Clinical Implications of Asthma Endotypes and Phenotypes

Dennis K. Ledford, MD, MPH
Ellsworth and Mabel Simmons Professor of Allergy/Immunology
Morsani COM and James A. Haley VA Hospital
University of South Florida

Competing Interests

- Funded research: AstraZeneca, Genentech,Novartis
- Consultant: AstraZeneca, BioCrys, Genentech, GSK
- Speaker Bureau: AstraZeneca, Genentech, GSK, Novartis, Sanofi Regeneron
- Legal Opinions: Anaphylaxis, asthma death, indoor mold exposure
- Royalties: UpToDate, Taylor Francis (Allergens and Allergen Immunotherapy)
- Organization: AAAAI (Ask the Expert)
- Data Safety Committee: Galderma (α- IL31, nemolizumab)

Learning Objectives

- Define, compare and contrast the spectrum of phenotypes and endotypes in asthma
- Discuss treatment options based upon asthma phenotypes utilizing randomized trials and available biomarkers
- Review a potential algorithm to help select asthma therapy based upon phenotypes

Outline

- Definitions
- Examples of phenotypes and endotypes
- Phenotype- and biomarker-based treatment algorithm
- General overview of treatment options
- Special thank you to Juan Carlos Cardet, MD, MPH

Definitions

Phenotype

- An individual's observed characteristics that result from gene-environment interactions (e.g., atopy, obesity)

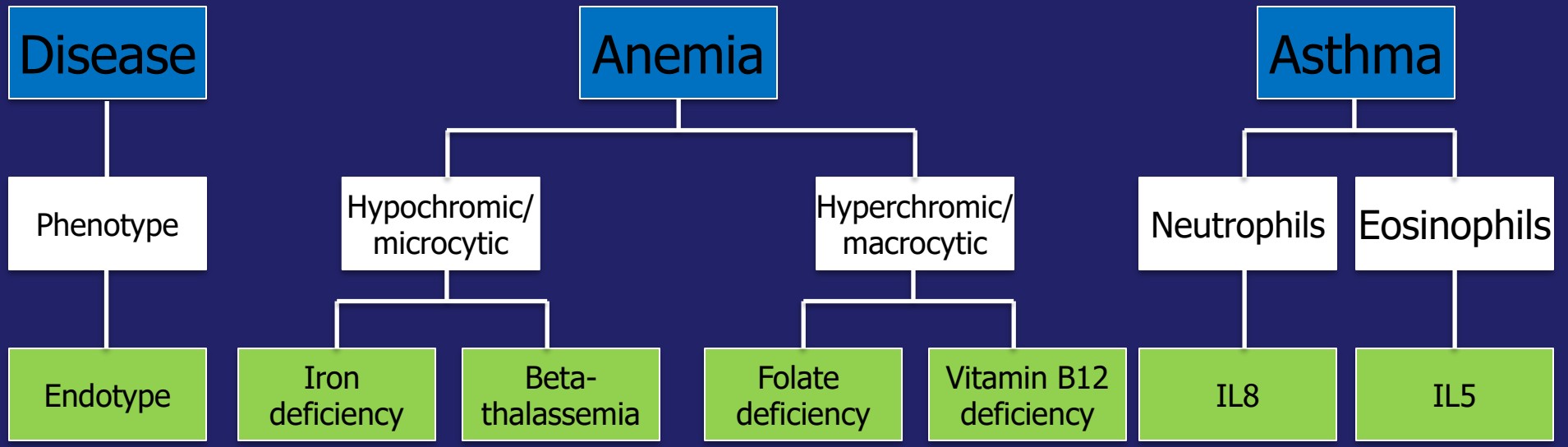
Endotype

- A subtype of a condition defined by a distinct and functional pathobiologic mechanism (e.g., AERD, eosinophilic*, T_H2-high*)

* Commonly used as example of endotype but pathophysiogic mechanism variable

Wenzel SE. *Nat Med.* 2012;18(5):716-725. Lang DM. *Allergy Asthma Proc.* 2015;36:418-424.

Phenotype versus Endotype



Definitions

PRACTALL Consensus report, EAACI and AAAAI

Asthma endotypes: A new approach to classification of disease entities within the asthma syndrome

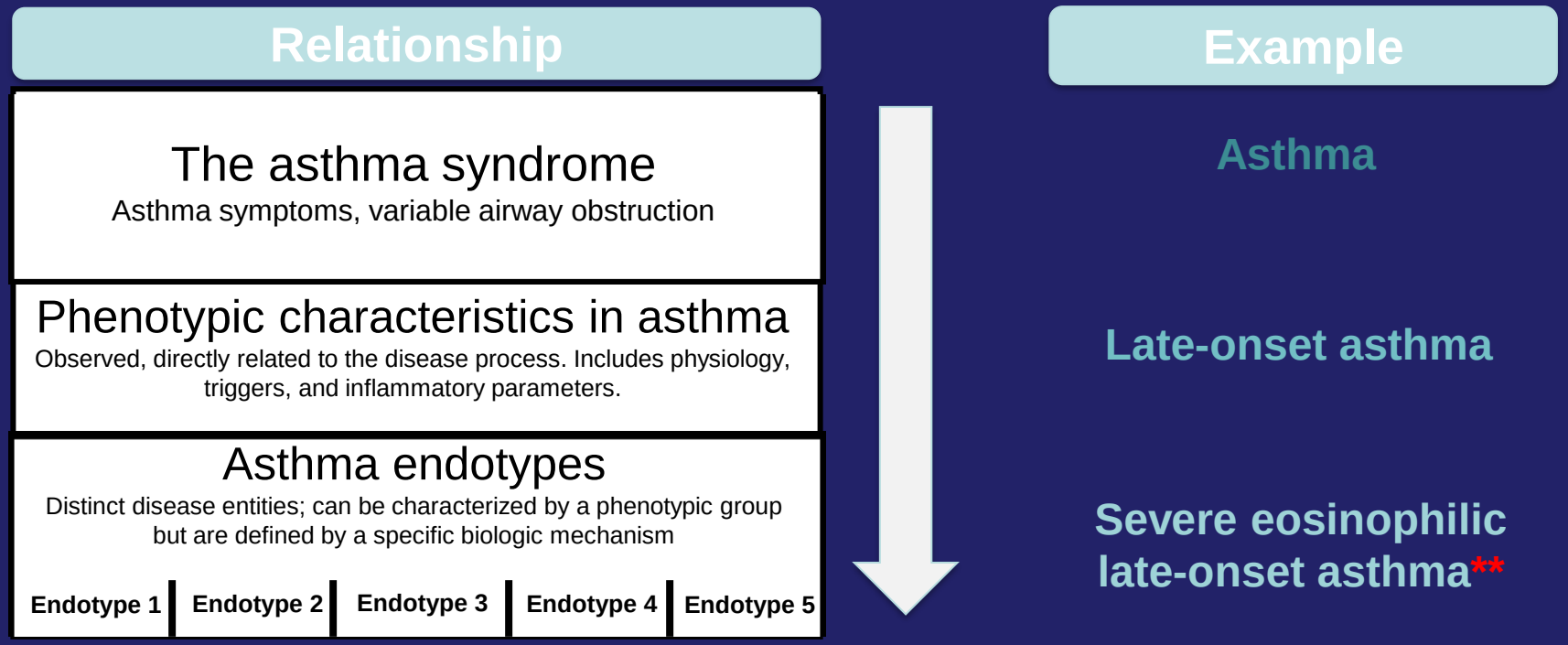
Jan Lötvall, MD,[a] Cezmi A. Akdis, MD,[b] Leonard B. Bacharier, MD,[c] Leif Bjermer, MD,[d] Thomas B. Casale, MD,[e] Adnan Custovic, MD,[f] Robert F. Lemanske, Jr, MD,[g] Andrew J. Wardlaw, MD,[h] Sally E. Wenzel, MD,[i] and Paul A. Greenberger, MD[j] *Göteborg and Lund, Sweden, Davos, Switzerland, St Louis, Mo, Omaha, Neb, Manchester and Leicester, United Kingdom, Madison, Wis, Pittsburgh, Pa, and Chicago, Ill*

(J Allergy Clin Immunol 2011;127:355-60.)

Requirement for defining an ‘endotype’:
--must fulfill at least 5 of 7 parameters:

1. Clinical characteristics
2. Biomarkers
3. Pulmonary physiology
4. Genetics
5. Histopathology
6. Epidemiology
7. Response to treatment

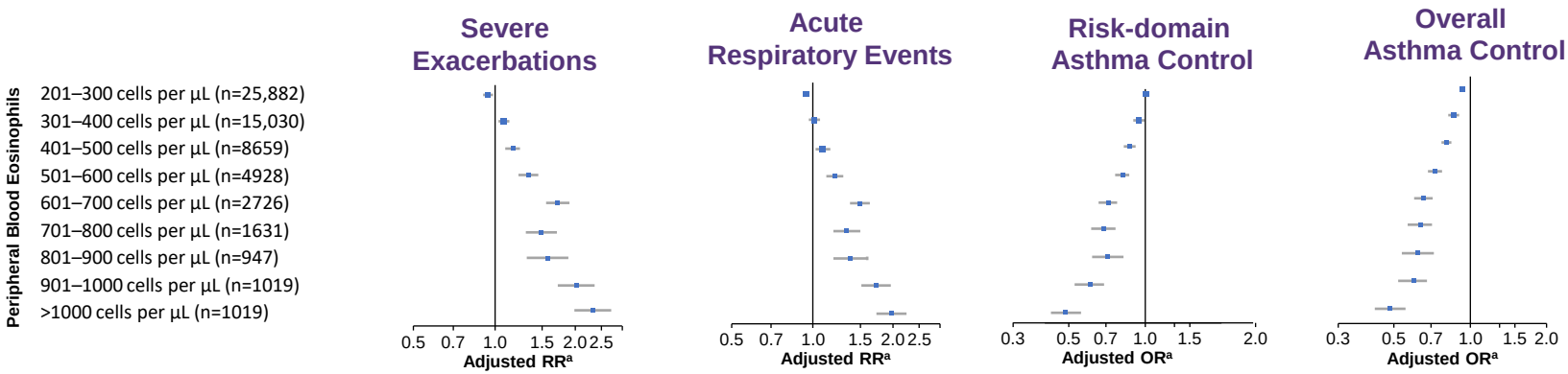
The Relationship Between Phenotype and Endotype



Adapted from Lotvall J et al. J Allergy Clin Immunol. 2011;127:355-60

Eosinophil Levels Correlate With Asthma Exacerbations And Asthma Control

Elevated eosinophil counts are associated with asthma severity, severity of exacerbations, and level of asthma control[1-3]

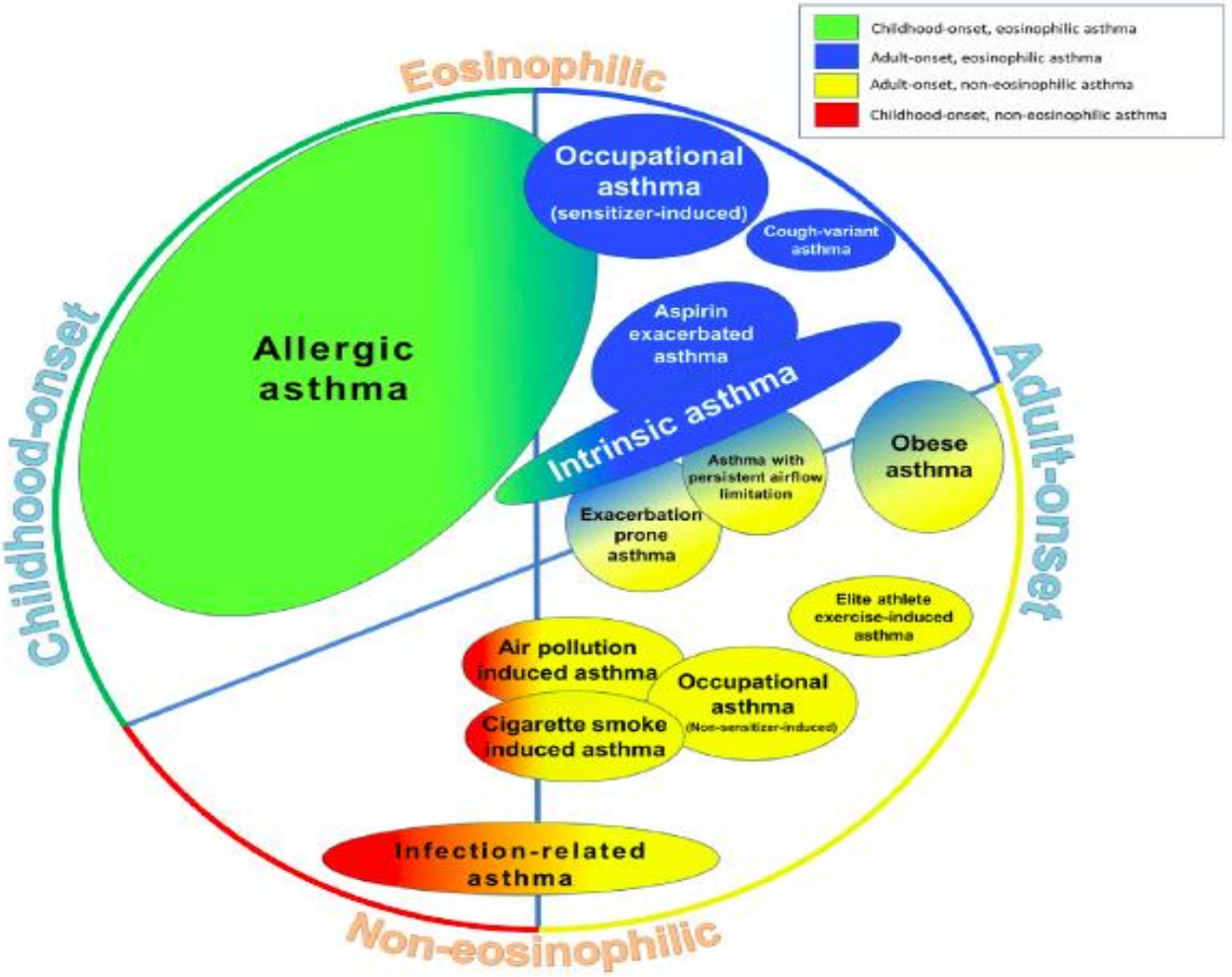


[a]Data from medical records of asthmatics aged 12–80 years with 2 years of continuous records, including 1 year before (baseline) and 1 year after (outcome) their most recent eosinophil count. Patients assigned to 9 eosinophil count categories compared with a reference category of 200 cells per µL or less (n=68 407). Adjusted for age, sex, body-mass index, smoking status, and Charlson comorbidity index score.

RR=rate ratio; OR=odds ratio.

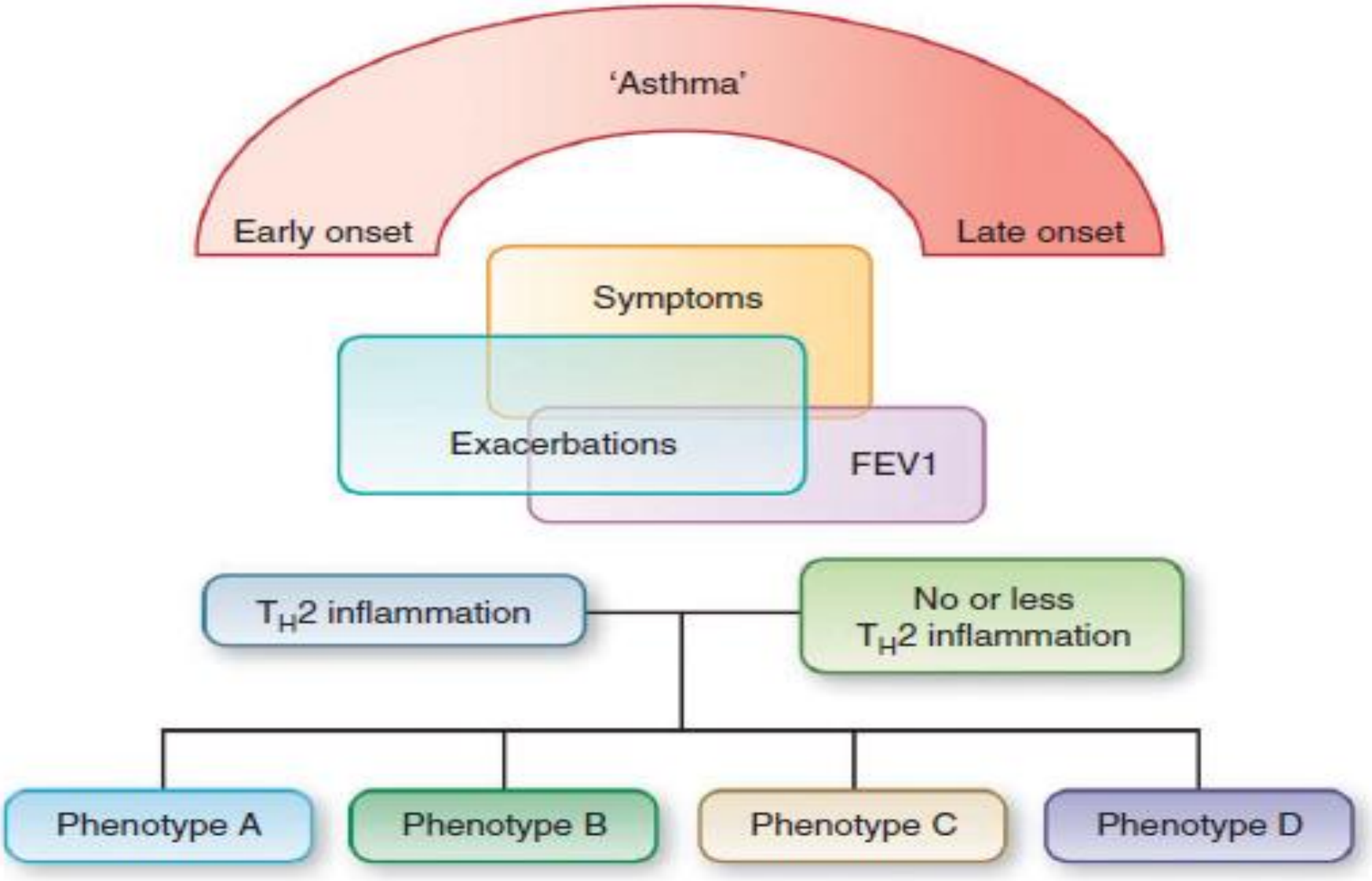
1. Price DB et al. *Lancet Respir Med.* 2015;3(11):849-58. 2. Wenzel SE et al. *Am J Respir Crit Care Med*. 1999;160:1001-1008. 3. Price DB et al. *J Asthma Allergy.* 2016;9:1-12.

Asthma Phenotypes



Hekkin P et al. JACI Pract Nov-Dec 2014

Phenotype versus Endotype: T2 High is Phenotype

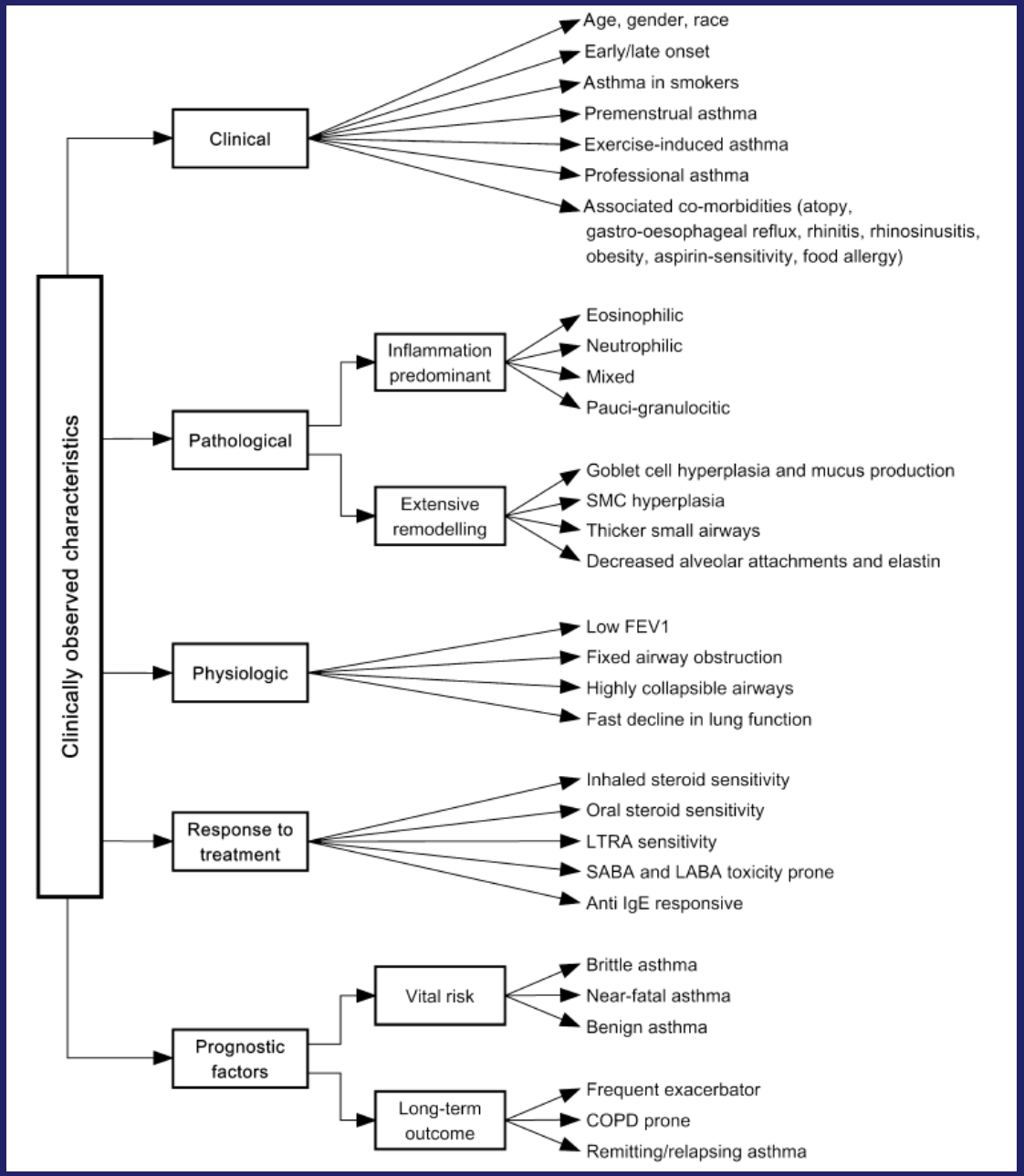


Problems with This Definition

"Severe eosinophilic late-onset asthma"

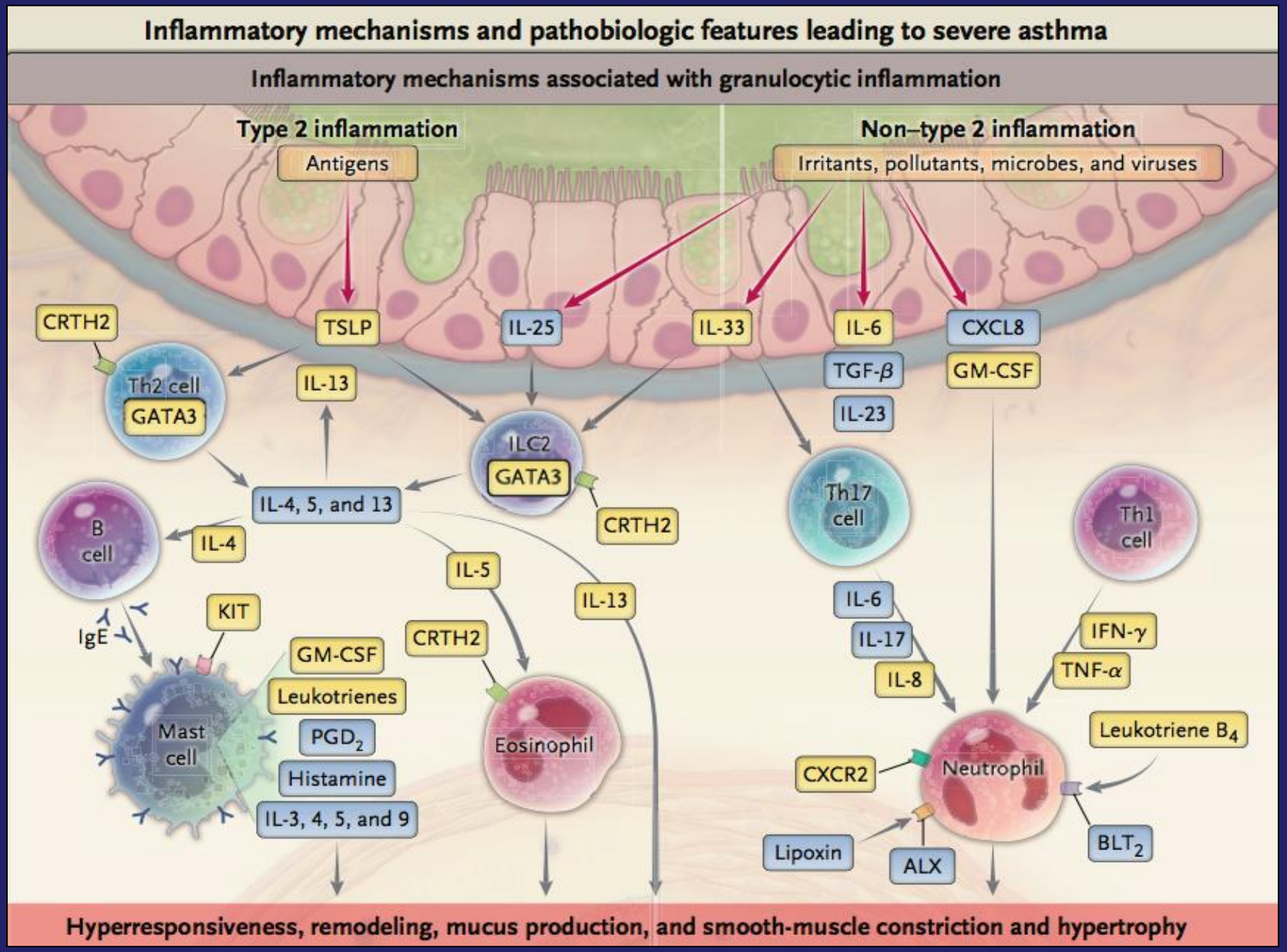
- Not really hypereosinophilic (normal blood count)
- Severity, age, disease duration, and the presence of eosinophils are *phenotypic descriptions*
- Eosinophils: neither necessary nor sufficient to cause severe asthma.
- Allergy: neither necessary nor sufficient to cause severe asthma.
- The presence of "hypereosinophilia" does not denote the pathobiologic mechanism or pathway.

Asthma: A Heterogeneous Disease



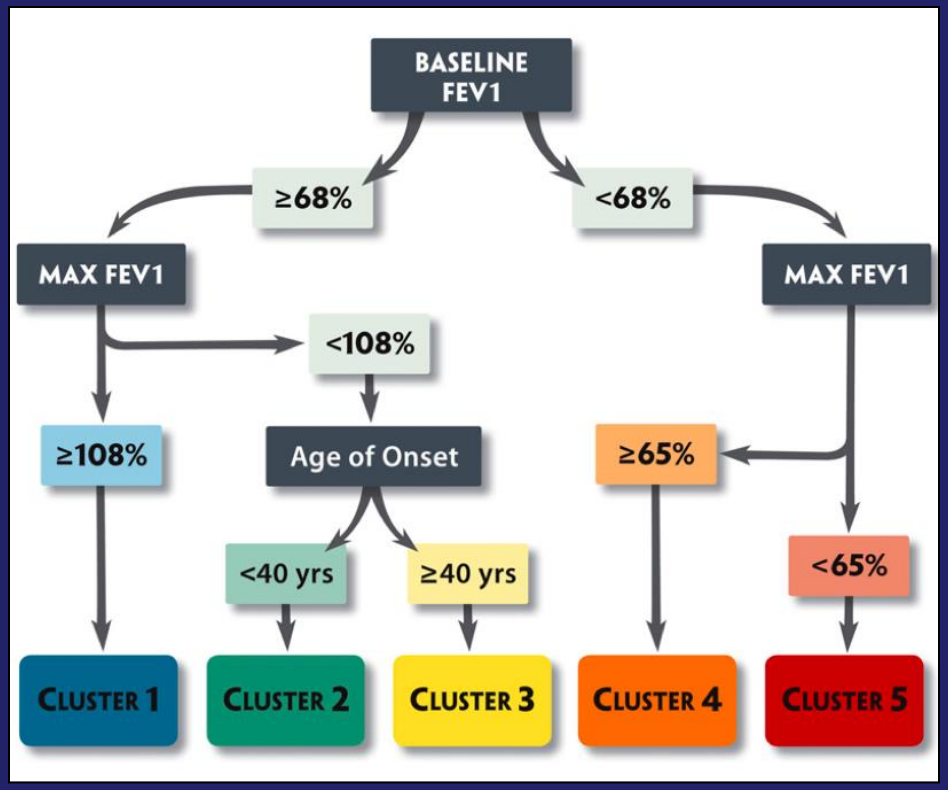
Agache et al Allergy 2012; 67: 835–846

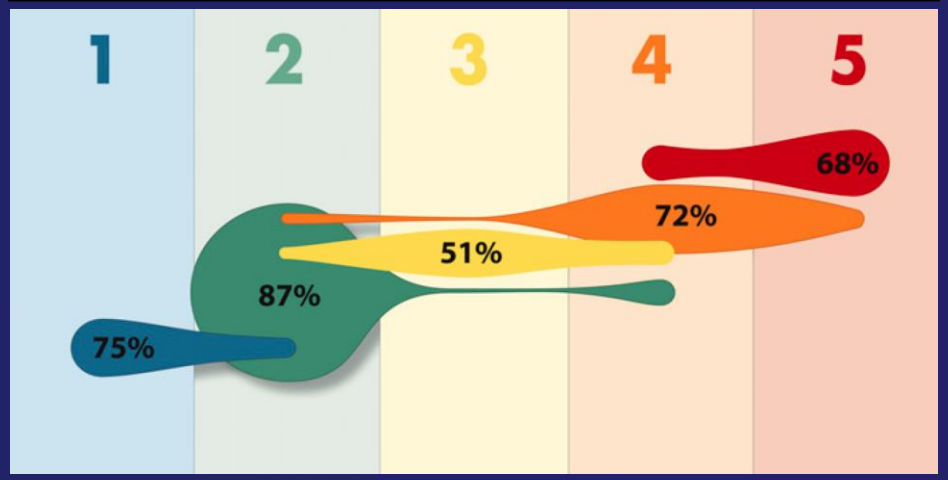
Types of Inflammation, 1 versus 2



Israel NEJM 2017

Phenotypes: Unbiased Data-Driven Analysis

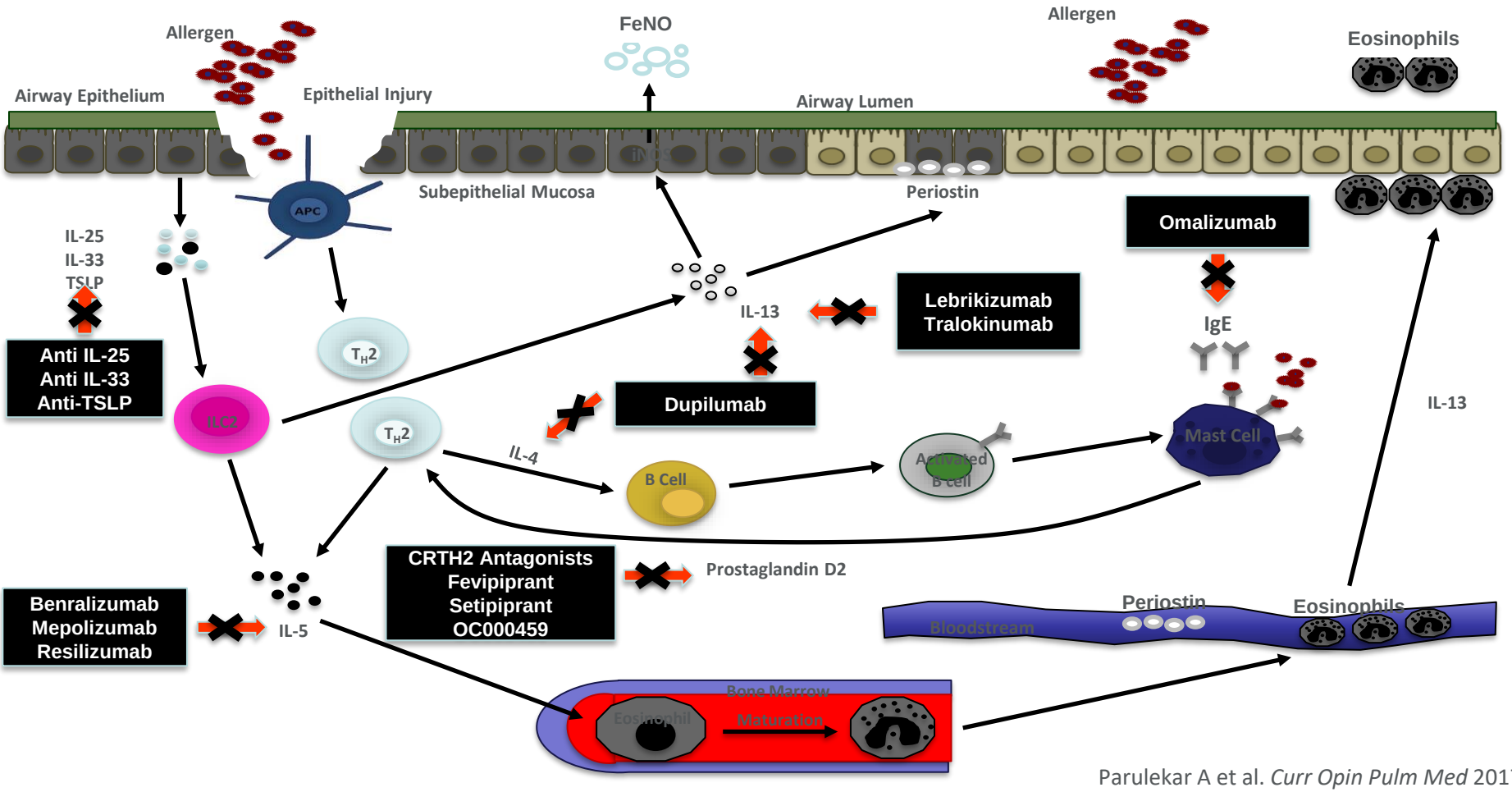




1. Mild atopic asthma
2. Mild-moderate atopic asthma
3. Non-atopic late-onset asthma
4. Severe atopic asthma
5. Severe asthma with fixed airflow obstruction

Moore AJRCCM 2010

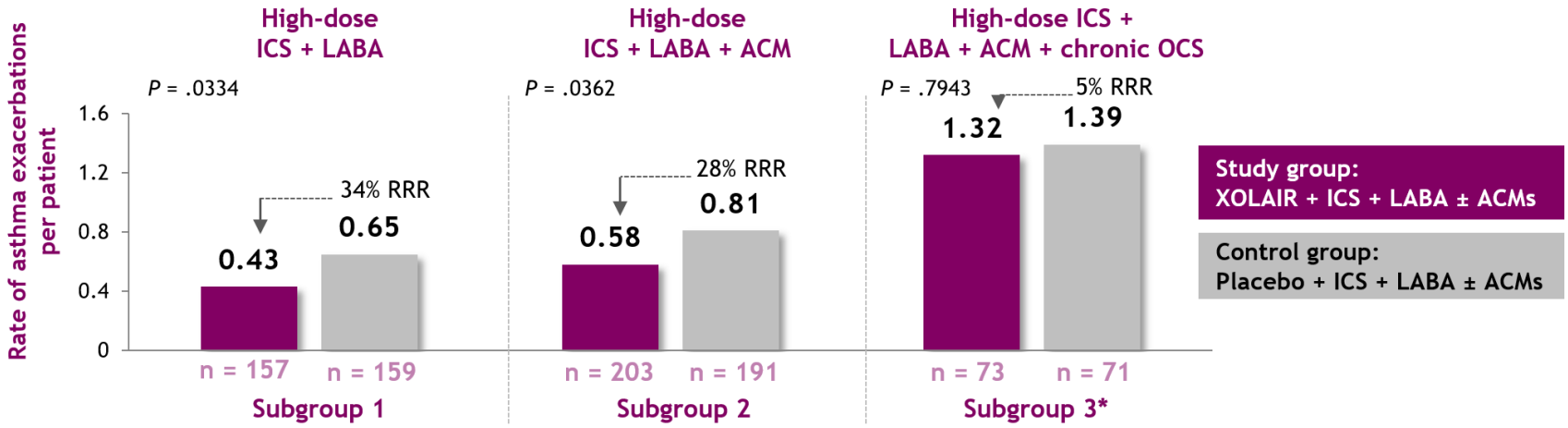
Novel Therapies Targeting T2 High Asthma



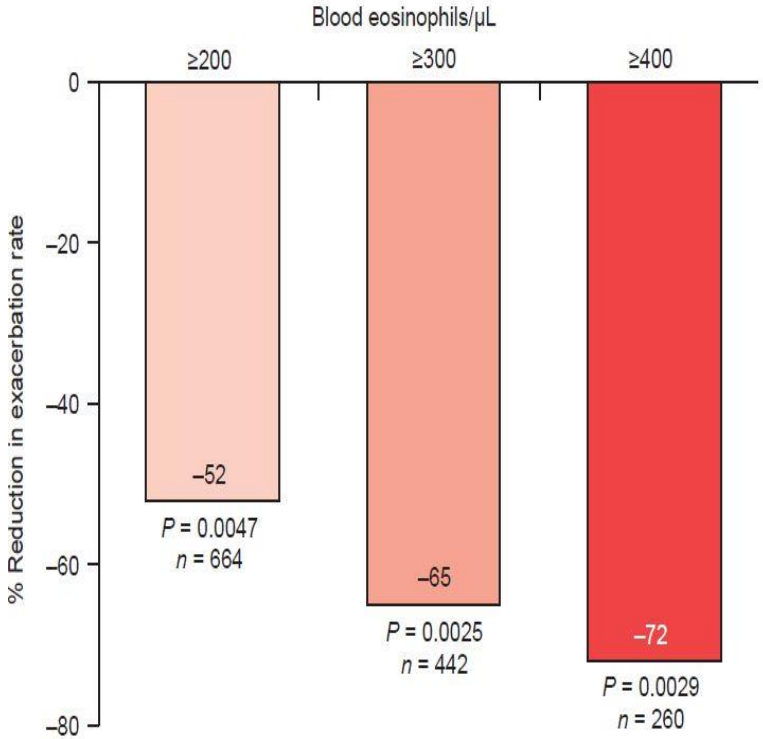
Parulekar A et al. *Curr Opin Pulm Med* 2017

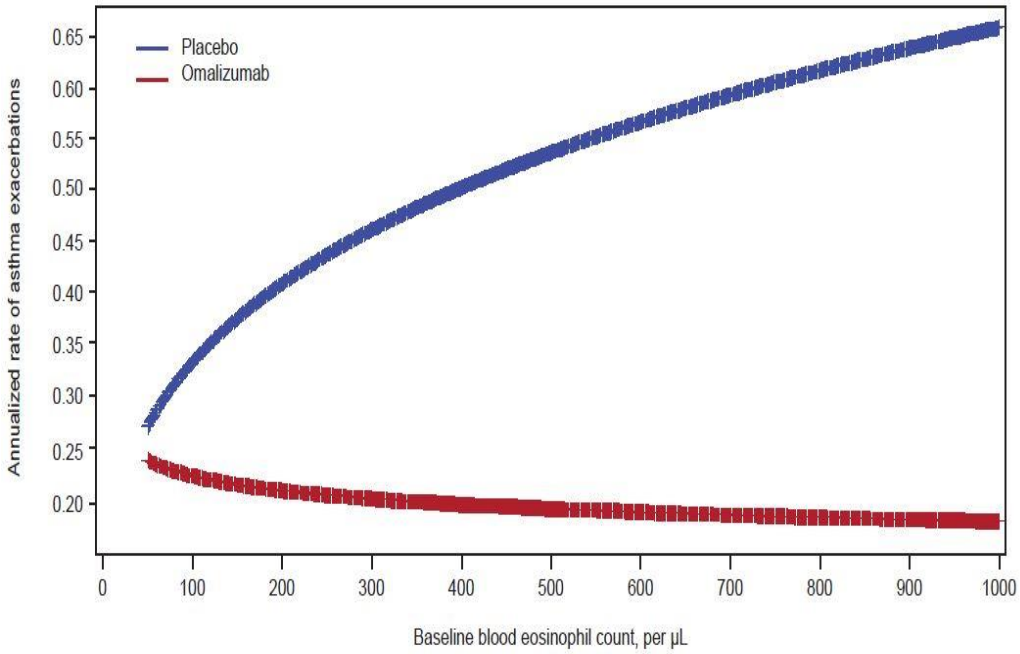
Hanania NA et al. Ann Int Med 2011;154:573-582

Significant Reduction in Exacerbations in Patients Not Taking Chronic OCS[1,2,*,†,‡]



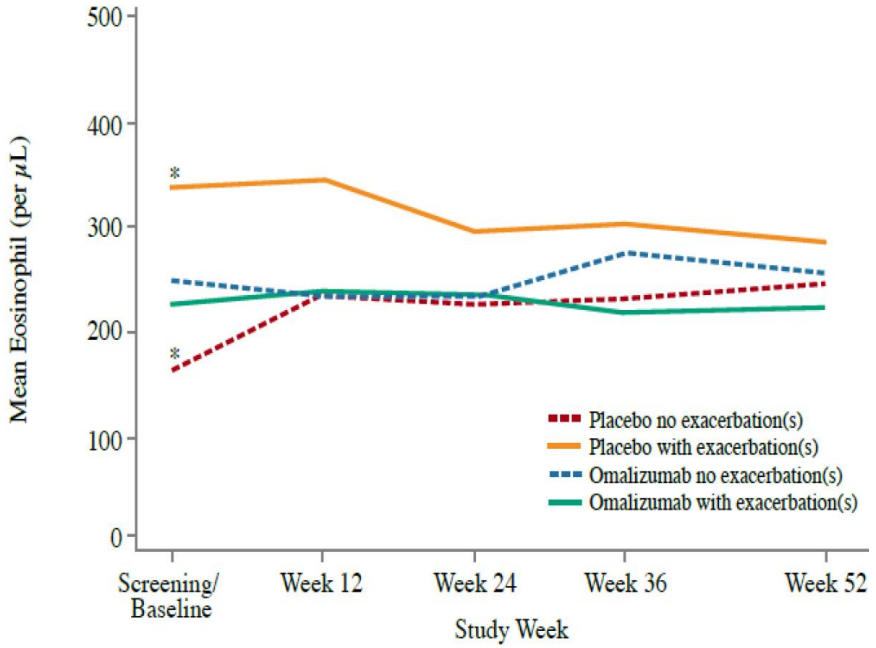
Asthma Exacerbation Reductions in Omalizumab Pivotal Clinical Trials by Eosinophil Strata

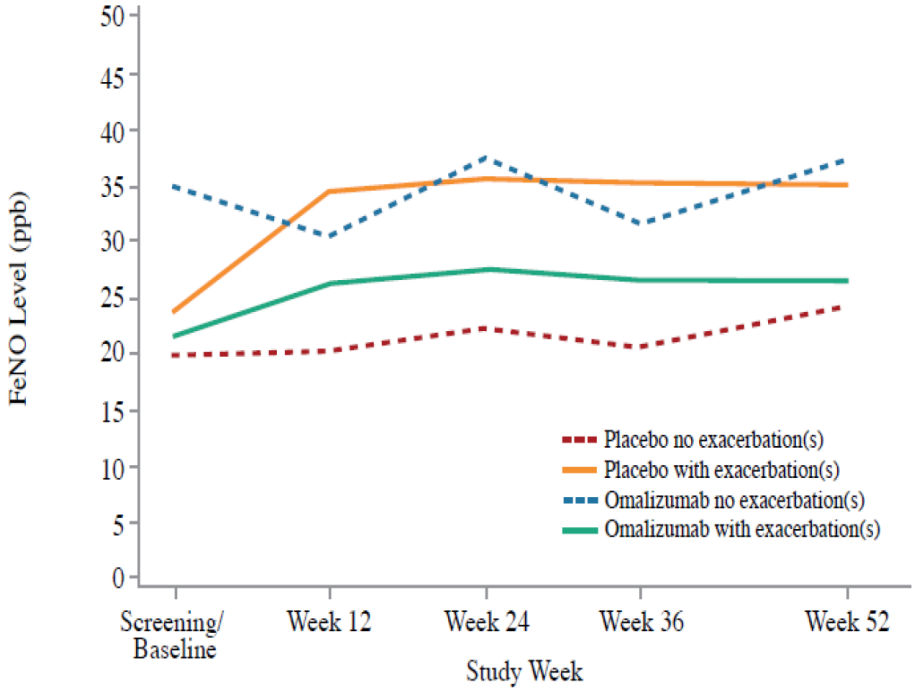




Casale et al, Allergy 2018

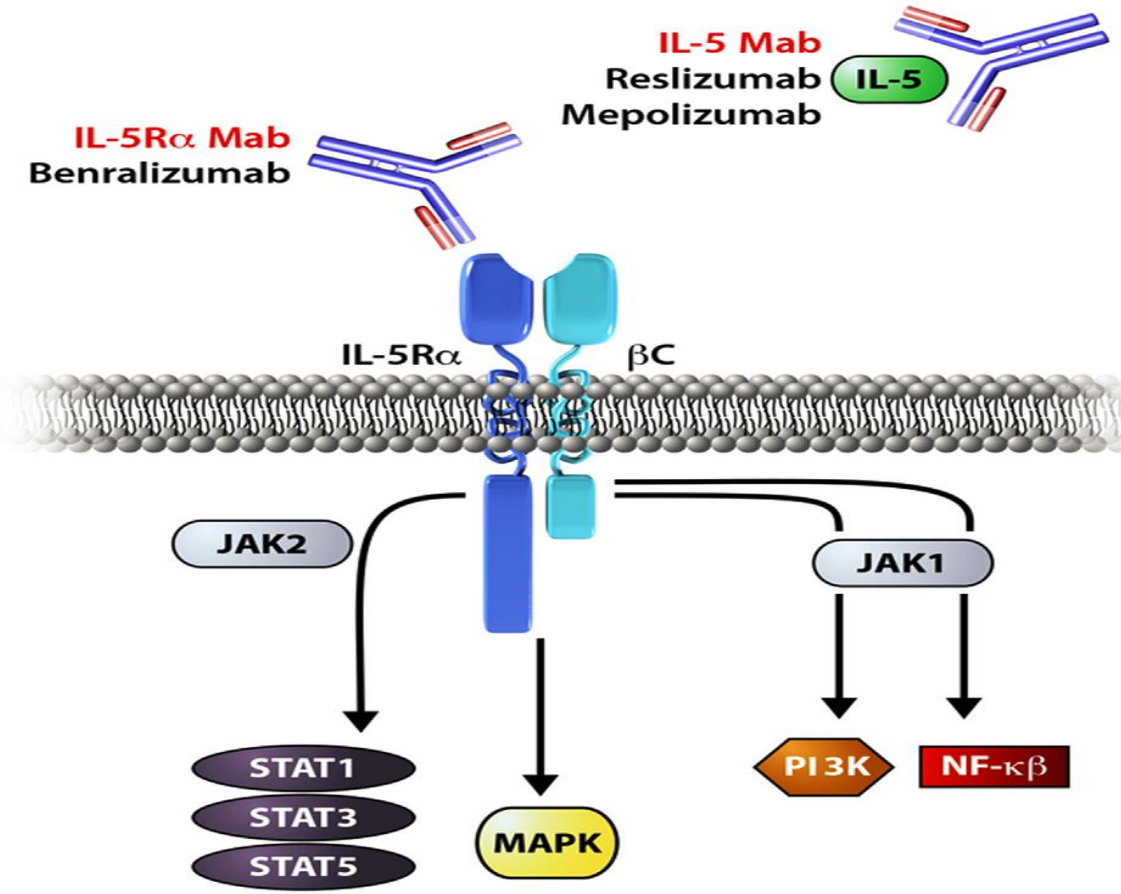
Omalizumab Persistence After Discontinuation of Long Term Rx: Prediction of Relapse or Remission (EXCEL extended or EXPORT)





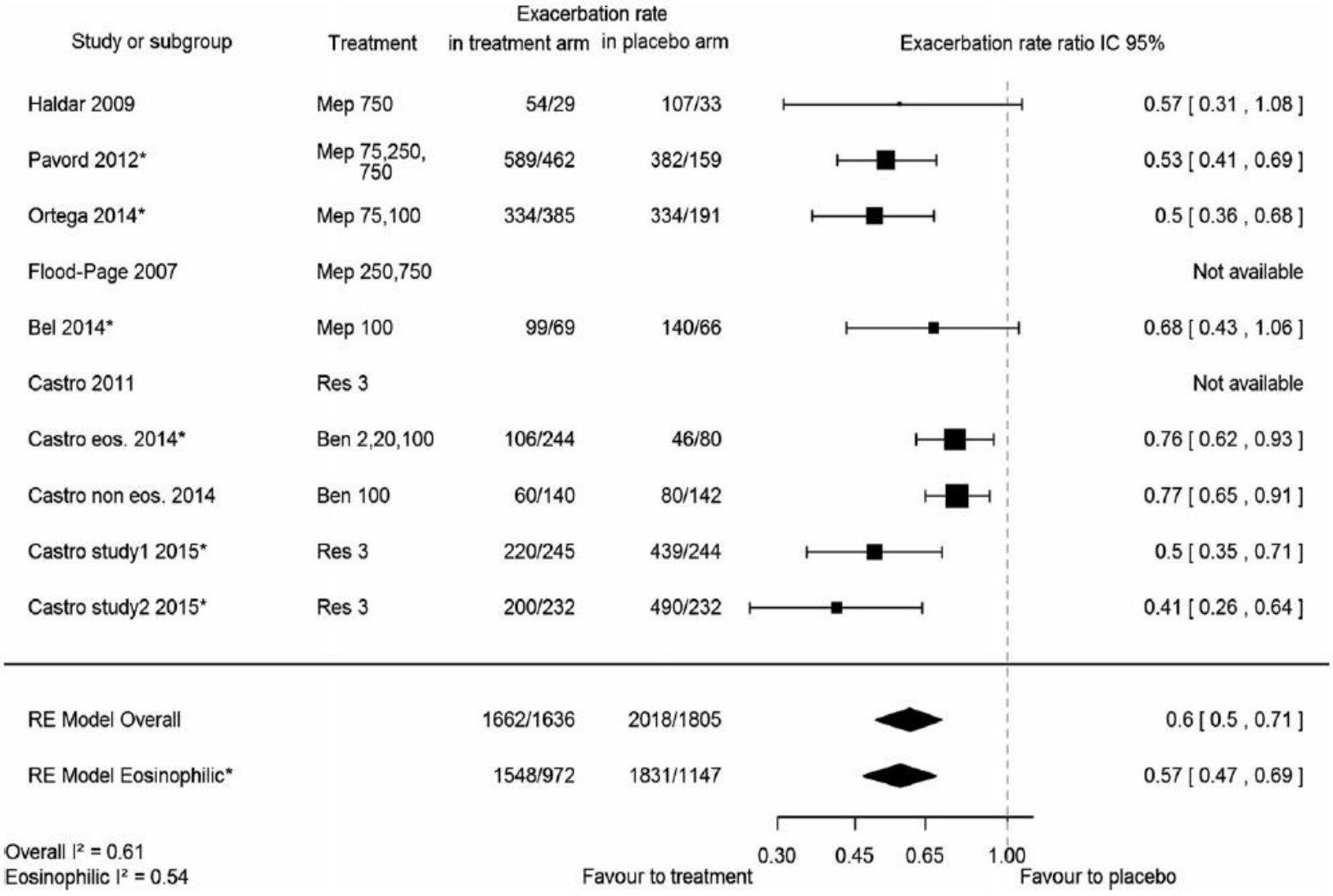
Ledford, Dennis, et al. *Journal of Allergy and Clinical Immunology* 140.1 (2017): 162-169.

The Targets:
IL-5 or Eosinophils/Basophils (IL-5Rα)



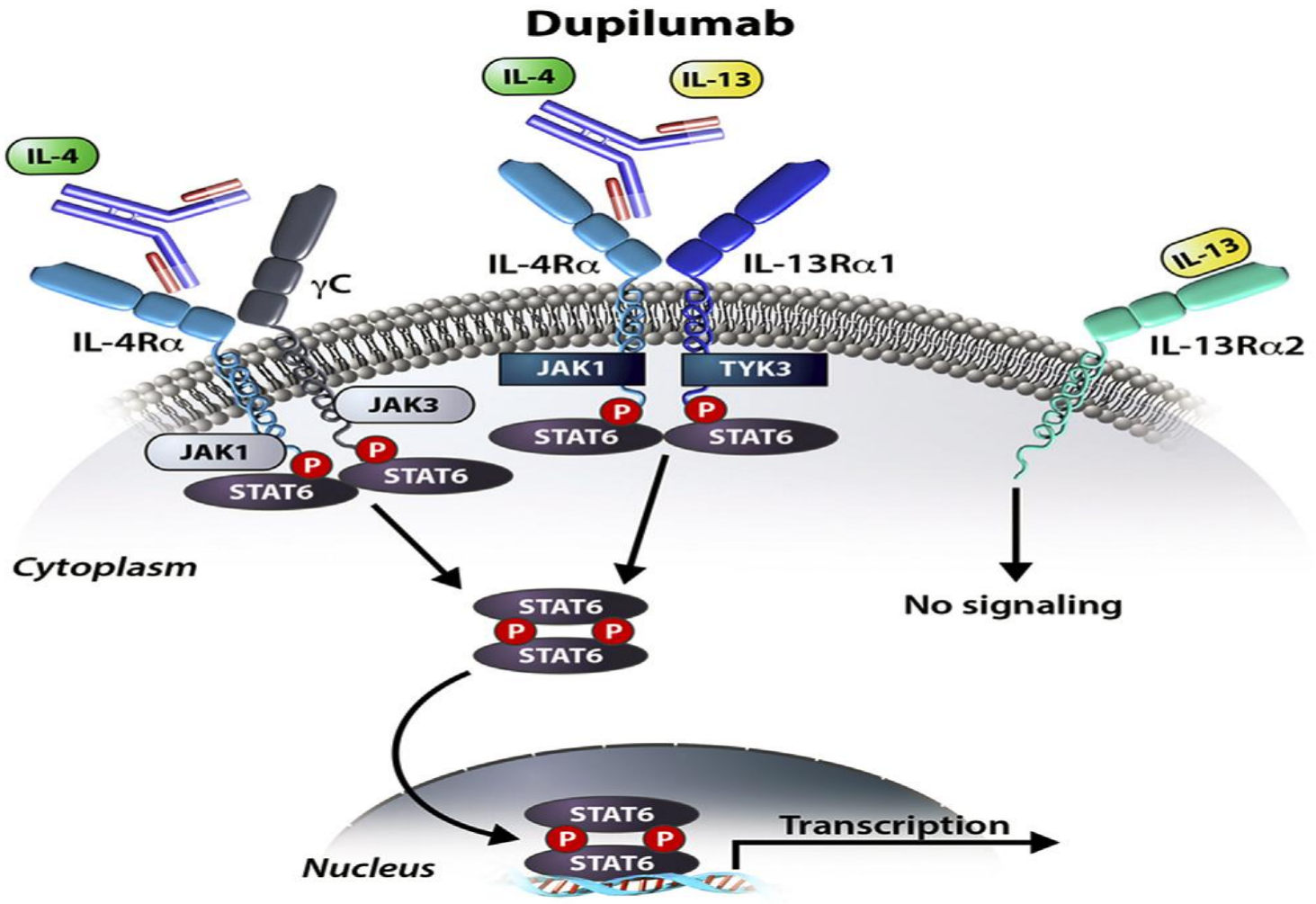
Casale, JACI. 2017

Exacerbation Rate Reduction Similar Among IL-5 Blockers



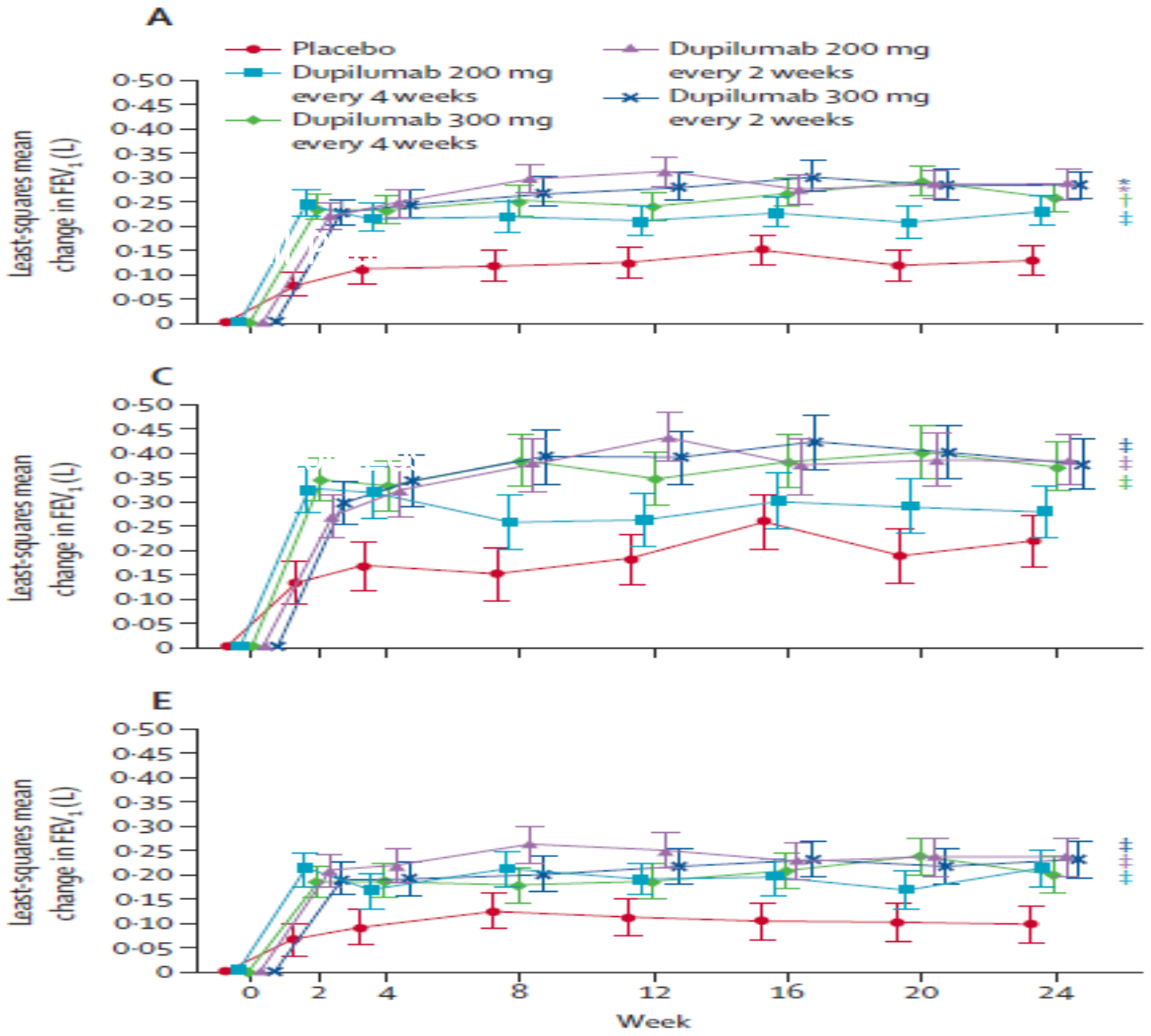
Carbon et al, Clin Expt Allergy, 2016

Dupilumab: Fully Human mAb to IL-4Rα



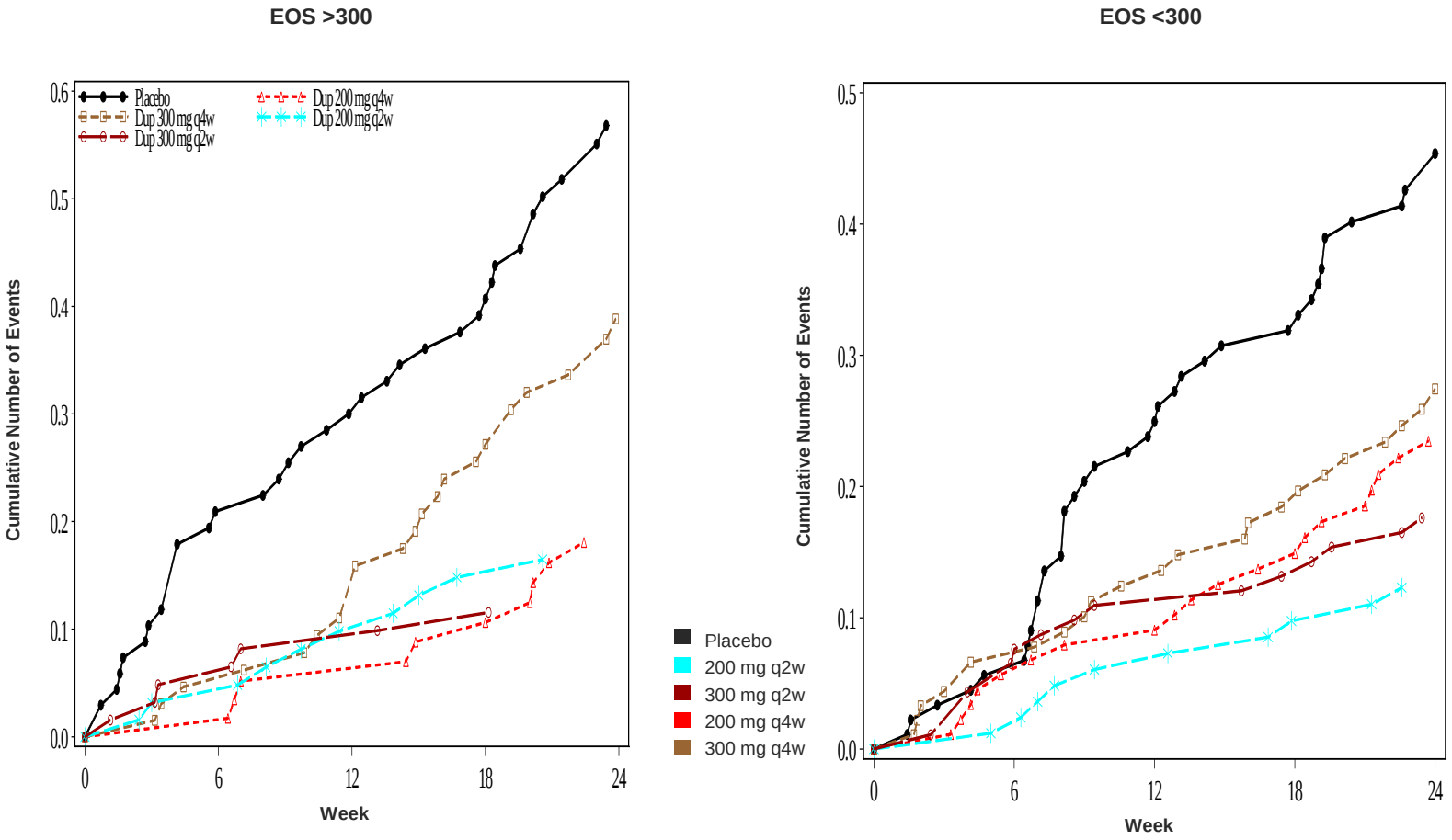
Casale, JACI,2017

Dupilumab Phase 2b FEV1 Results



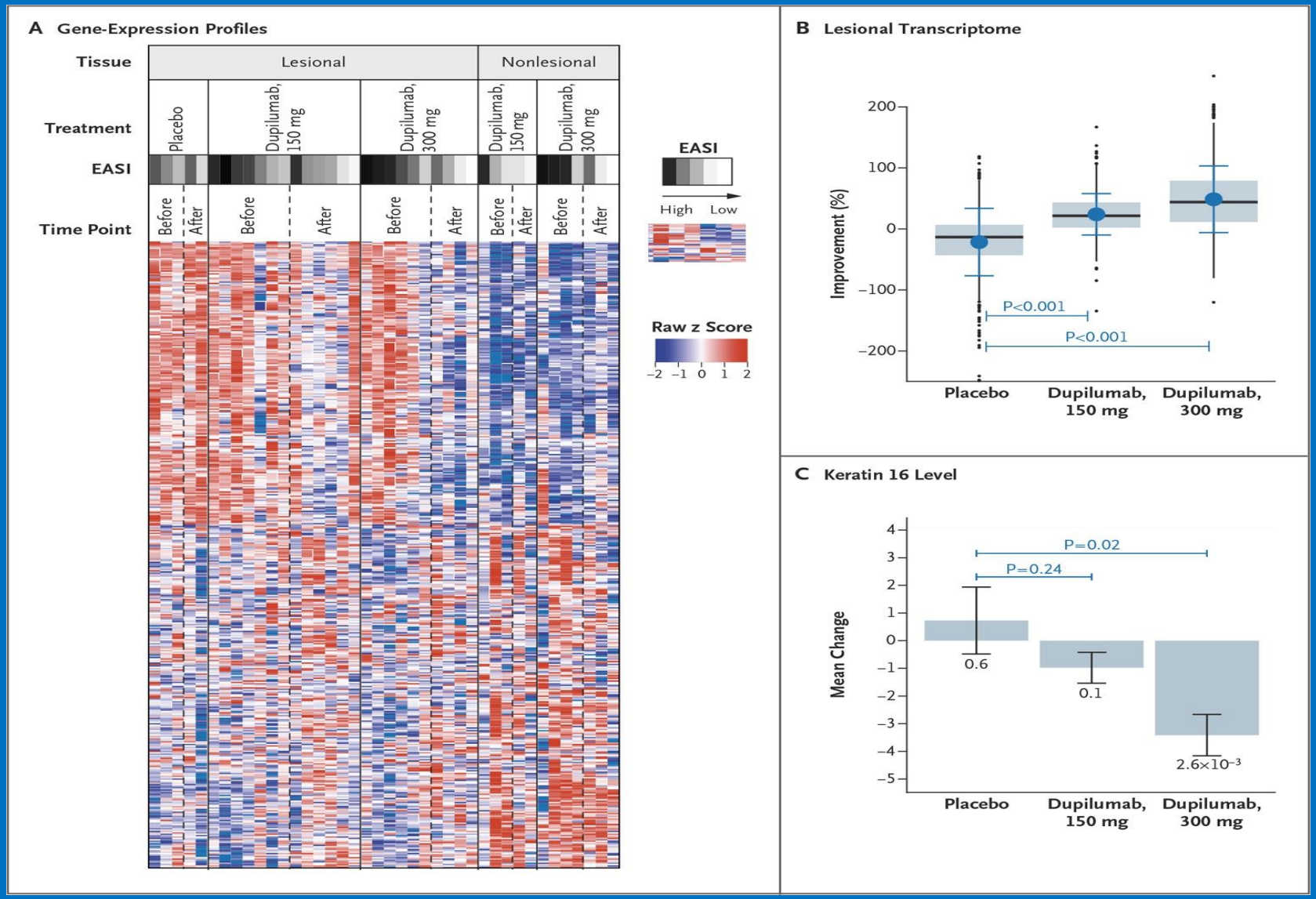
Wenzel, et al, Lancet, 2016

Dupilumab Phase 2b Exacerbation Results



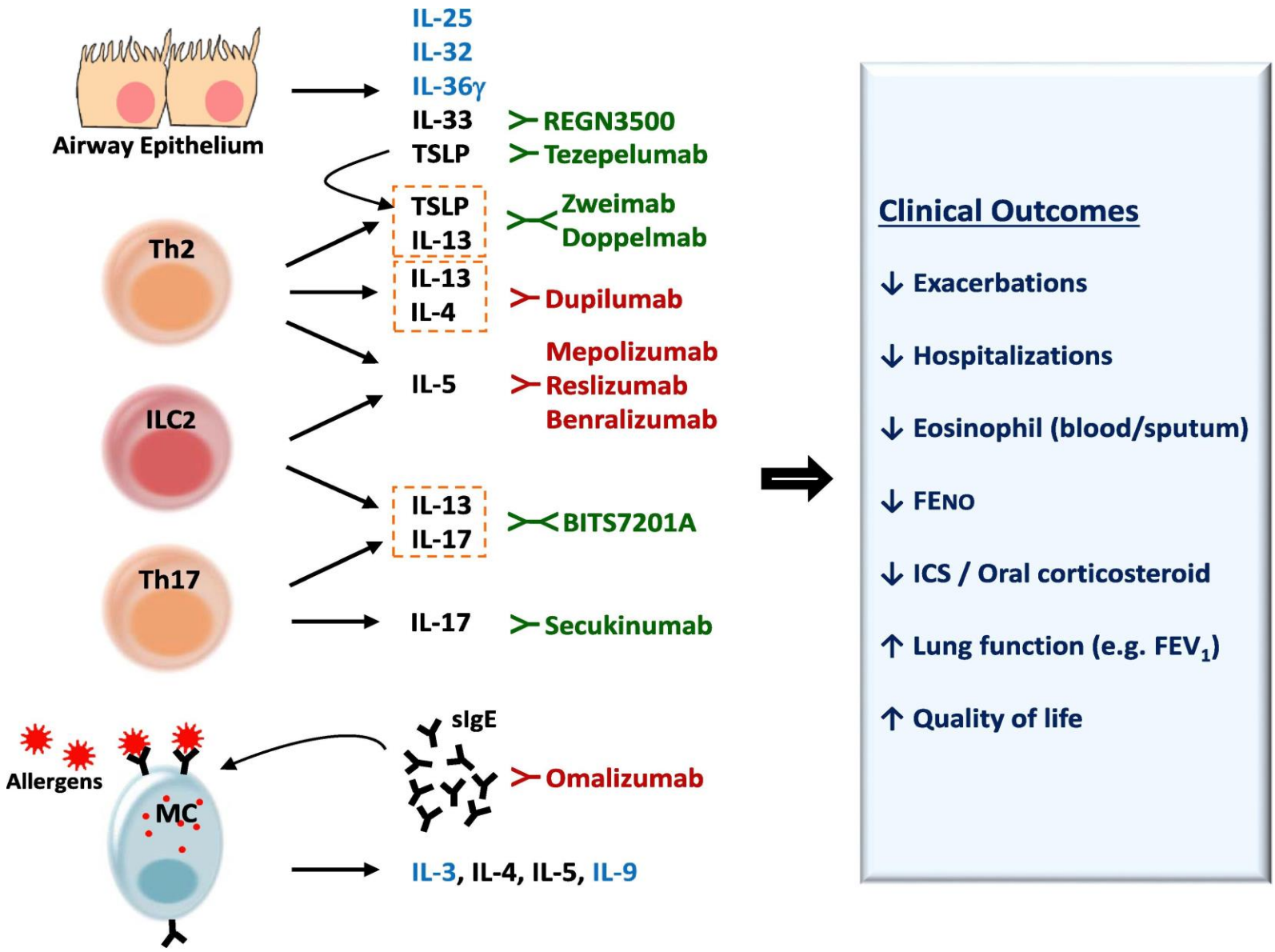
Wenzel, et al, Lancet, 2016

Molecular Changes in the Atopic Dermatitis Transcriptome in Studies M4A and M4B.

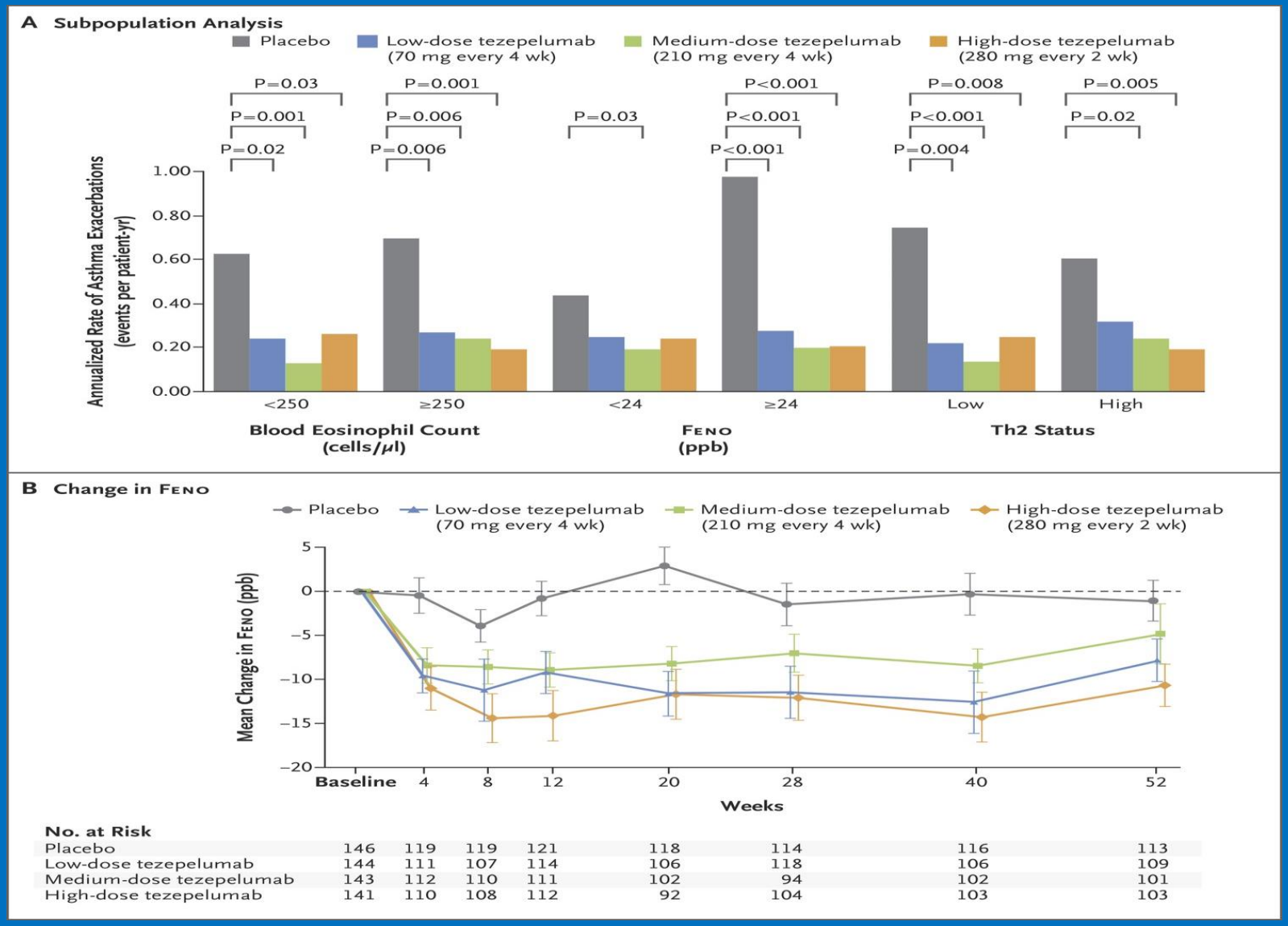


Beck LA et al. N Engl J Med 2014;371:130-139

The NEW ENGLAND JOURNAL of MEDICINE


Airway Epithelium
IL-25
IL-32
IL-36γ
IL-33
REGN3500
TSLP
Tezepelumab
TSLP
IL-13
Zweimab
Doppelmab
Th2
IL-13
IL-4
Dupilumab
Mepolizumab
IL-5
Reslizumab
Benralizumab
ILC2
IL-13
IL-17
BITS7201A
Th17
IL-17
Secukinumab
sIgE
Allergens
MC
Omalizumab
IL-3, IL-4, IL-5, IL-9
Clinical Outcomes
↓ Exacerbations
↓ Hospitalizations
↓ Eosinophil (blood/sputum)
↓ FENO
↓ ICS / Oral corticosteroid
↑ Lung function (e.g. FEV1)
↑ Quality of life

Annualized Rate of Asthma Exacerbations at Week 52, According to Baseline Biomarker Status, and Change from Baseline in the Fraction of Exhaled Nitric Oxide (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

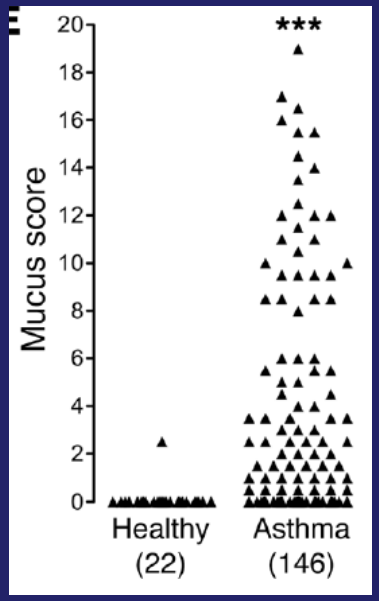
Corren J et al. N Engl J Med 2017;377:936-946

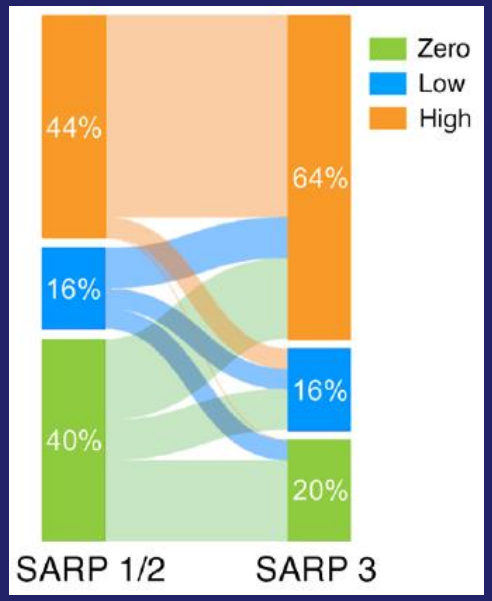
The NEW ENGLAND JOURNAL of MEDICINE

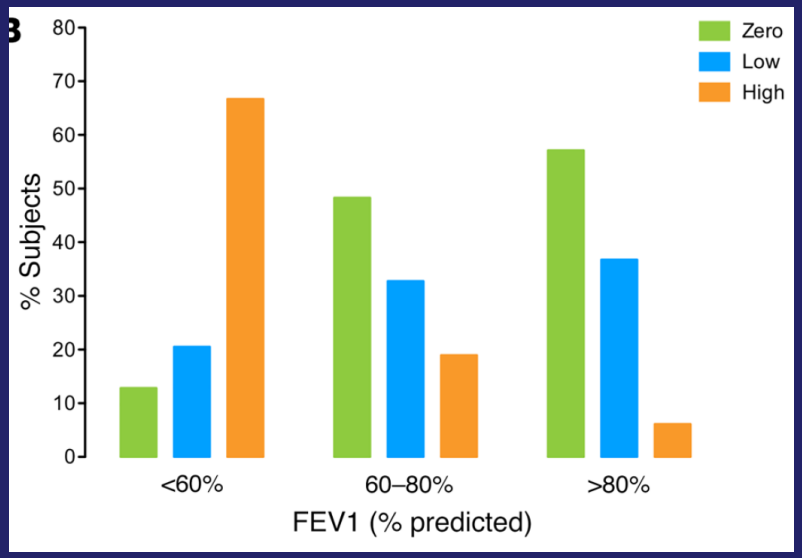
Tezepelumab OCS Sparing?

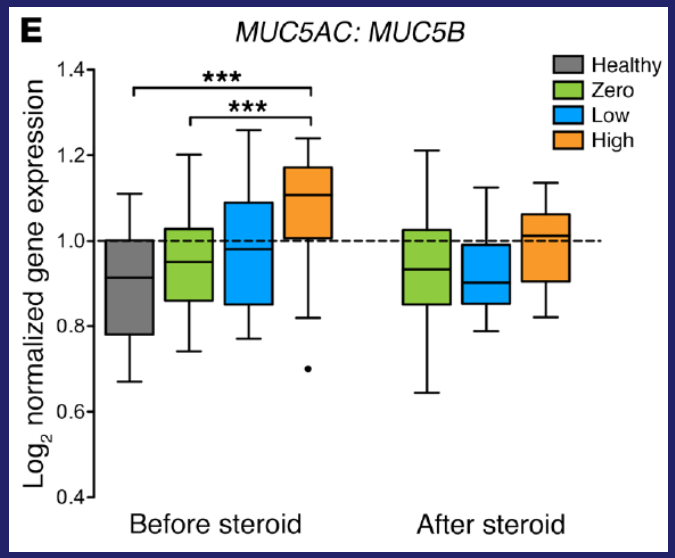
- Embargoed until May 12, 2021
- Lead author Michael Wechsler
- Press release suggested did not reach outcome…is it possible a therapeutic effective in more diverse population may not demonstrate CS sparing effect expected with Type 2 selective therapies such as CS?

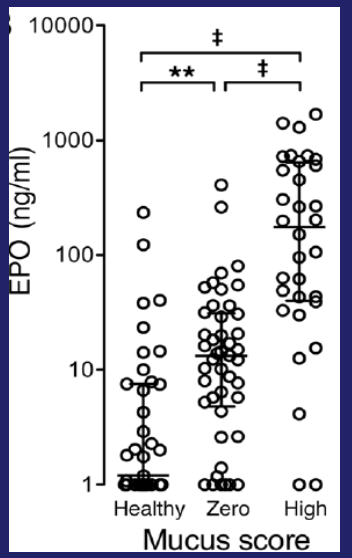
Radiologic Phenotype: Mucus impaction, Proposed Endotype MUC5AC:MUC5B:high, EPO:high











Dunican et al JCI 2018

Table 1

Potential factors or pathways and their mechanisms implicated in non-T2 asthma

Factors/pathways	Mechanisms	References
Th17 pathway	Secretion of IL-17 and IL-6 with promotion of neutrophil infiltration in the airway	[4,5,9,10•]
Th1 pathway	Secretion of IFN-γ with suppression of secretory leukocyte protease inhibitor associates with AHR development	[12]
NETs	Activation of the inflammasome and secretion of IL-1β, causing airway epithelial injury	[13,15,17•]
Airway dysbiosis	Sputum microbiome is less diverse and dissimilar in bacterial taxa, but underlying mechanism is unclear	[19•,20,21,22•]
Nitric oxide signaling	Decreased levels of NO in the airway of obese asthmatics may result in impaired bronchodilation	[37,38•]
Nerve growth factor	Sensory hyperinnervation contributing to AHR	[24,25]
ORMDL3	Reduced serum sphingolipids contributing to AHR and airway remodeling	[28•,31]
RGS	Reduced termination of GPCR signaling may result in more severe AHR	[32–35]

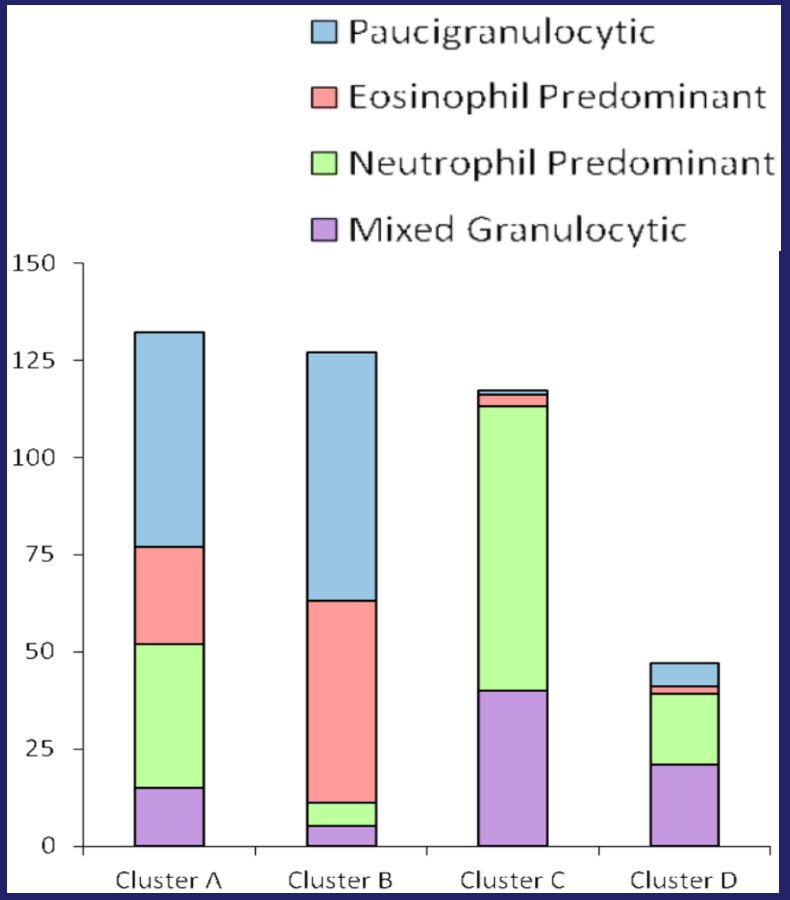
AHR: Airway hyperresponsiveness; GPCR: G protein-coupled receptor; NET: neutrophil extracellular traps; ORMDL3: Oromucoid-like 3; RGS: Regulator of GPCR signaling.

Hudey, Cardet Ledford. Curr Opinion Immunol 2020;66:123-28

Phenotype: Neutrophilic Asthma

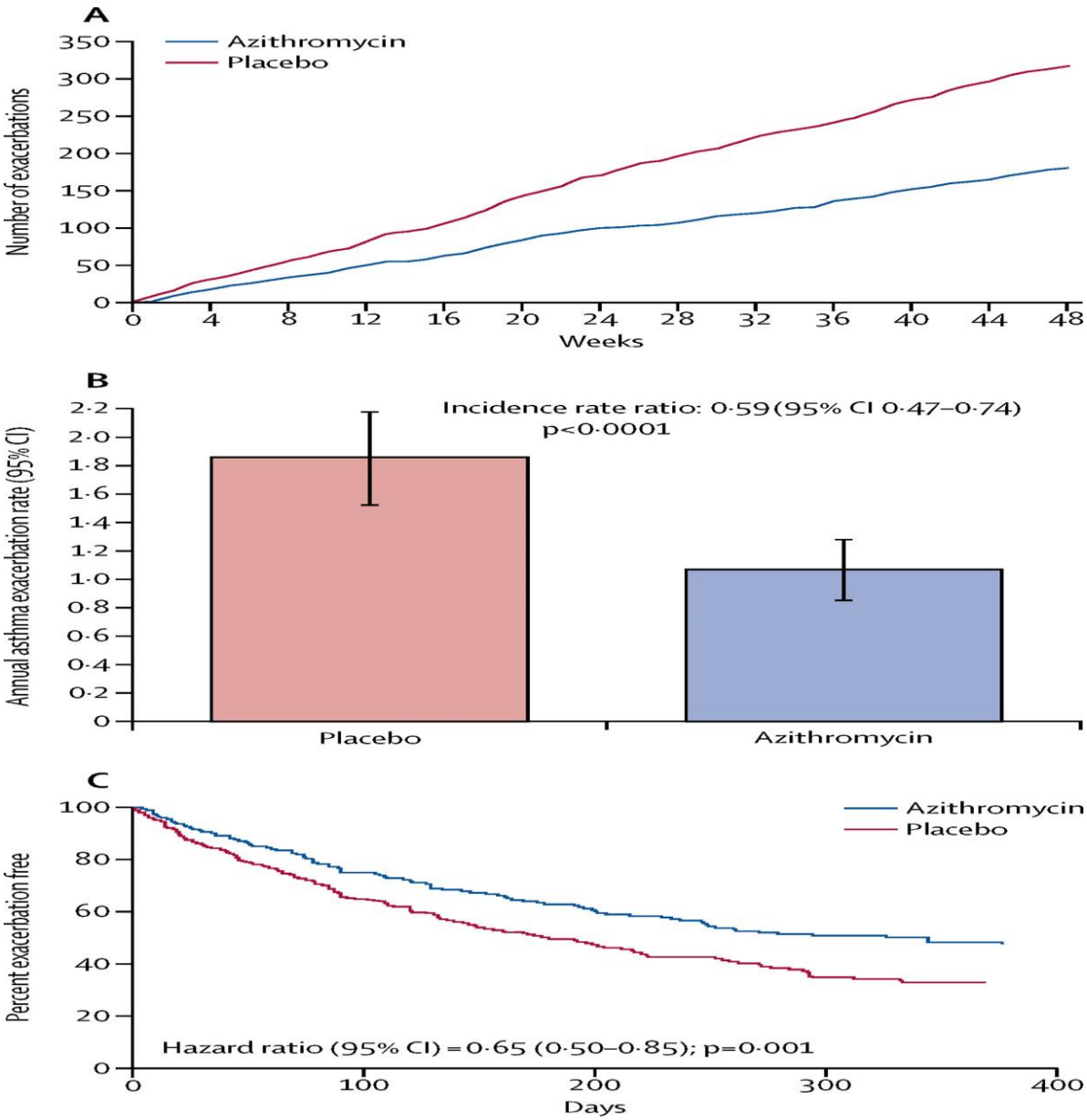
Demographics and Clinical Characteristics of Subjects in Clusters

	Cluster A	Cluster B	Cluster C	Cluster D	
Number of Subjects	**132**	**127**	**117**	**47**	**p-value¶**
Age at Enrollment (yrs)	27(10)	35 (11)	42 (14)	50 (10)	<0.0001
Gender (% Female)	73%	61%	62%	43%	0.003
Race (% White)	70%	58%	62%	79%	0.03
Body Mass Index (BMI)	28 (6)	31 (9)	32 (10)	31 (6)	0.0001
% with BMI > 30	28%	46%	50%	57%	<0.0001
Age of Asthma Onset (yrs)	12 (13)	12 (12)	17 (16)	22 (18)	0.001
% with onset ≥ 12 years old	37%	41%	52%	60%	.01
Asthma Duration (yrs)	15 (8)	23 (13)	24 (14)	28 (18)	<0.0001
% of Subjects with Severe Asthma	15%	24%	38%	66%	<0.0001
Baseline Lung Function*					
FEV1 % predicted	97 (10)	73 (13)	76 (13)	47 (15)	<0.0001
FVC % predicted	104 (11)	87 (12)	87 (12)	65 (14)	<0.0001
FEV1/FVC	0.80 (0.1)	0.70 (0.1)	0.71 (0.1)	0.59 (0.1)	<0.0001
Post-bronchodilator Lung Function†					
FEV1 % predicted	107 (10)	86 (11)	88 (12)	61 (14)	<0.0001
FVC % predicted	108 (12)	96 (13)	96 (11)	79 (15)	<0.0001
Change in % predicted FEV1	12 (13)	20 (20)	19 (23)	31 (28)	<0.0001
PC_{20} Methacholine (mg/ml)‡§	1.66 (0.7)	0.89 (0.8)	1.07 (0.7)	0.93 (0.5)	0.02
Atopy Status					
Total Serum IgE (IU/ml)‡	120 (0.6)	178 (0.6)	135 (0.6)	118 (0.7)	0.09
Number Positive SPT++	4.0 (2.9)	4.8 (3.2)	4.2 (3.1)	4.0 (3.5)	0.14
% with ≥1 Positive SPT++	85%	90%	83%	76%	0.13
Exhaled Nitric Oxide (ppb)‡	30 (0.4)	34 (0.4)	26 (0.4)	32 (0.4)	0.22



Step	Variable	Partial R-Square	F value	p value
1	Baseline FEV1 % predicted*	0.59	201.22	< 0.0001
2	% Sputum neutrophils	0.52	151.58	< 0.0001
3	Current Age (years)	0.16	27.01	< 0.0001
4	Maximal FEV1 % predicted†	0.07	9.75	< 0.0001
5	Asthma Duration (years)	0.03	4.36	0.005
6	% Sputum eosinophils	0.04	5.82	0.0007
7	Body Mass Index (BMI)	0.03	4.58	0.004
8	Number of asthma controllers††	0.02	3.17	0.02

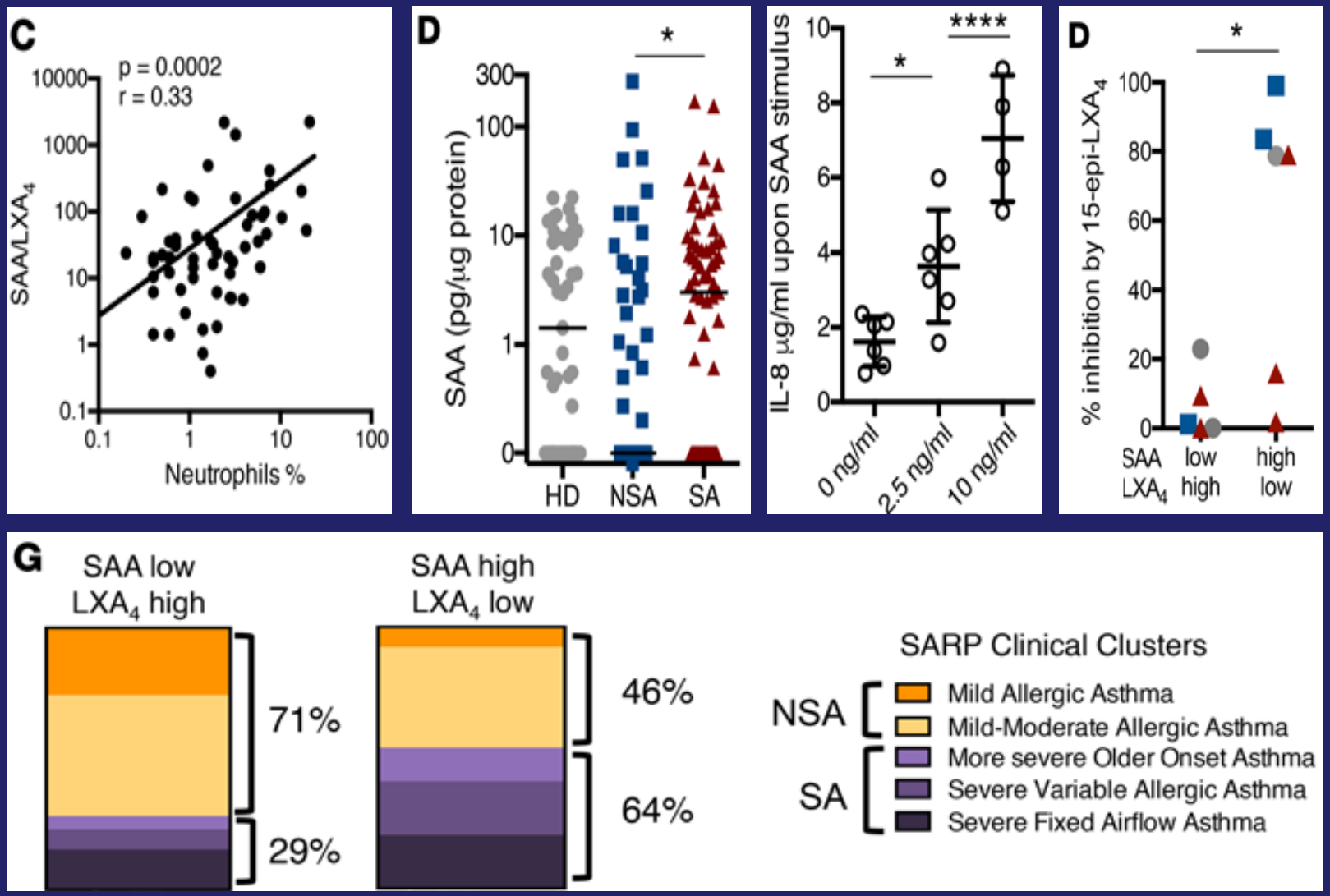
Moore JACI 2014



Gibson PG et al. Lancet 2017;390:12-18

Neutrophilic Asthma: Proposed Endotype of Low-LXA4 and SAA-high

% inhibition of IL8 production by epithelial cells exposed to BALF from patients



Rickleffs I et al. JCI Insight 2018 Mar 22;3(6)

Endotype:
Aspirin Exacerbated Respiratory Disease
AERD or NERD

A disease with many names

What it is

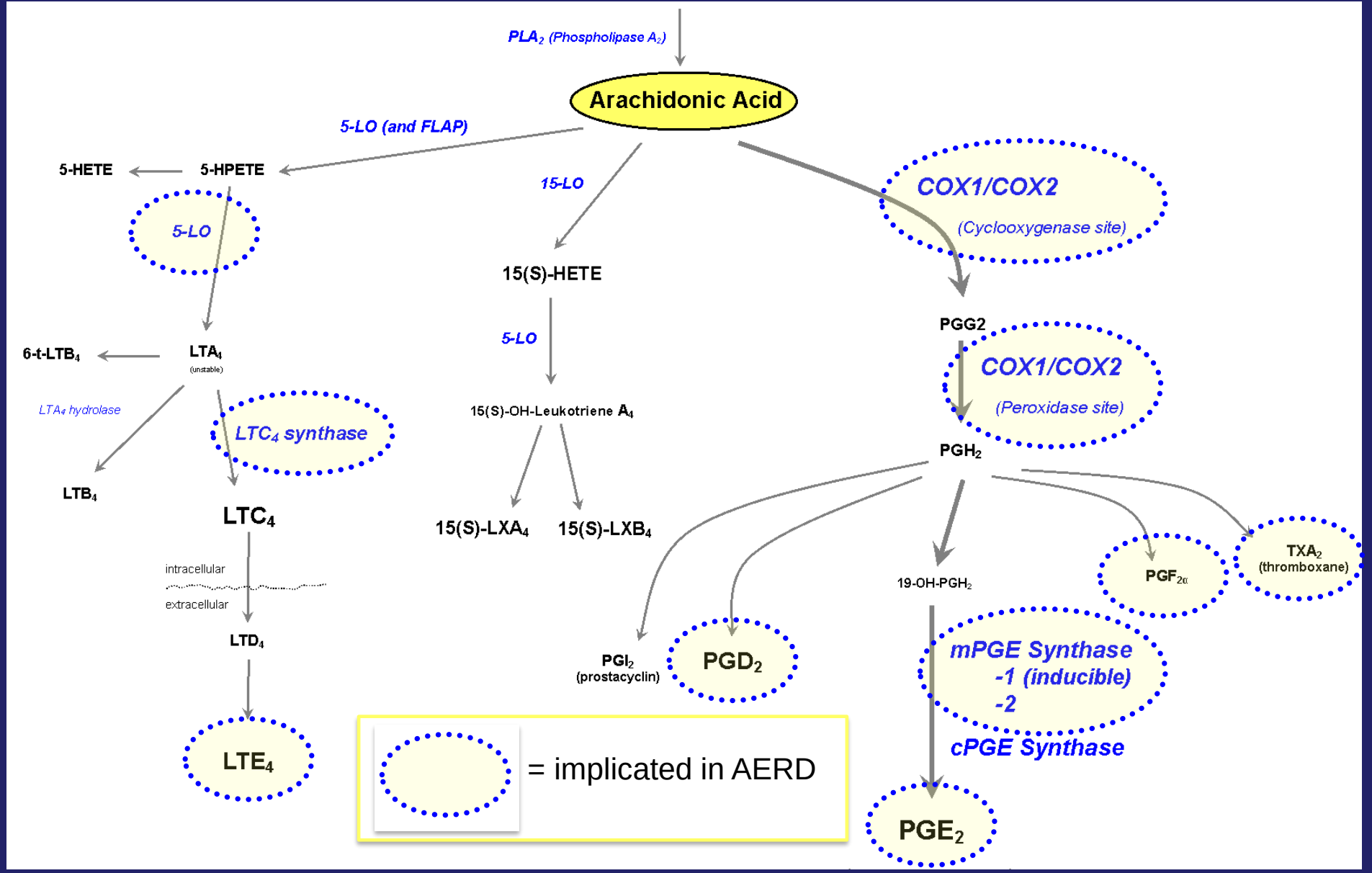
- Asthma
- Nasal polyposis (NP) with chronic hyperplastic eosinophilic rhinosinusitis
- Sensitivity to COX-1 inhibitors

What it is not

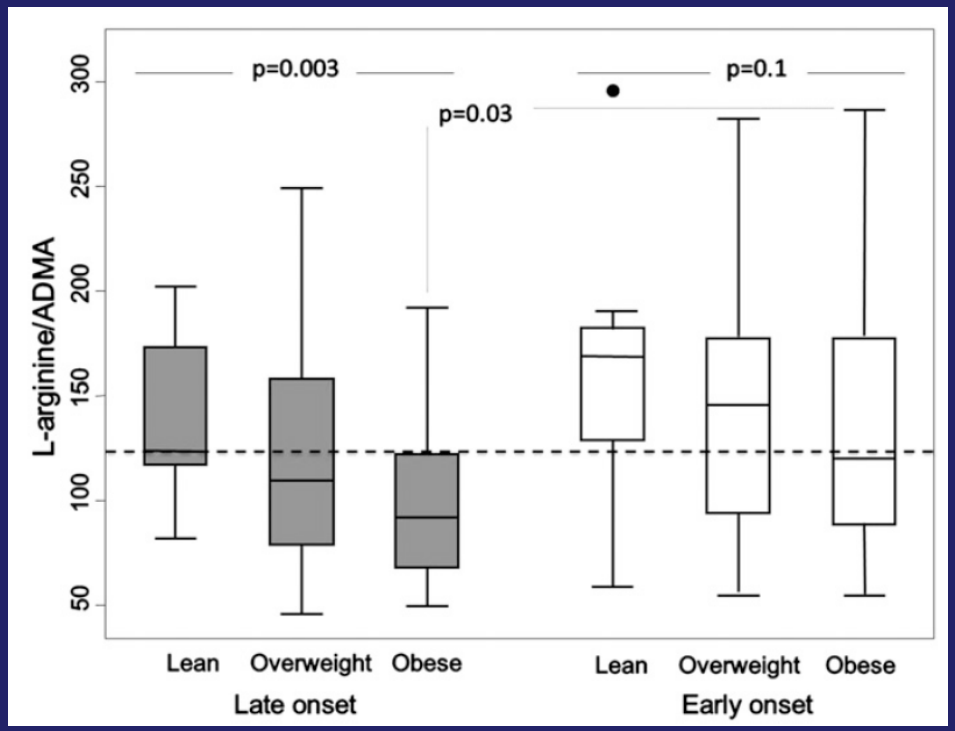
- Not IgE-mediated allergy to aspirin
- Not Mendelian inheritance
- Not childhood disease
- Not due to obvious environmental trigger
- Not transient

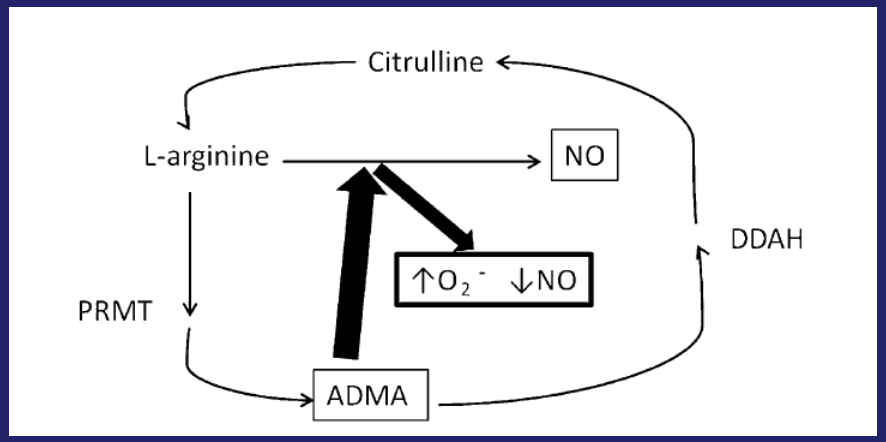
Ledford JACI IP 2016

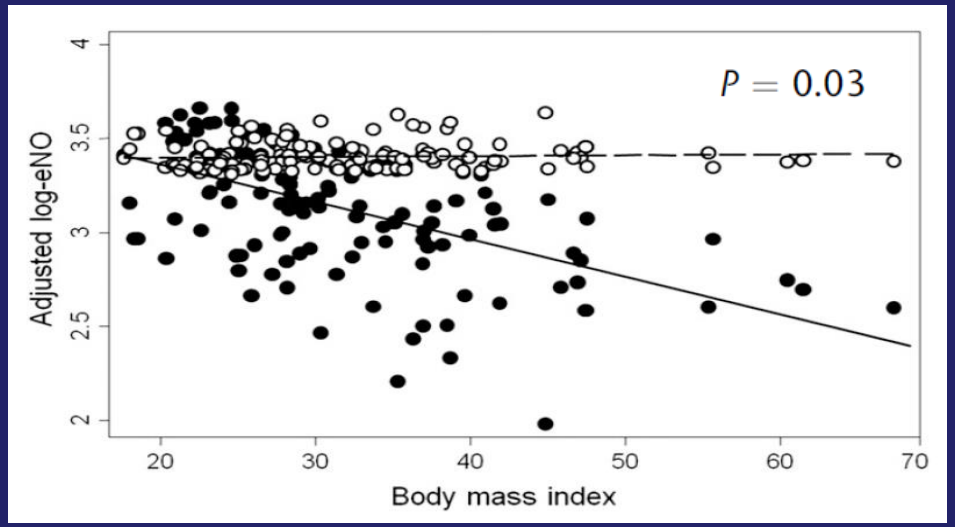
AERD: Eicosanoid Dysregulation Relates to the Pathobiologic Mechanism of the Endotype

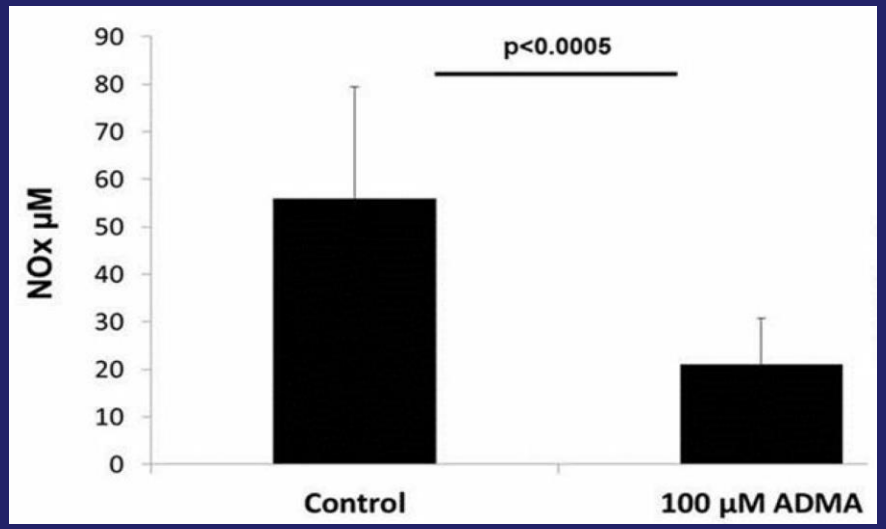


Late-onset Asthma Associated with Obesity: Proposed Endotype with Reduced eNO Due to Increased Catabolism



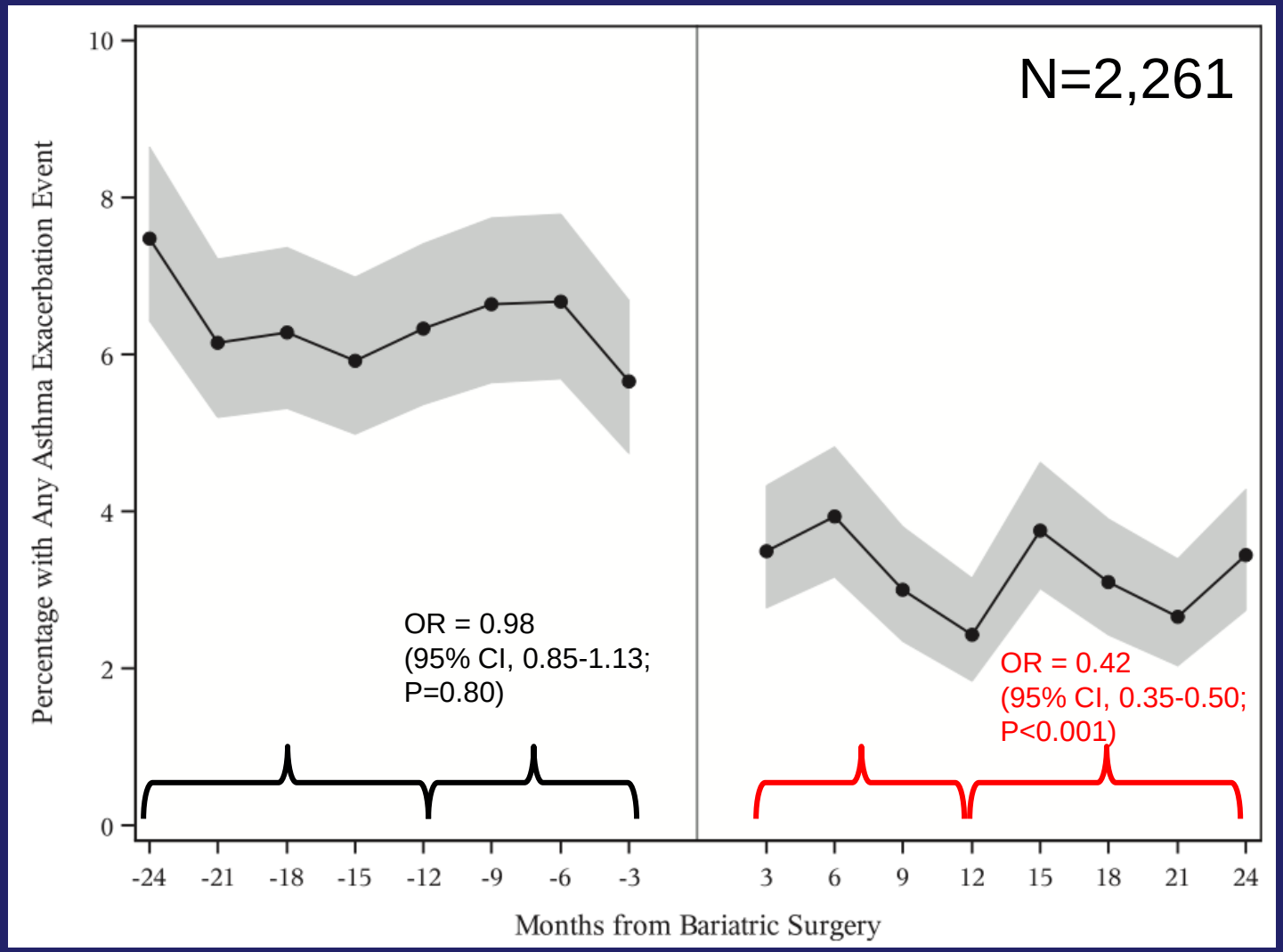






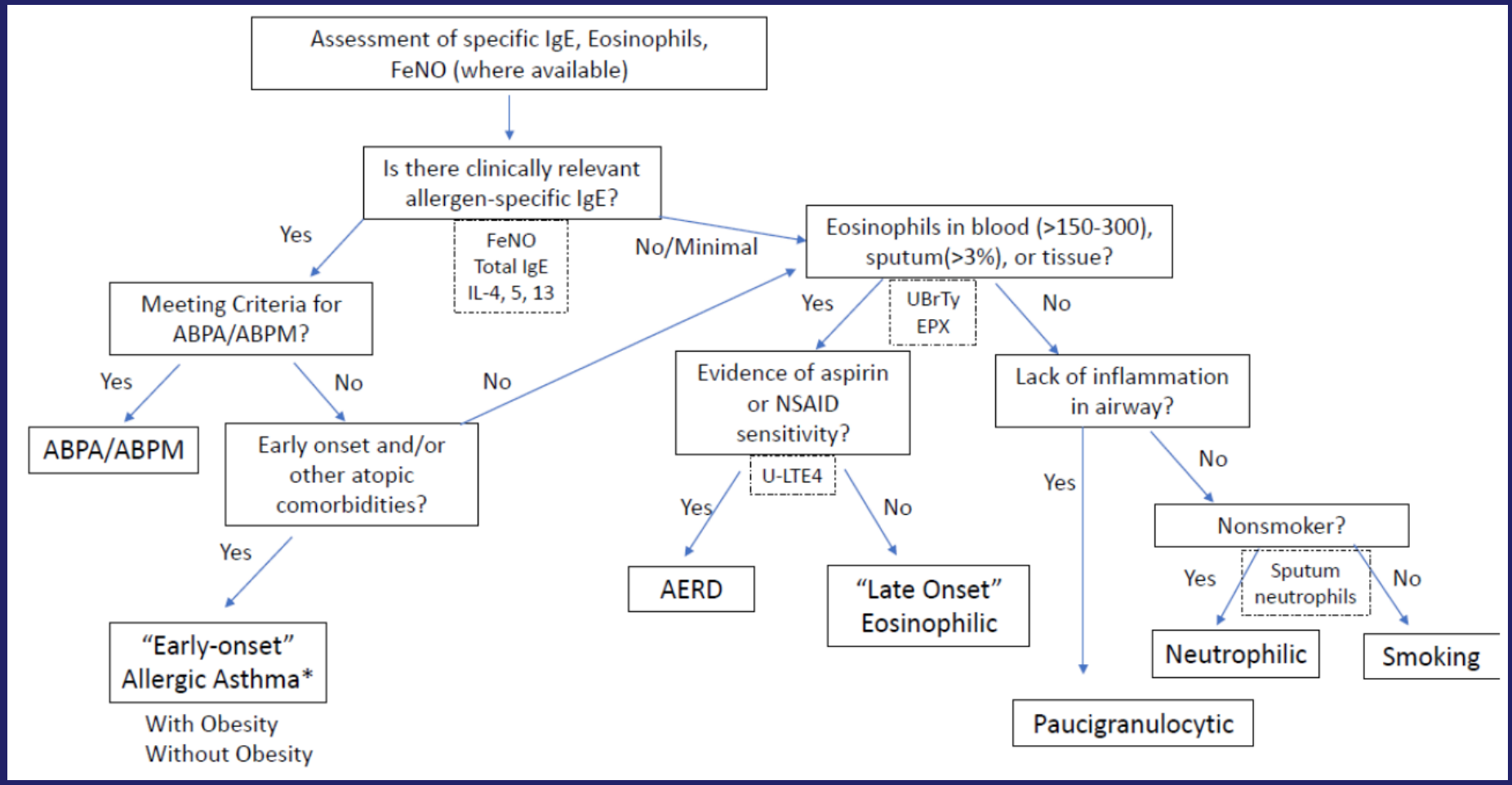
Holguin AJRCCM 2013; Winnica CEA 2017

Response to Weight Reduction in Obese Asthma



Hasegawa et al JACI 2015

Phenotype- and Biomarker-Based Treatment Algorithm



Carr et al AAAI 2018

Phase 2/3 Trial Asthma Cemetery

Summary

1. Asthma is heterogeneous.
2. Knowledge is limited of endotypes defined by molecular aberrations consistently demonstrated in longitudinal analyses.
3. There are only a few existing treatments geared towards particular asthma phenotypes.
4. Endotypes help select the ‘right patient for the right drug’ but effective therapies for multiple phenotypes are appealing as a worthy trial in challenging or severe asthma

References

1. Wenzel SE. *Nat Med.* 2012;18(5):716-725
2. Lang DM. *Allergy Asthma Proc.* 2015;36:418-424.
3. Agache et al. Allergy 2012; 67: 835–846
4. Moore et al. Am J Respir Crit Care Med 2010; 181: 315–323
5. Lotvall et al. JACI 2011; 127: 355-60
6. Israel et al. N Engl J Med. 2017; 377: 965-976
7. Carr T AAAI 2018 in press
8. Choi S et al. JACI 2017;140:690-700
9. Dunican et al JCI 2018; vol 128 pp 997-1009
10. Denlinger et al. AJRCCM 2017 195(3):302-313
11. Ledford et al. JACI IP 2016 vol 4 pp 590-8
12. Muthus et al. Clin Exp Allergy. 2018 pp1–30
13. Holguin AJRCCM 2013 Vol 187, Iss. 2, pp 153–159
14. Winnica et al. Clin Exp Allergy. 2017; 47: 190–199
15. Hasegawa et al. J Allergy Clin Immunol 2015 vol 136 pp288-94
16. Moore et al J Allergy Clin Immunol 2014 vol 133 pp1557–1563
17. Green R, et al. Lancet. 2002; 360(9347):1715-21.
18. Price DB et al. Lancet Resp Med. 2015;3:849-58.
19. Patel et al. Expert Opin Biol Ther. 2018 July ; 18(7): 747–754.
20. Evans et al. JACI 2018 ;142:415-23
21. Ricklefs et al. JCI Insight. 2018 Mar 22;3(6)
22. Wechsler