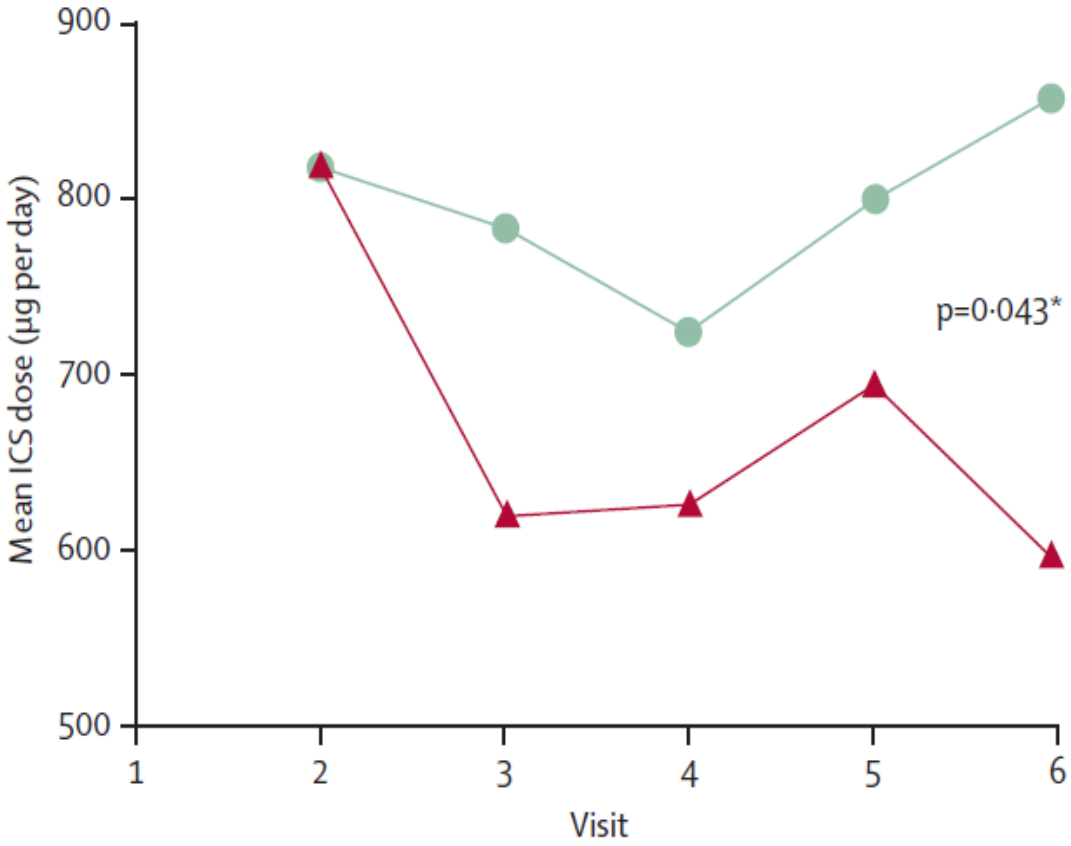
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%



Petsky HL et al., Thorax 2018;0:1–10. doi:10.1136/thoraxjnl-2018-211540

FeNO strategy in Pregnancy

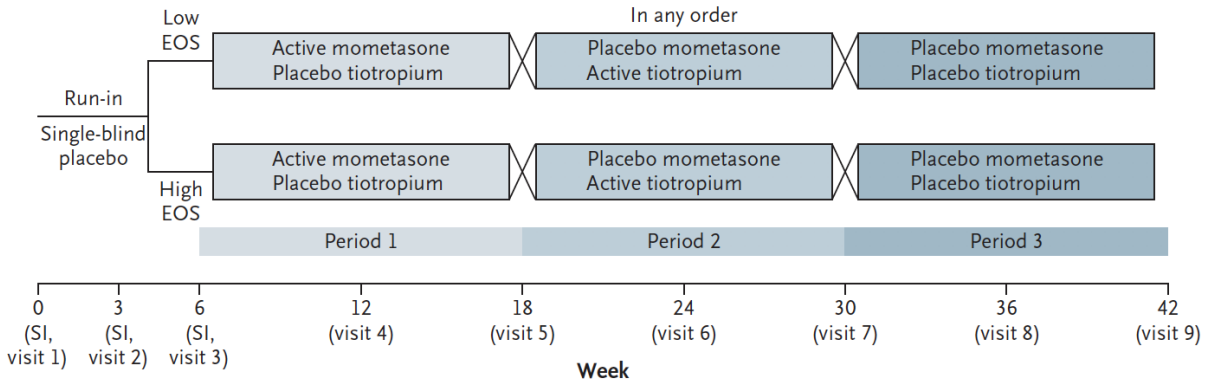




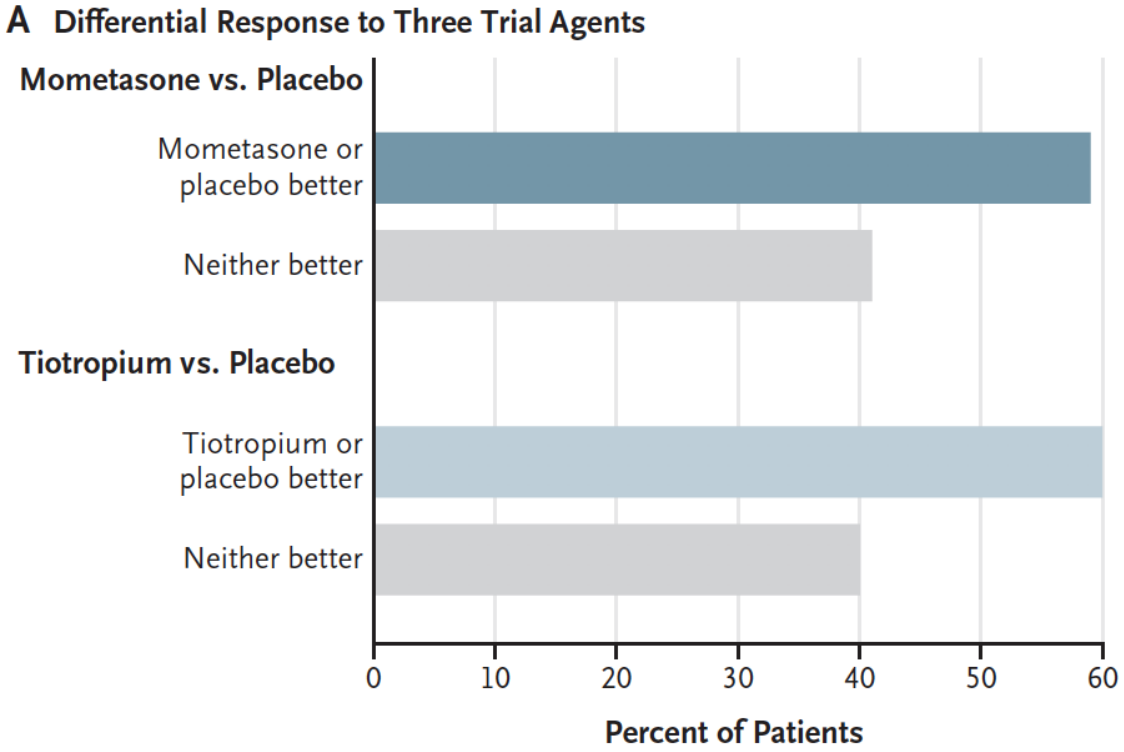
Exacerbations: 0.288 vs 0.615 exacerbations per pregnancy
Incidence rate ratio (IRR) **0.496**, 95% CI 0.325-0.755; p=0.001 (**NNT = 6**)
FeNO group: ↑ quality of life & ↓ neonatal hospitalizations

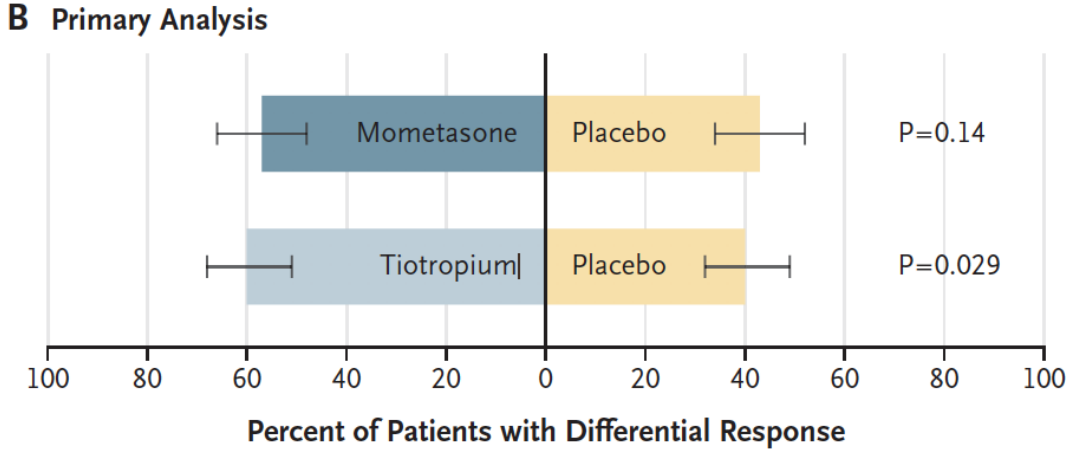
Powel H et al., Lancet 2011; 378: 983–90

ICS or TIO for Mild Asthma with Low Sputum EOS (SIENA)



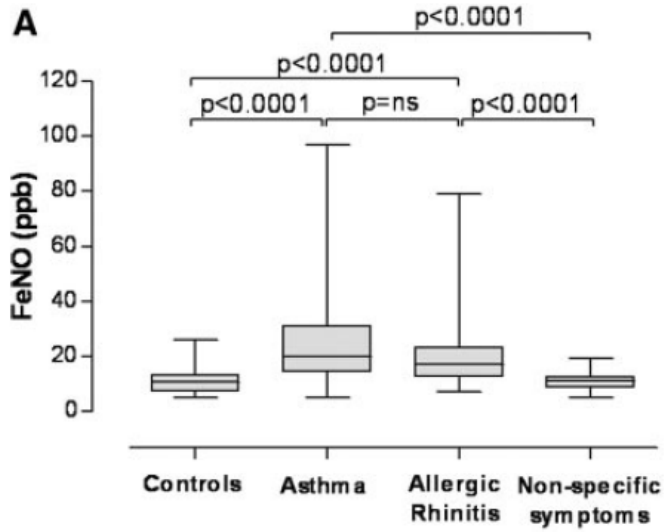
73% were classified as having a low eosinophil level (<2%)

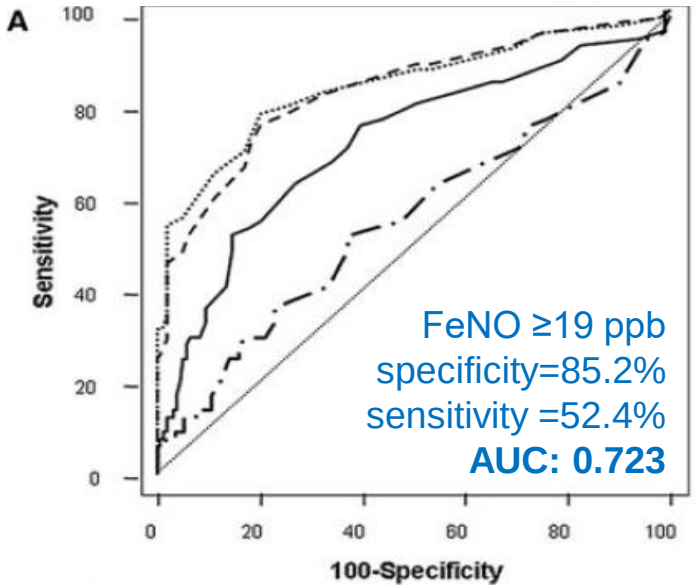




Lazarus SC et al, N Engl J Med 2019

FeNO for asthma diagnosis in young adults





Cut-off Points	All		Nonsmokers		Smokers	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
> 30 ppb	25.4 (15.3–37.9)	94.9 (90.1–97.8)	41.0 (25.6–57.9)	94.3 (88.1–97.9)	4.8 (1.6–14.4)	96.0 (86.3–99.4)
> 25 ppb	30.2 (19.2–43.0)	91.7 (86.2–95.5)	46.2 (30.1–62.8)	91.5 (84.5–96.0)	6.2 (3.7–21.2)	92.0 (80.7–97.7)
> 20 ppb	49.2 (36.4–62.1)	85.3 (78.7–90.4)	64.1 (47.2–78.8)	84.9 (76.6–91.1)	25.0 (9.8–46.7)	86.0 (73.3–94.2)
> 15 ppb	68.3 (55.3–79.4)	66.0 (58.0–73.4)	79.5 (63.5–90.7)	65.1 (55.2–74.1)	50.0 (29.1–70.9)	68.0 (53.3–80.5)
> 10 ppb	85.7 (74.6–93.2)	34.6 (27.2–42.6)	94.9 (82.6–99.2)	30.2 (21.7–39.9)	70.8 (48.9–87.3)	44.0 (30.0–58.7)

Asthma vs. Other ALL
Combined Asthma or Rhinitis vs. Other
Asthma vs. Other (excl. Rhinitis)
Asthma vs. Rhinitis

Kostikas K. et al., Chest 2008; 133: 906-13

FeNO Predicts Control in DTT Asthma

- 102 consecutive patients with suboptimal asthma control received SFC 50/500 for 1 month - then, those who remained uncontrolled received oral CS for 1 month

- 53 patients (52%) gained control

- Those who achieved control were more likely to have
  - **positive skin results (60.4 % vs. 34 %; p = 0.01)**
  - **positive bronchodilator test (57.1 % vs. 35.8 %; p = 0.02)**
  - **PEFR variability ≥20% (71.1 % vs. 49.1 %; p = 0.04)**

- FeNO ≥30 ppb demonstrated a sensitivity of 87.5% and a specificity of 90.6% for the identification of responsive asthmatics (AUC=0.925)

Pérez de Llano LA et al., Eur Respir J 2010; 35: 1221–1227

ΔFeNO and Asthma Control: Smoking & Allergic Rhinitis

Non Smokers

- A single measurement of FeNO >45 ppb was related to poor asthma control (NPV 88%)
- FeNO reduction by 40% was associated with asthma control optimization (NPV 79%)
- FeNO increase by 30% was associated with loss of control (NPV 82%)

Smoking asthmatics

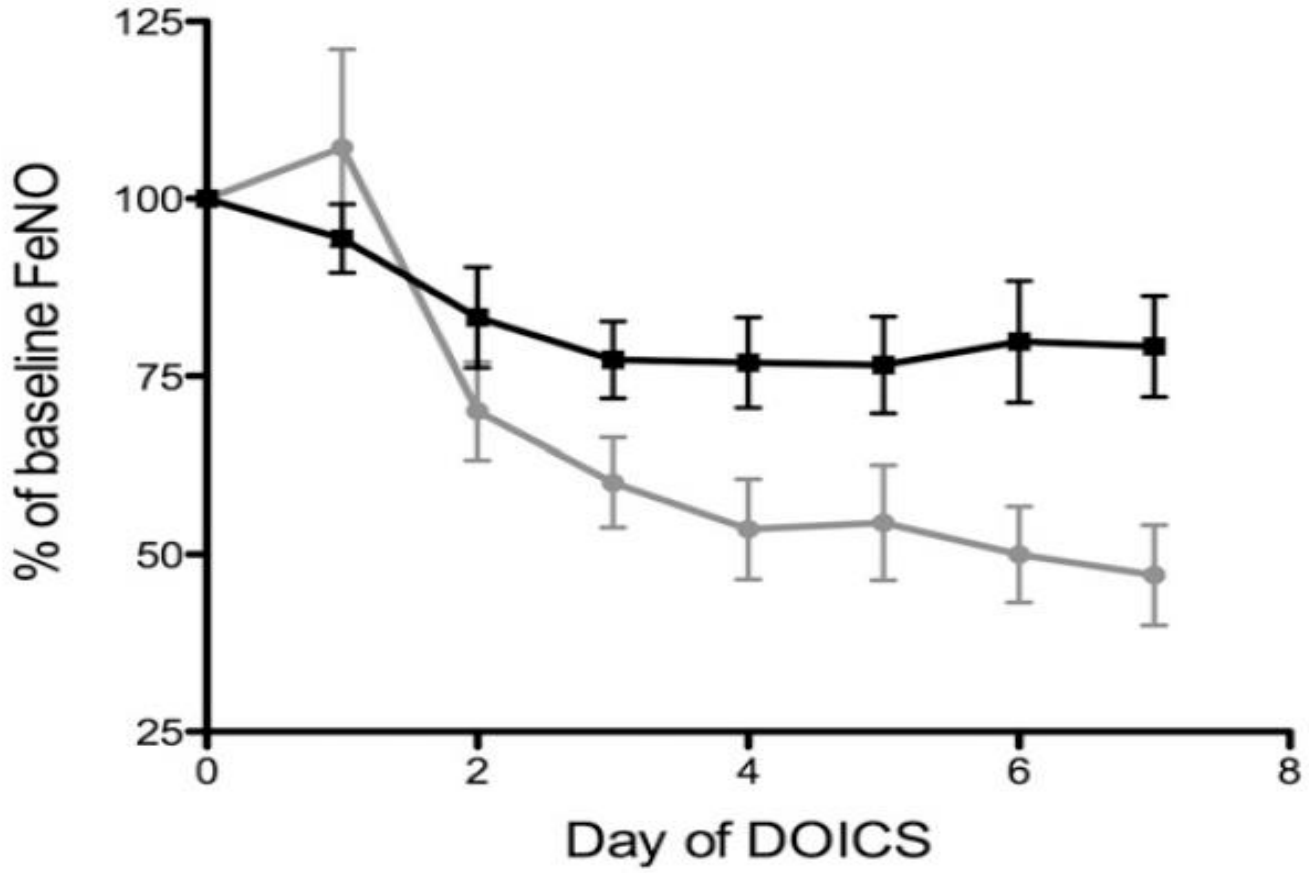
- FeNO decrease >20% precluded asthma control improvement (NPV 72%)
- FeNO increase <30% was not associated with asthma control deterioration (NPV 84%)

	Optimal cut-off point	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	AUC (95% CI)	p-value
Asthma without rhinitis#	>30%	0.83 (0.64–0.94)	0.87 (0.68–0.97)	0.89	0.81	0.893 (0.777–0.961)	<0.0001
Asthma with rhinitis¶	>40%	0.72 (0.53–0.86)	0.92 (0.74–0.98)	0.92	0.71	0.786 (0.657–0.884)	<0.0001

The optimal cut-off points represent values with the best combination of sensitivity and specificity. PPV: positive predictive value; NPV: negative predictive value; AUC: area under the receiver operating characteristic curve. #: n=52; ¶: n=58.

Michils A, Eur Respir J 2008; 31: 539–546; Michils A, Eur Respir J 2009; 33: 1295–1301; Papaioannou AI, … and Kostikas K, Eur Respir J 2009; 34(4): 1006-1007

ICS Nonadherence: FeNO Suppression Test

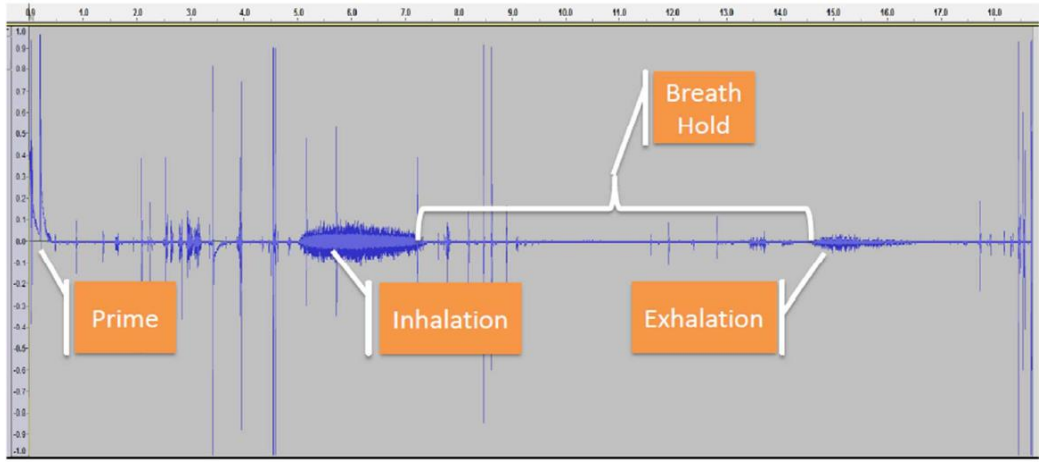


Adherent patients (n=13; black squares)
Nonadherent patients (n=9; gray circles)

Difficult asthma patients (GINA Steps 4 & 5) with an elevated FENO (>45 ppb)
Recruited as adherent (ICS prescription filling >80%) or nonadherent (filling <50%)
DOICS: directly observed inhaled corticosteroid treatment

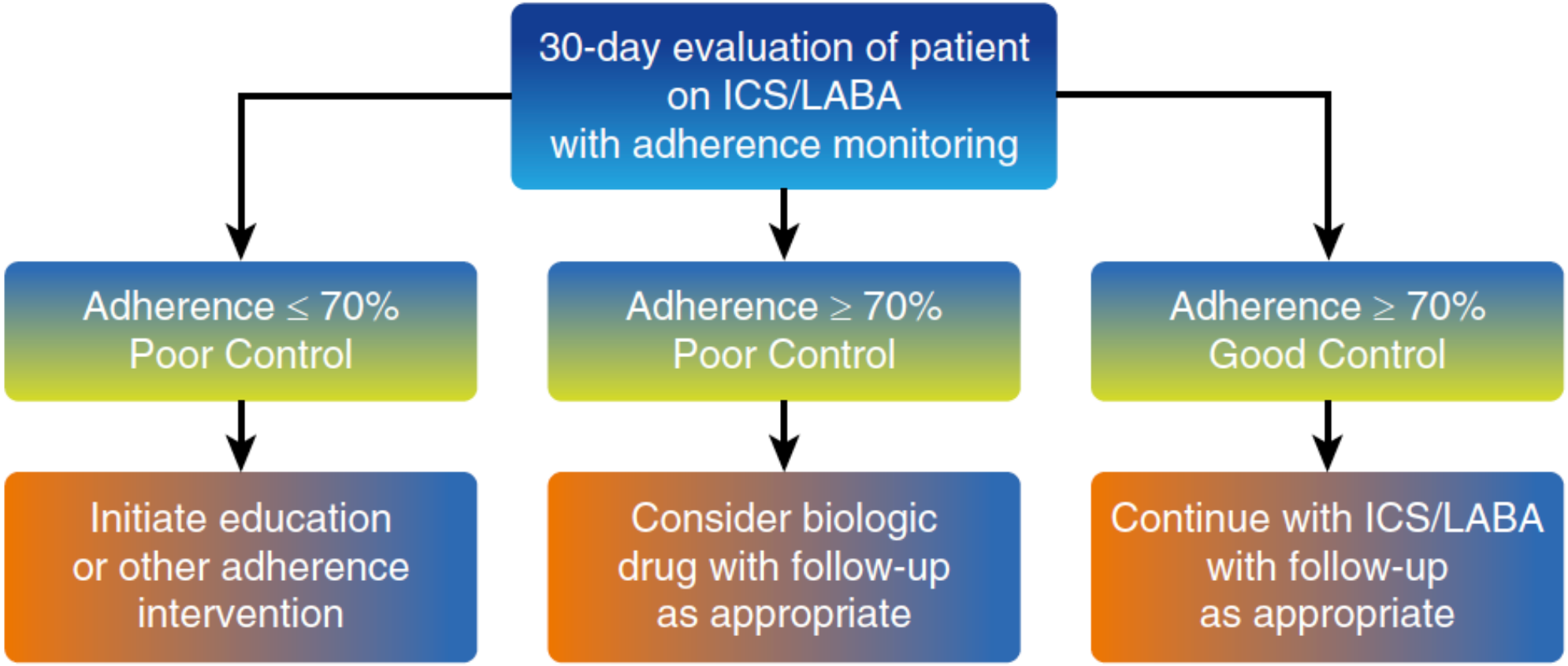
McNicholl DM et al., Am J Resp Crit Care Med 2012; 186(11): 1102-8

ICS Nonadherence: remote monitoring & FeNO Suppression Test



Heaney L et al., Am J Resp Crit Care Med 2019; 199(4): 454-464

Assessment protocol in consideration of biologic therapy



ICS = inhaled corticosteroid; LABA = long-acting b-agonist

Bender BG, AJRCCM 2019. 199(4): 400-402 (Editorial)

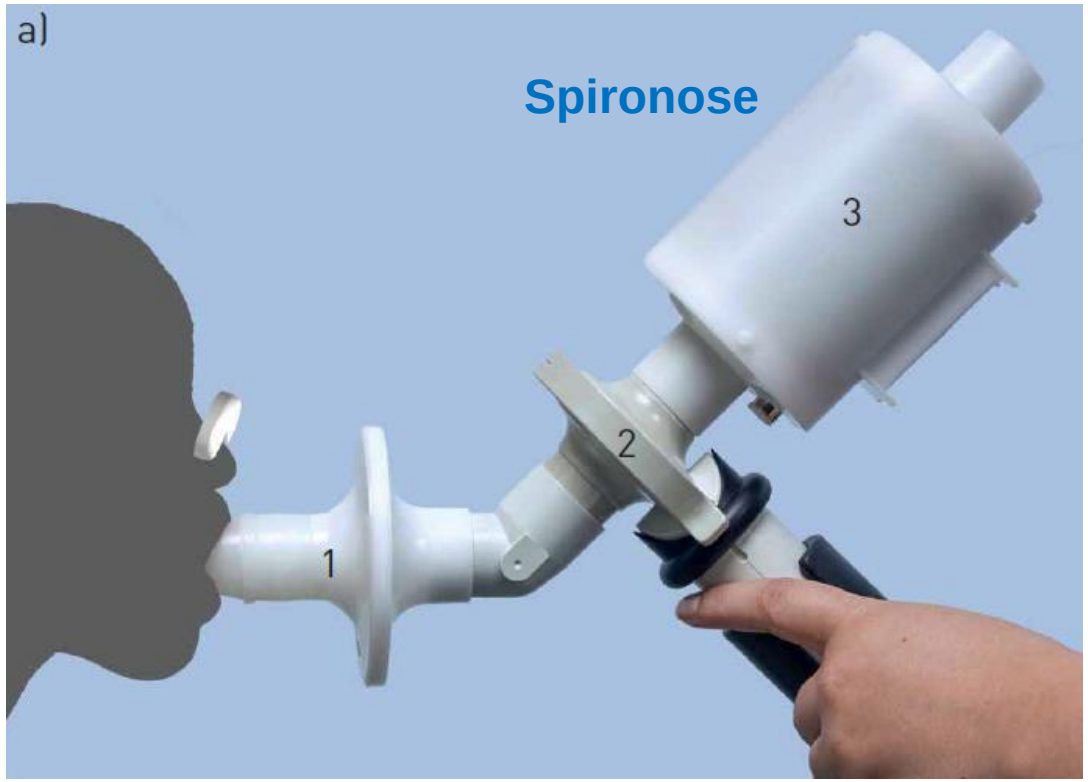
Biomarker-driven asthma management: ready for clinical practice?

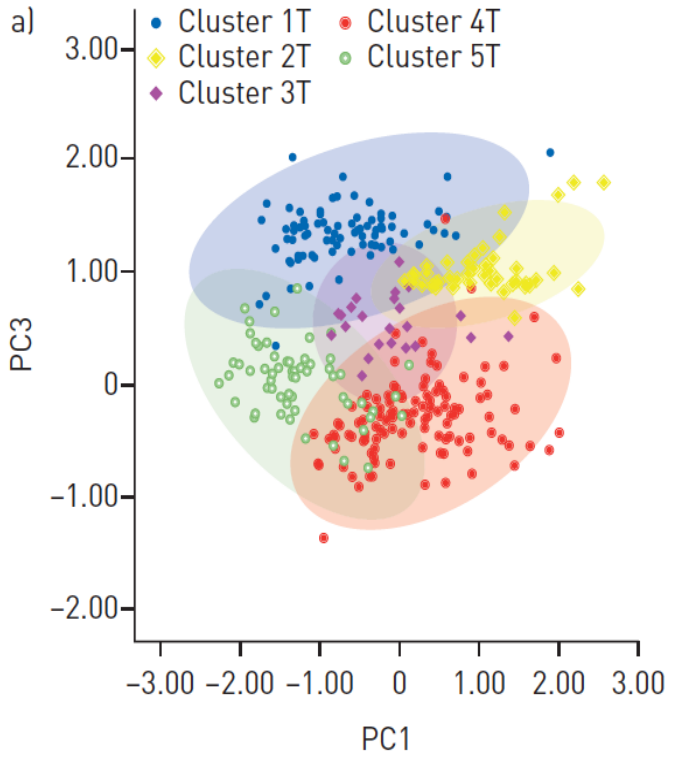
- The hype around biomarkers
- Blood vs. sputum vs. exhaled air
- Biomarkers and biologics
- Management of DTT asthma
- **The way forward**

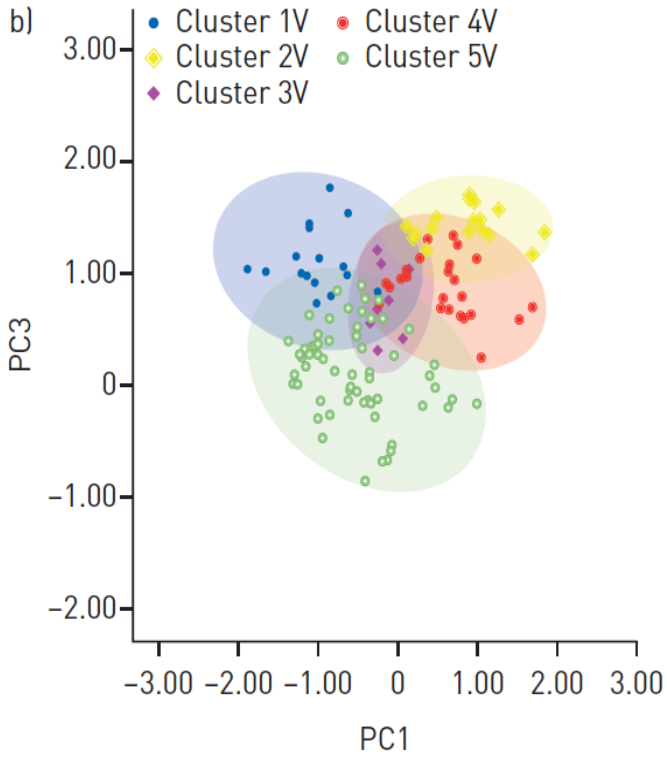
Open issues with current biomarkers

- **Sputum cell counts require a dedicated laboratory**
- **FeNO is confounded by ICS, smoking and atopy – but cost-effective (?)**
- **Blood eosinophils are a modest predictor of airways eosinophilia**
- **Cut-offs need to be refined**
- **Longitudinal studies including appropriate populations are needed**

Breathomics: Clinical and inflammatory phenotyping in chronic airway diseases irrespective of the diagnostic label

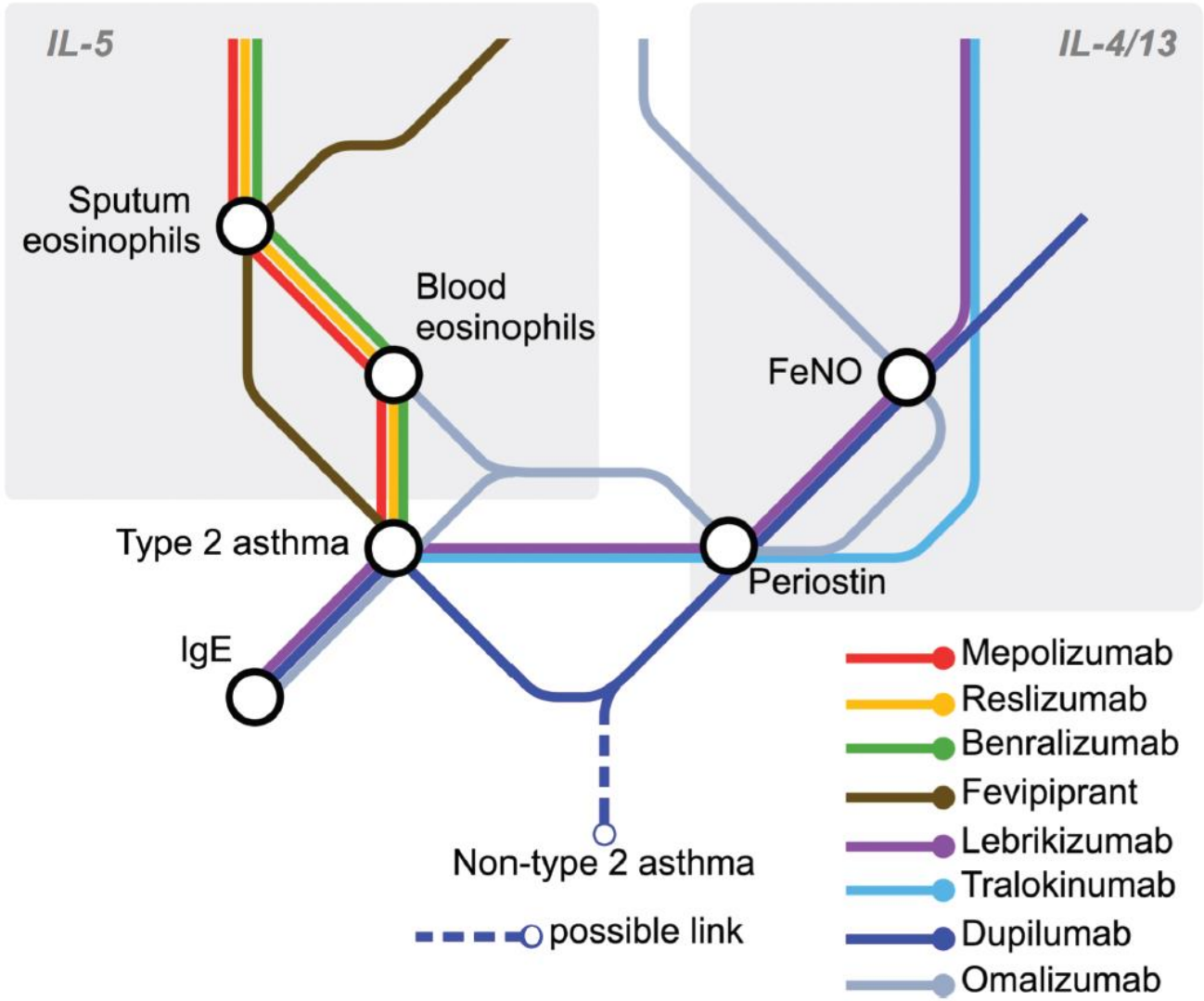






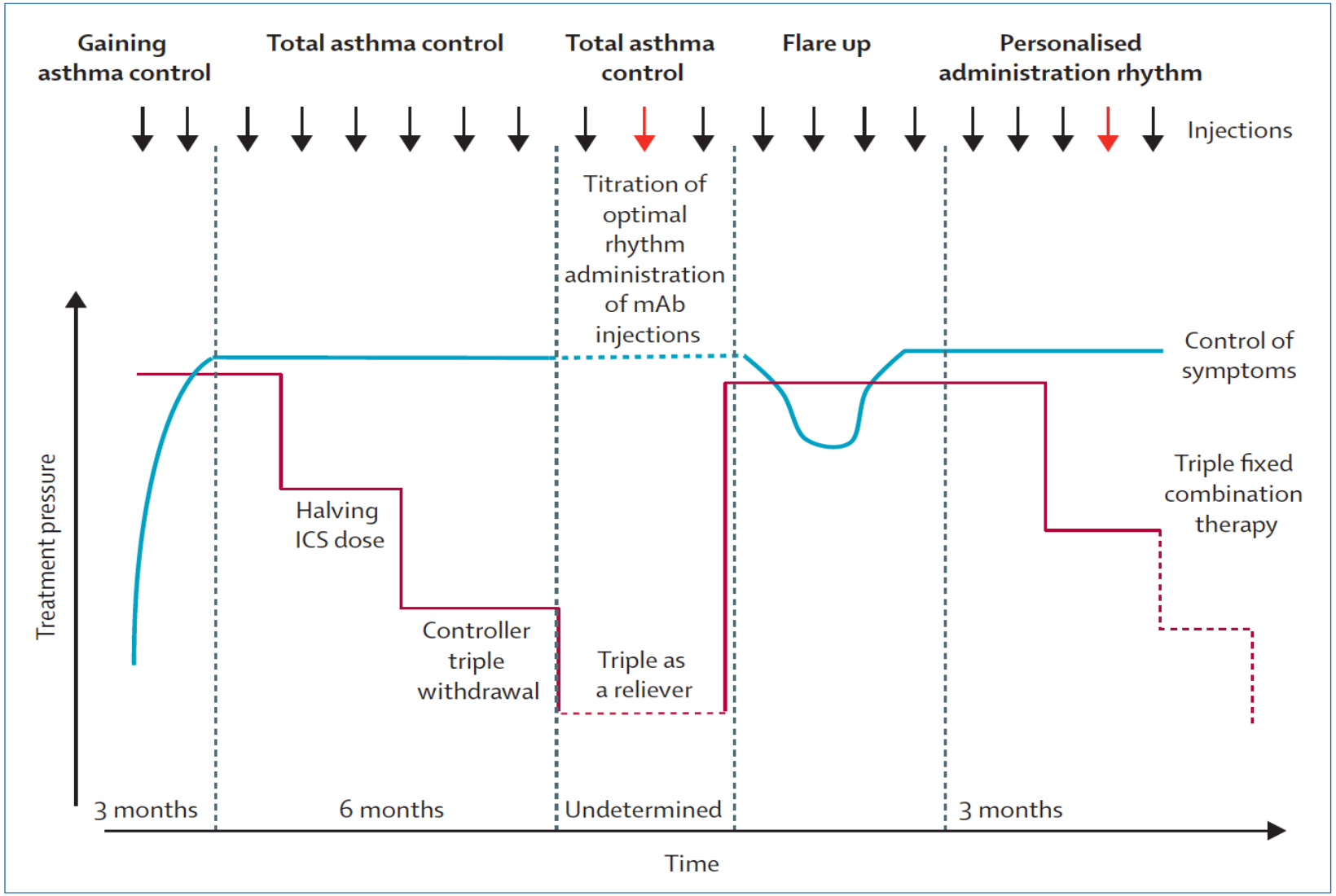
de Vries D et al., Eur Respir J 2018; 51: 1701817

Emerging biomarker networks for targeted treatment in asthma



Fricker M et al, Respirology 2017; 22: 430-42

Managing asthma in the era of biological therapies



Bardin P, et al, Lancet Res Med 2017; 5(5): 376–378

Would we ever consider that without biomarkers?