Φαινότυποι και ενδότυποι σοβαρού άσθματος: Ματιές στο μέλλον

Στέλιος Λουκίδης MD phD FCCP FERS
Ιατρική σχολή ΕΚΠΑ

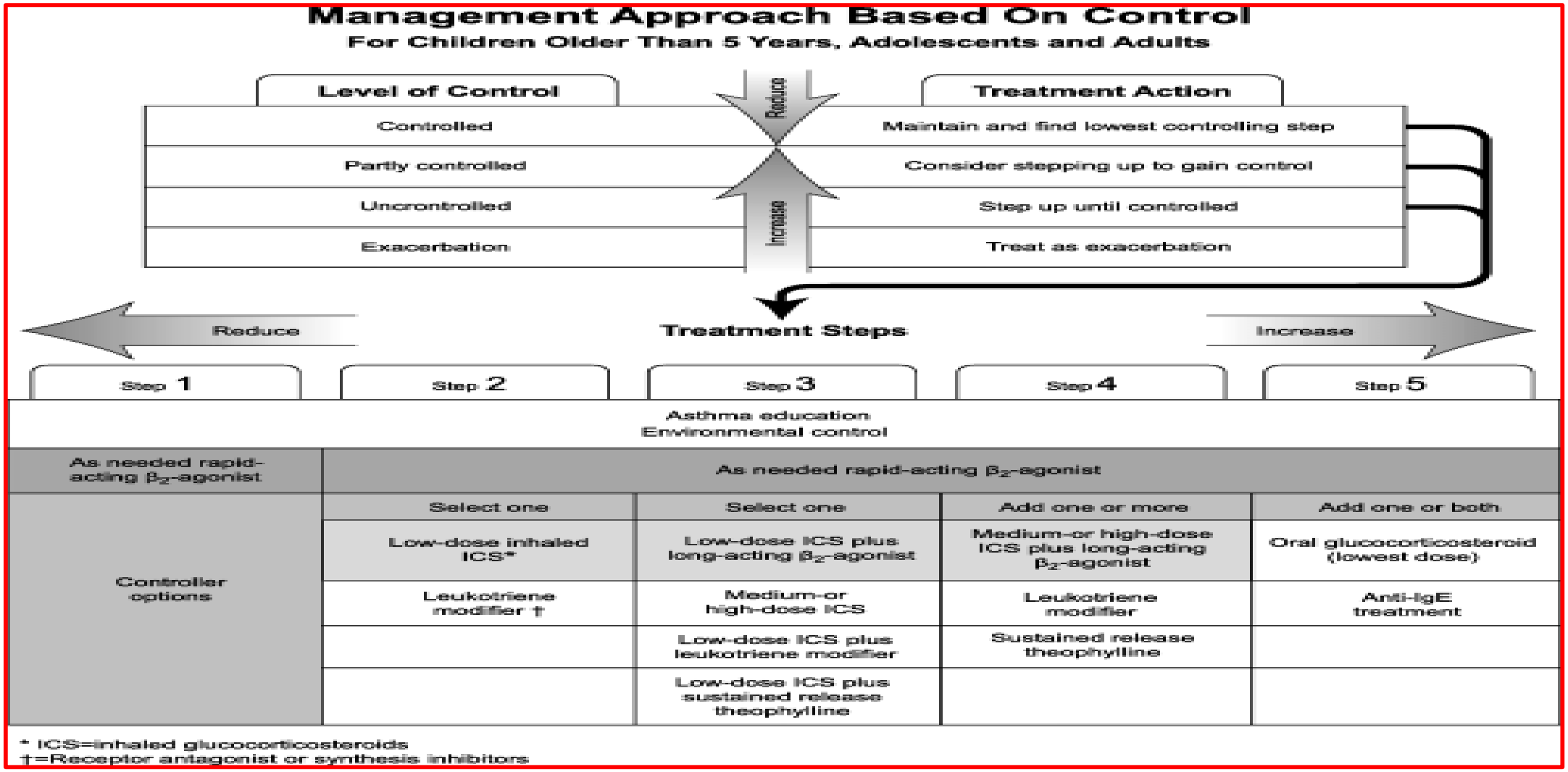
Conflicts [Honorarium fees]

- AstraZeneca Greece & Bulgaria & Poland
- Boehringer Ingelheim Greece& Europe
- Chiesi
- GlaxoSmithKline Greece & Denmark
- Elpen
- Menarini Helllas
- Novartis Hellas & Europe
- Pharmaten Hellas
- Vianex/MSD

Σχεδιασμός

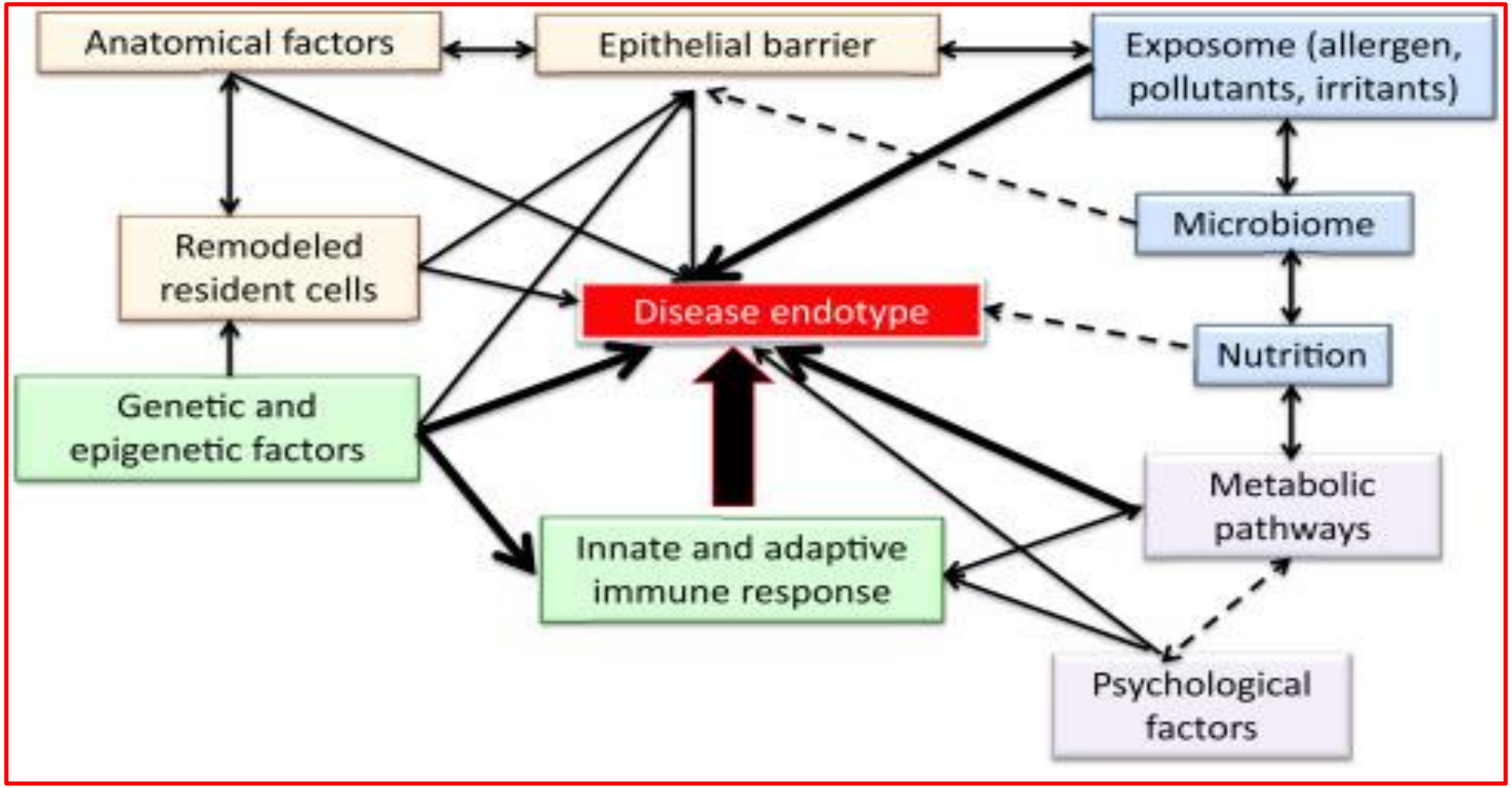
- **10 χρόνια πριν & εισαγωγικά σχόλια**

2007 Η θεραπεία του άσθματος: Έλεγχος και μονοκλωνικό αντίσωμα για την IgE



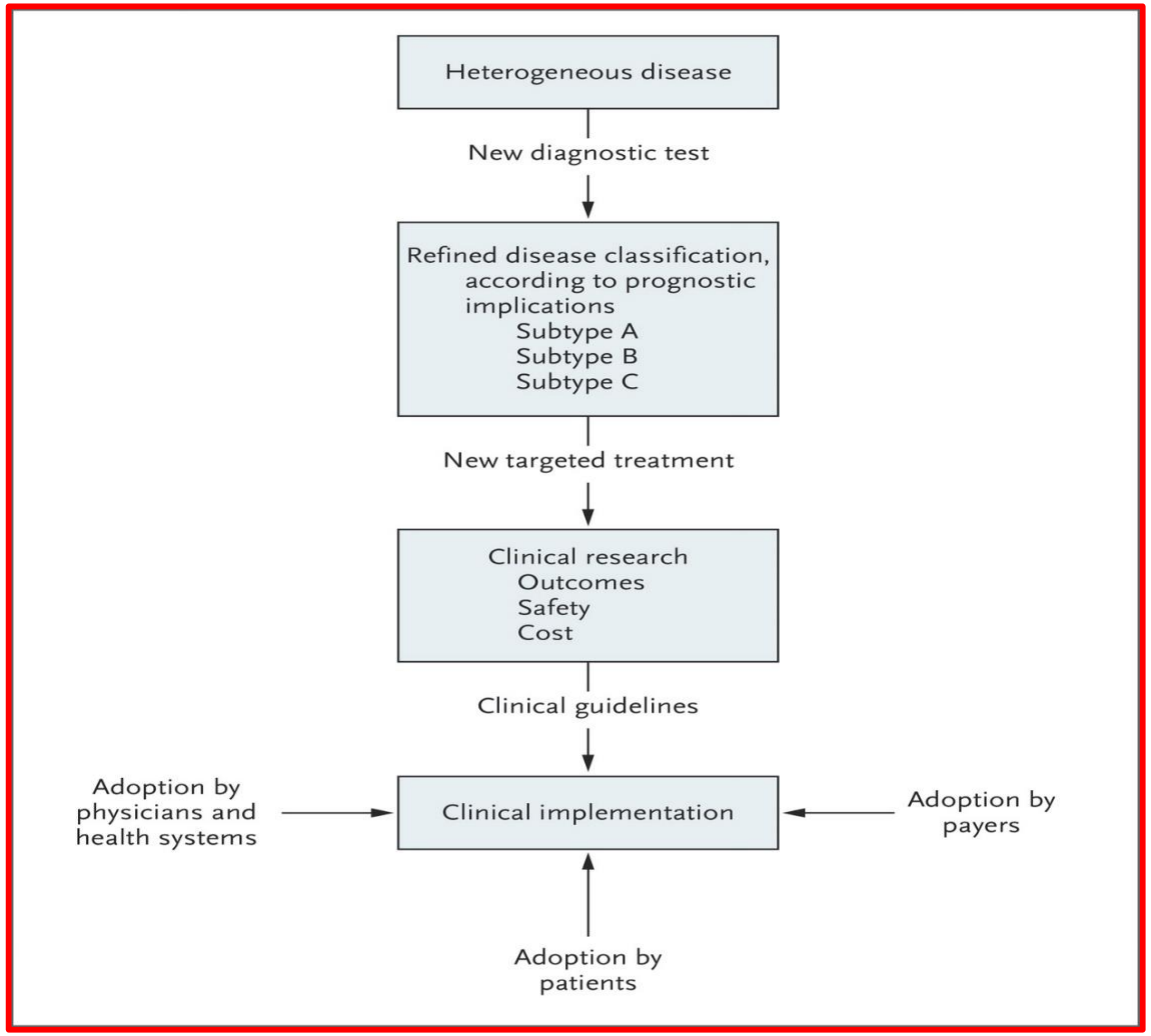
Bousquet J et al Allergy 2007

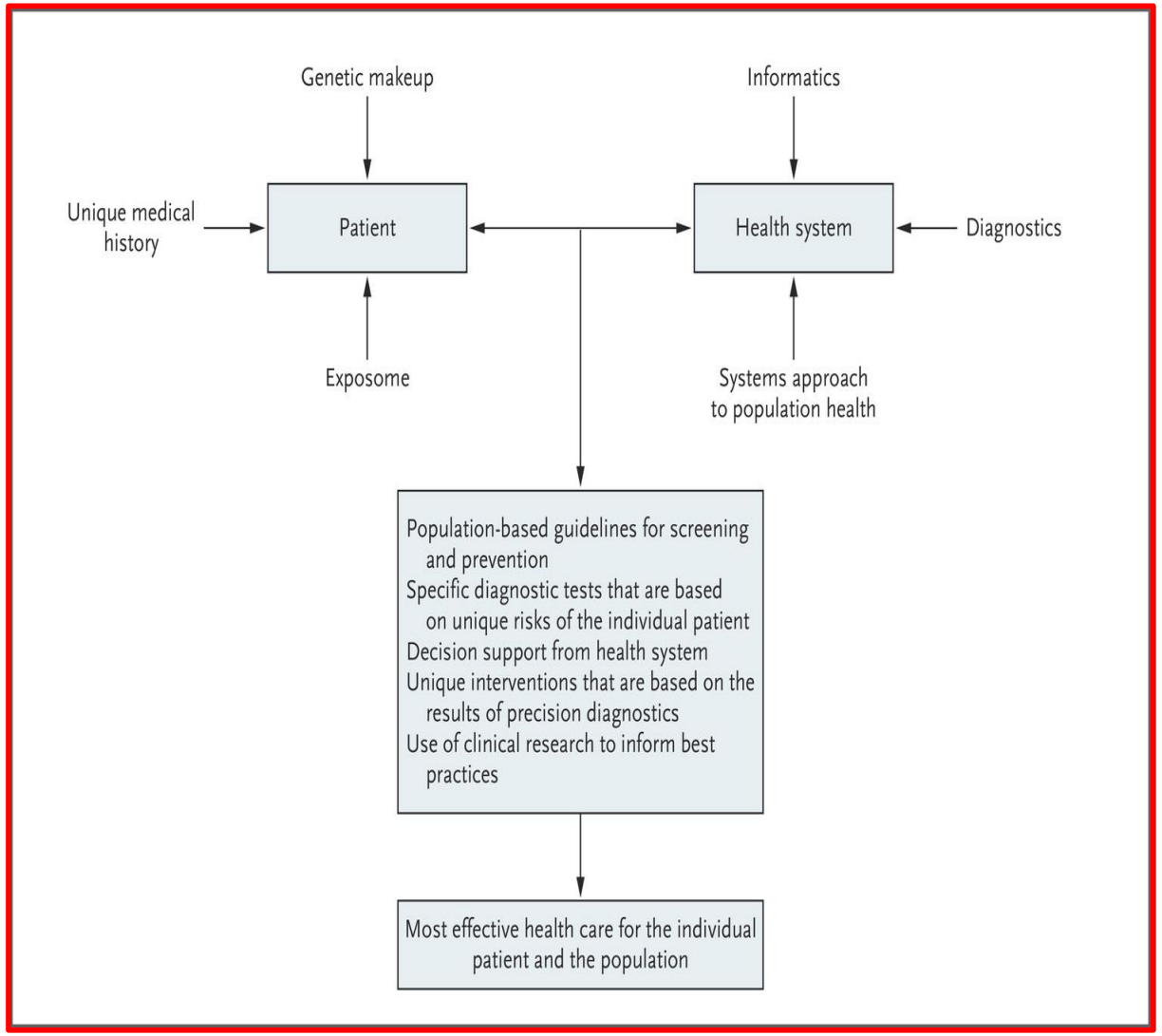
Ξεπερνώντας την απλουστευμένη εξήγηση



Agache I & Akdis CA Allerg Inter 2016

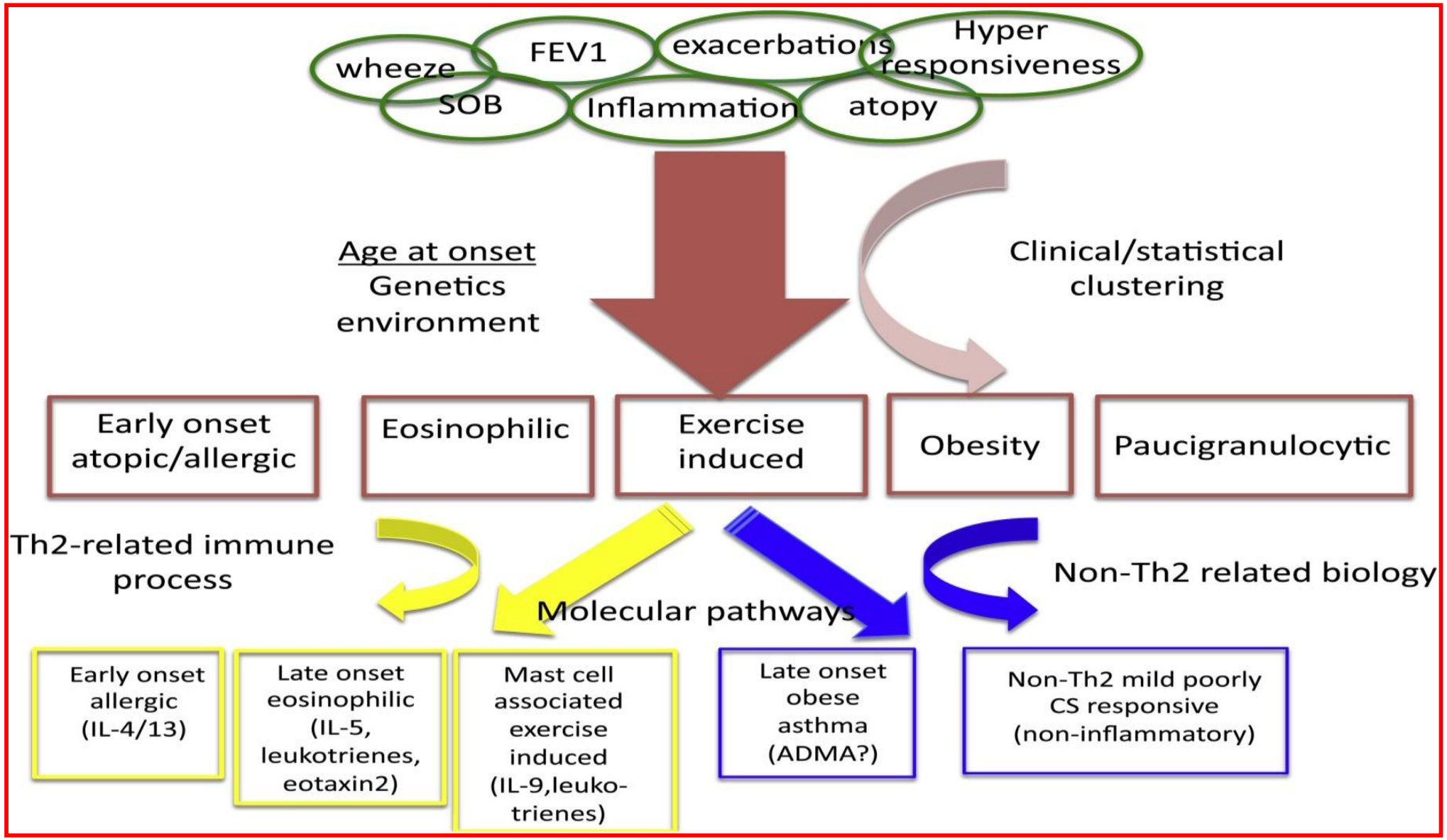
Προσωποποιημένη θεραπεία





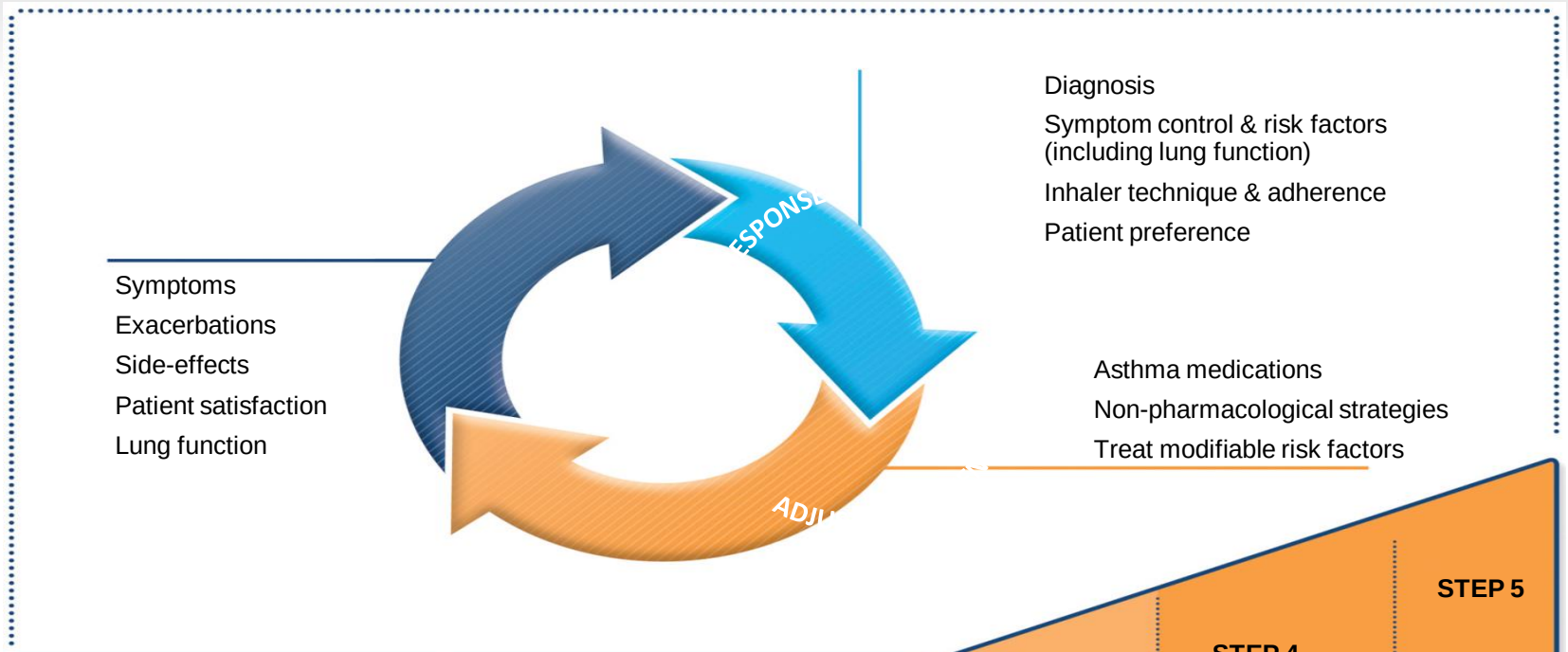
Precision medicine is a complicated process where the focus is on identifying which approaches will be effective for which patients based on genetic, environmental, and lifestyle factors.

Jameson JL, Longo DL. N Engl J Med 2015;372:2229-2234.



Sally E. Wenzel Pulmonary Pharmacology & Therapeutics 2013

2018 Φαινοτυπική και θεραπευτική προσέγγιση



	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER CHOICE		Low dose ICS	Low dose ICS/LABA**	Med/high ICS/LABA	Refer for add-on treatment e.g. tiotropium,*† anti-IgE, anti-IL5*
Other controller options		*Consider low dose ICS* *Leukotriene receptor antagonists (LTRA)* *Low dose theophylline**	*Med/high dose ICS* *Low dose ICS + LTRA (or + theoph*)*	*Add tiotropium*†* *Med/high dose ICS + LTRA (or + theoph*)*	*Add low dose OCS*
RELIEVER	As-needed short-acting beta2-agonist (SABA)			As-needed SABA or low dose ICS/formoterol#	

*Not for children <12 years

**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS

#For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

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- **10 χρόνια πριν & εισαγωγικά σχόλια**
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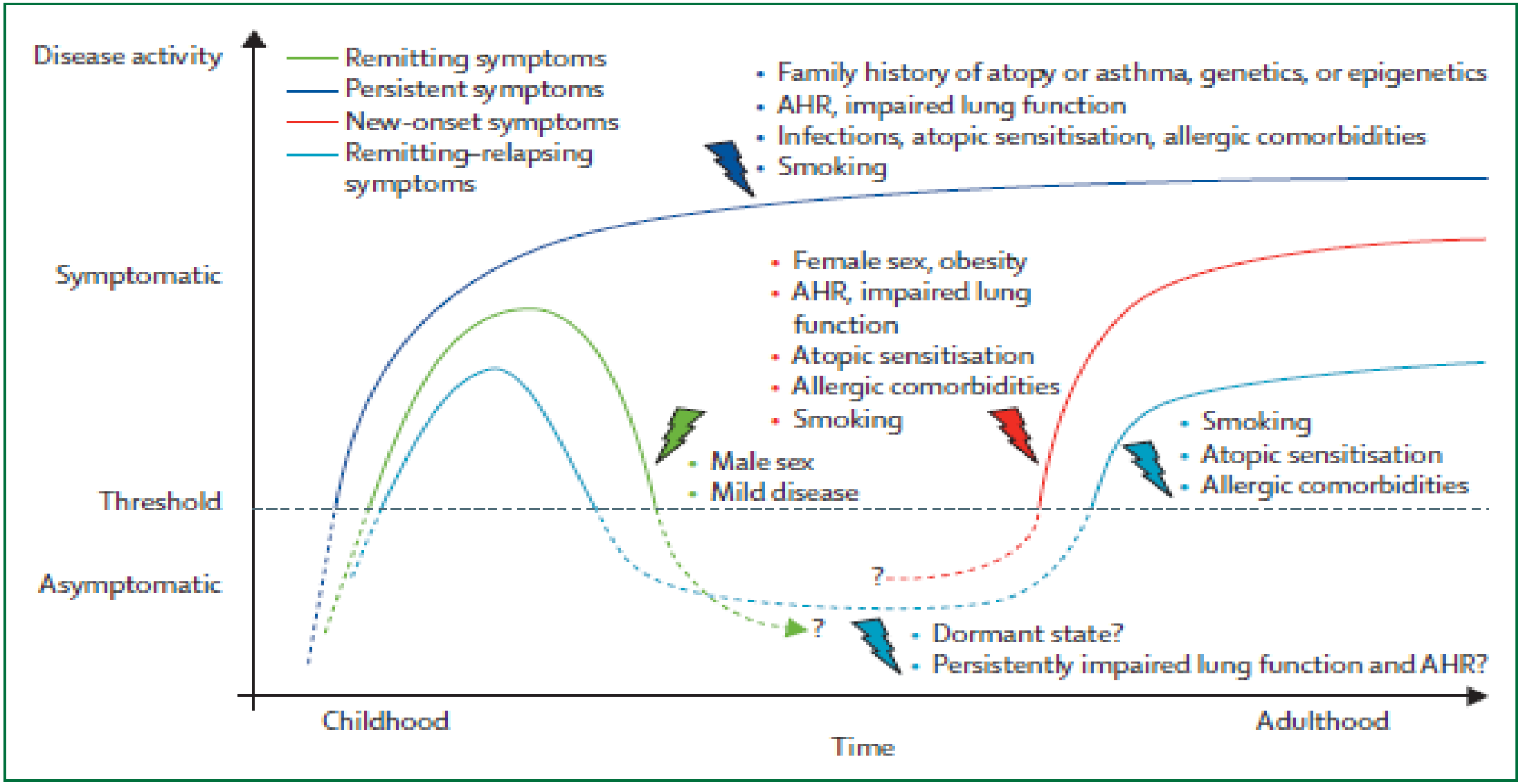
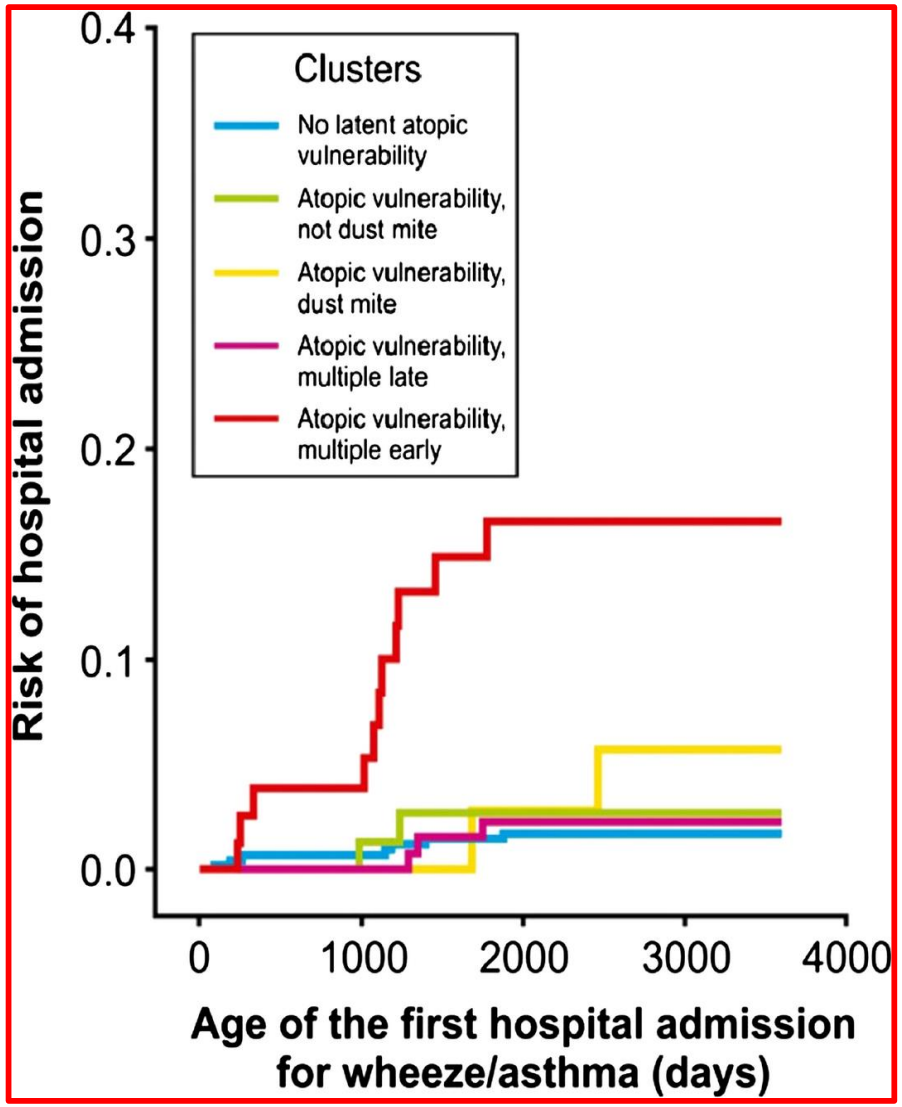
Κλείνει το κενό ή υπάρχουν μυστικά?

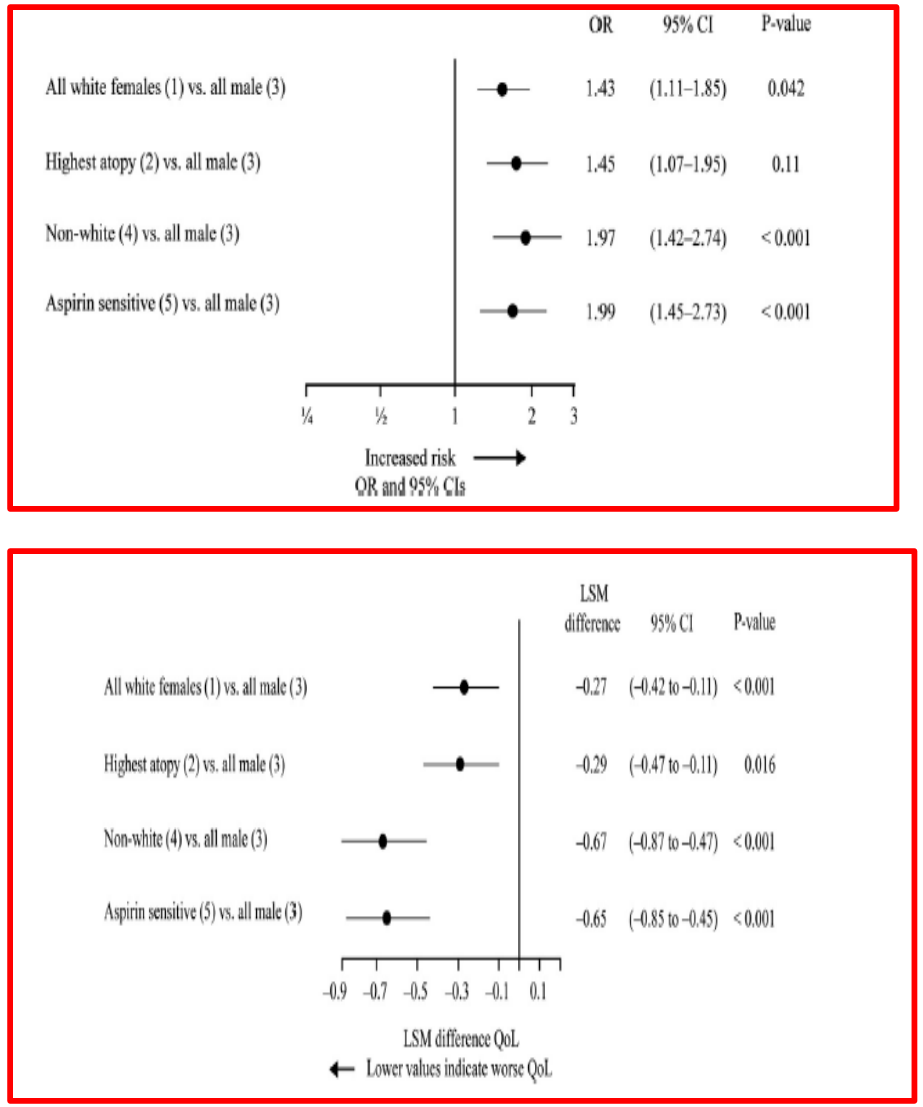


Fuchs O et al Lancet Respiratory 2017

Είναι η ατοπία στα παιδιά ο βασικός φαινότυπος για SRA

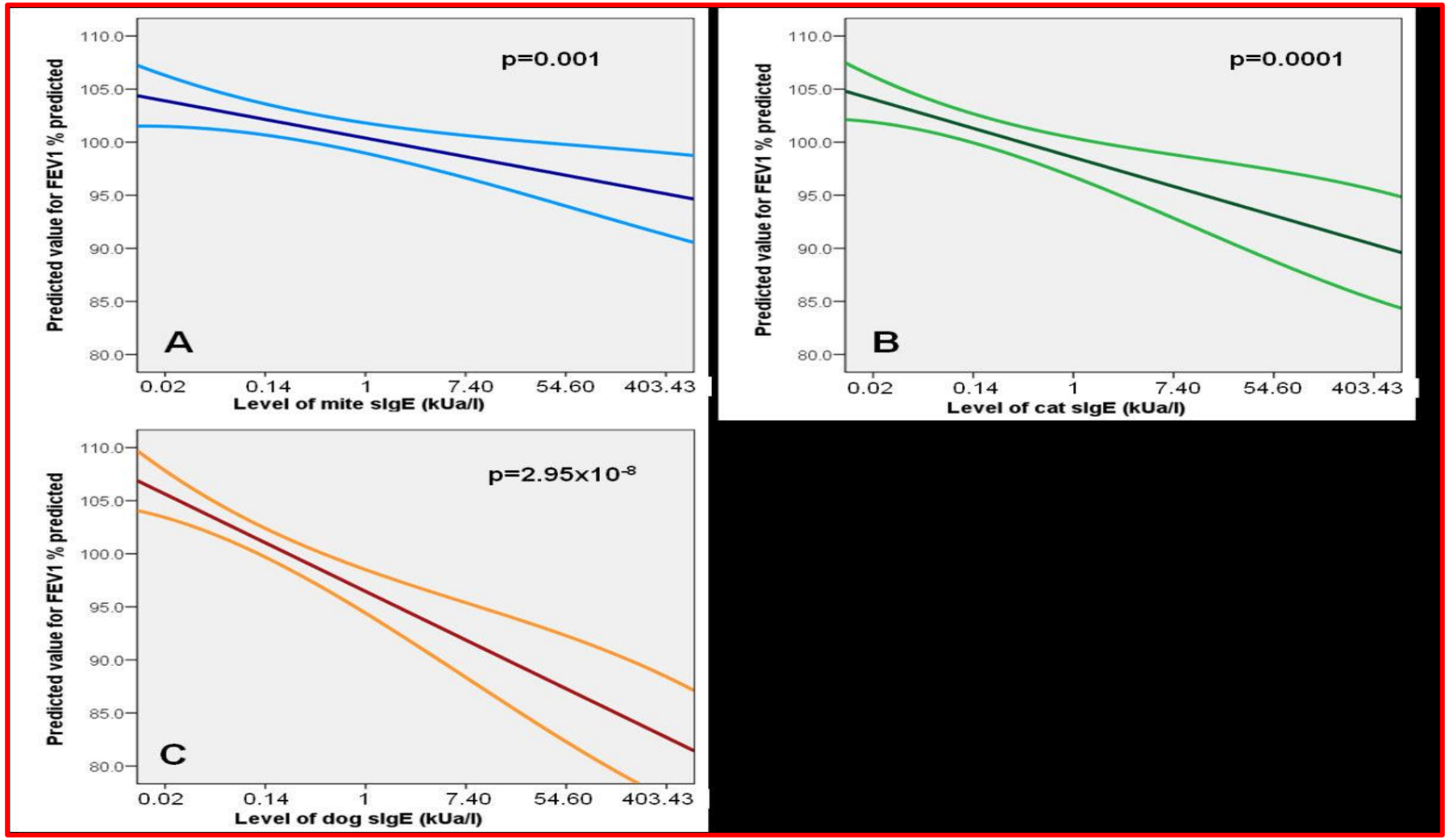


Simpson A et al Am J Respir Crit Care Med 2010



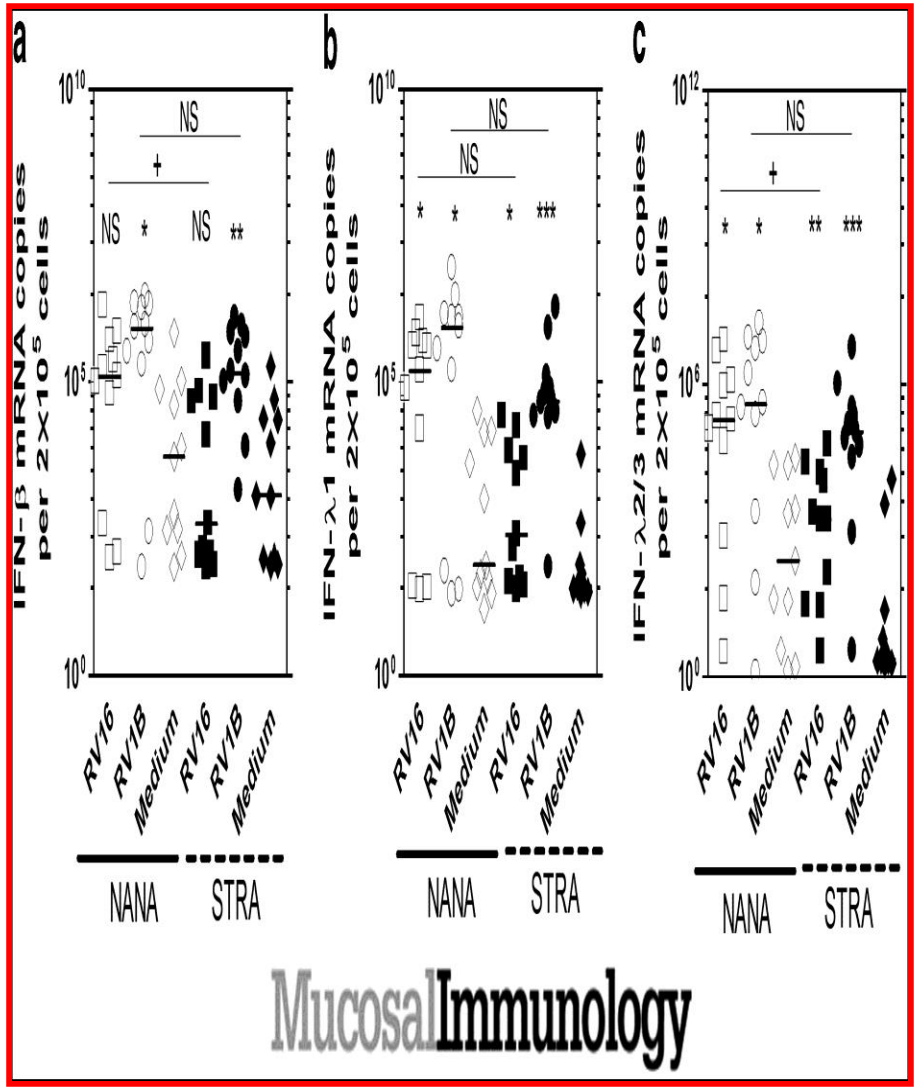
Schatz M et al JACI 2014

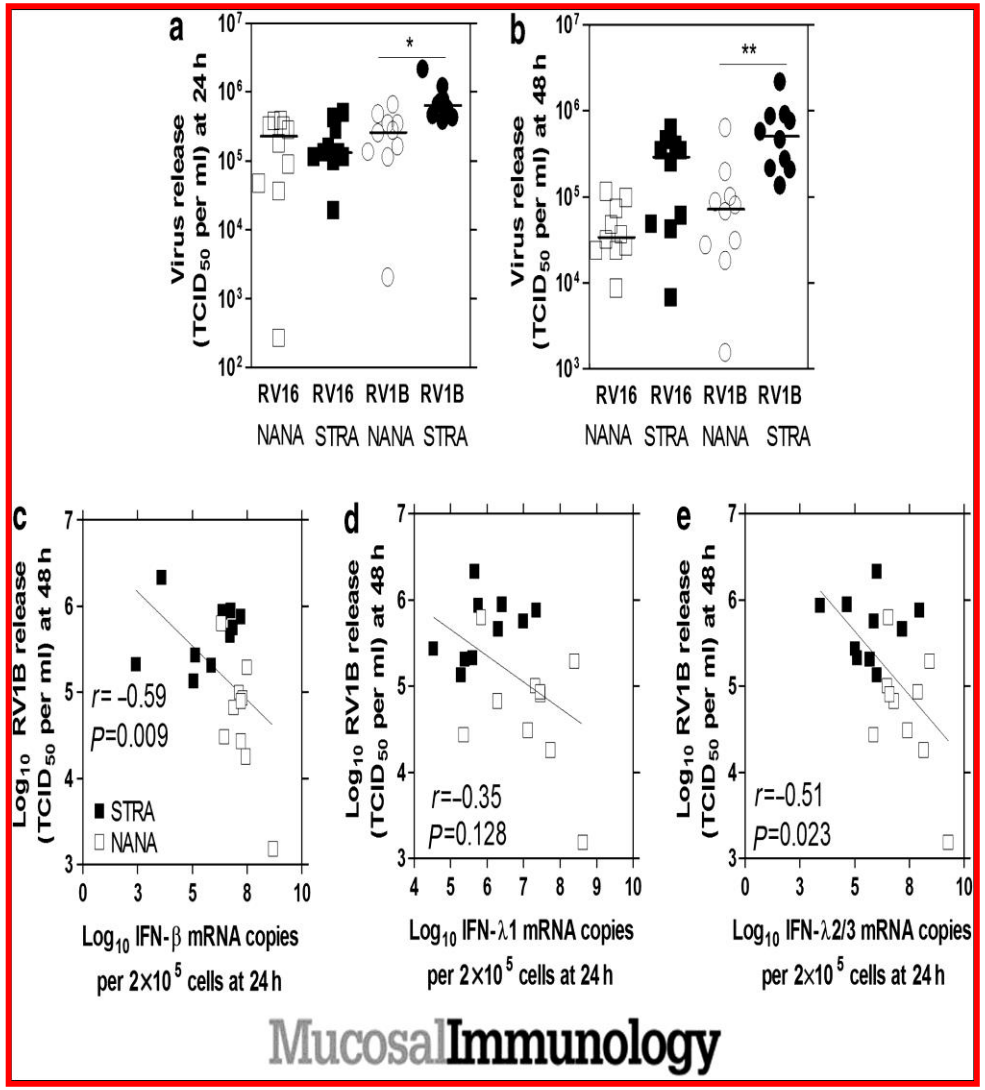
Δεν είναι διχοτομική παρέμβαση



Marinho S et al Clin Transl Allergy. 2011

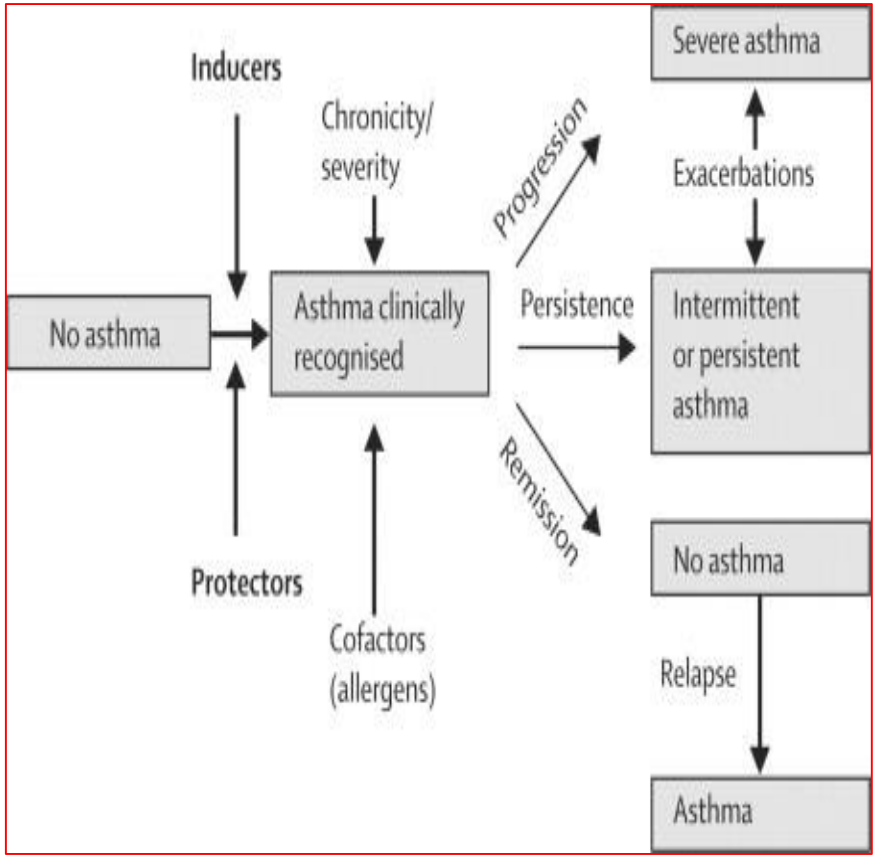
Ανοσιακή απάντηση σε παιδιά με ατοπία και παροξύνσεις

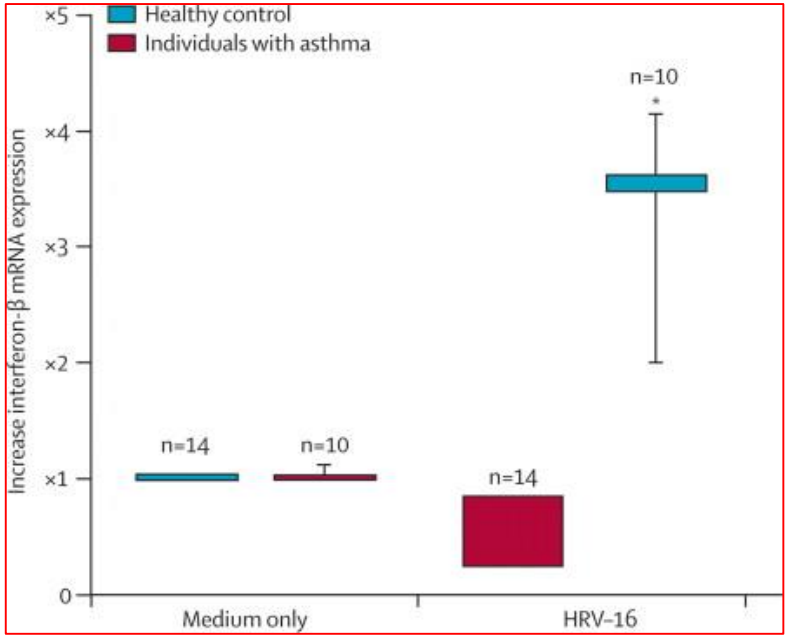


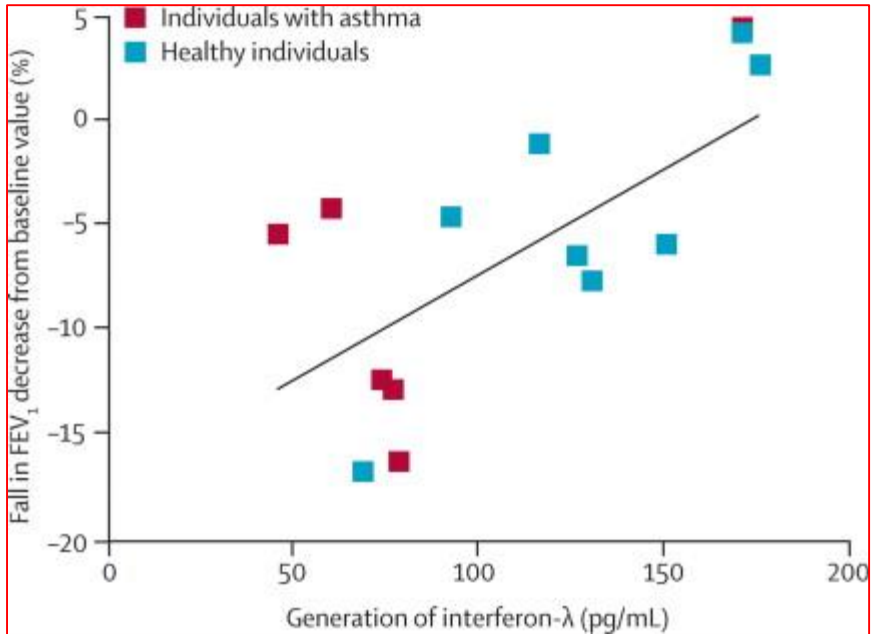


Edwards MR et al Mucosal Immunology **2013**

Ιογενείς λοιμώξεις – επιπρόσθετη παράμετρος

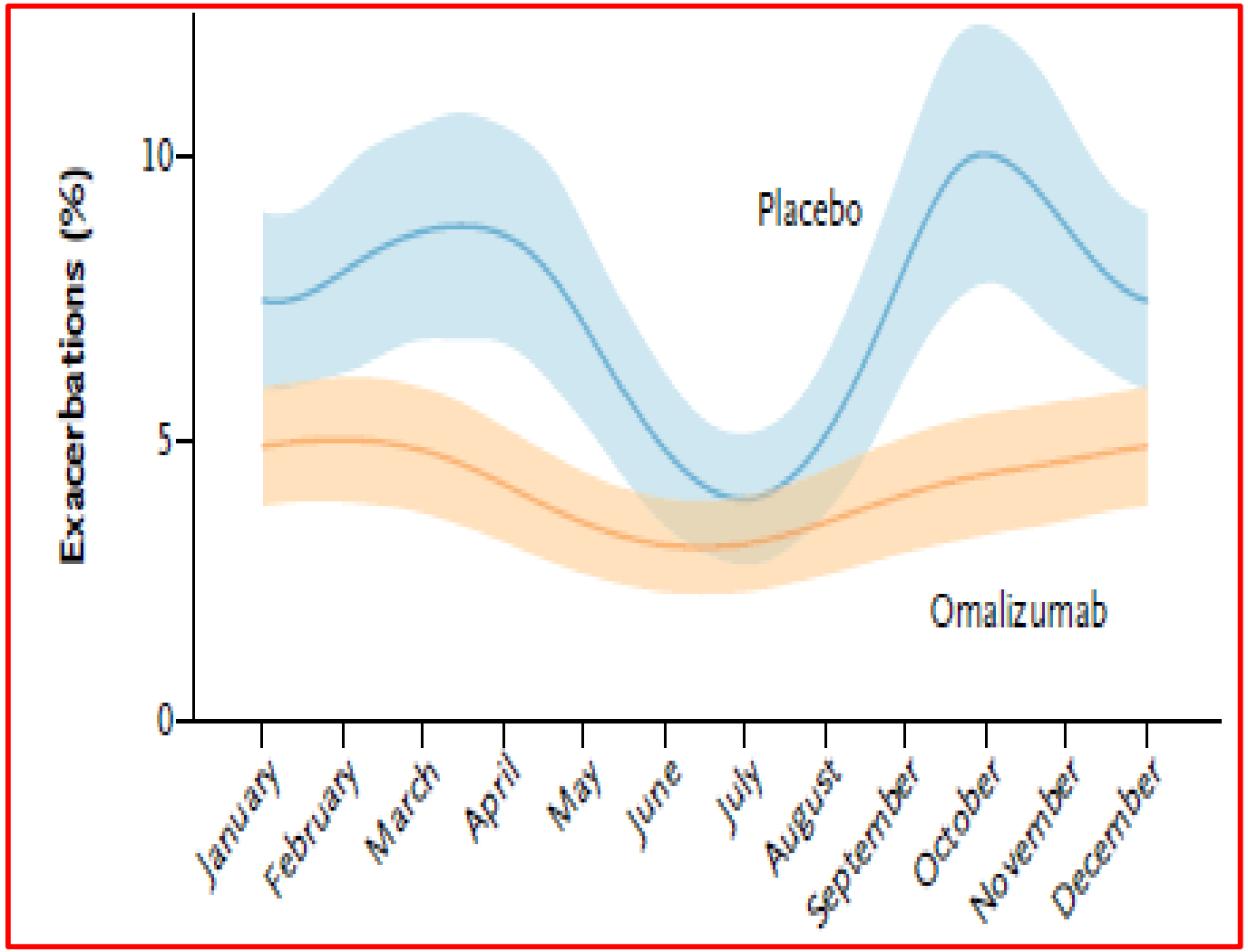


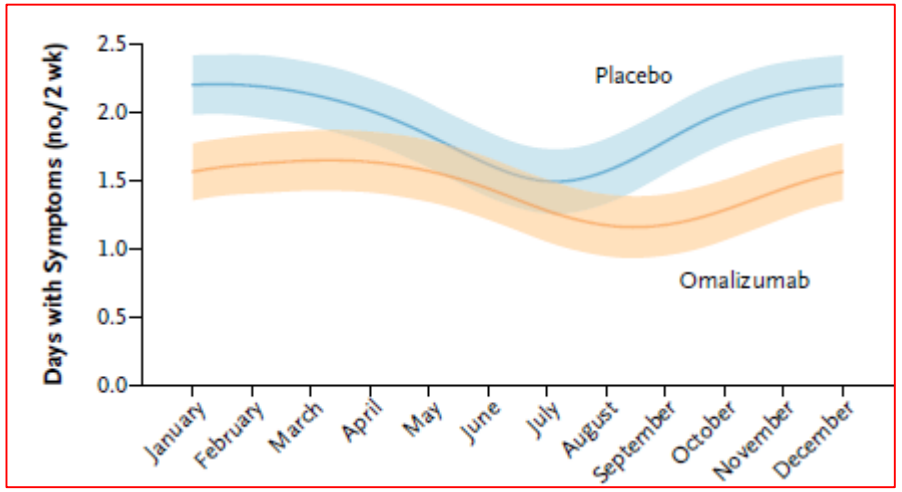


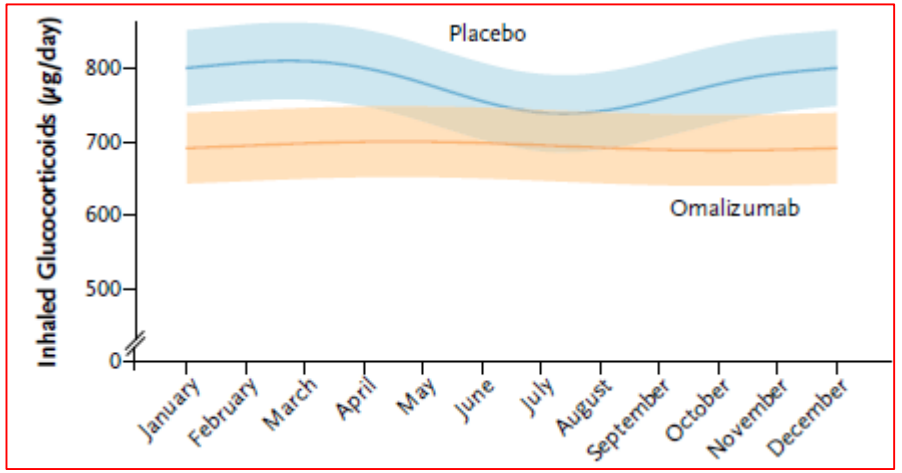


Busse WW et al, Lancet 2010
Lemanske RF et al JACI 2005
Wark Pa et al J Exp Med 2010

Η ένδειξη

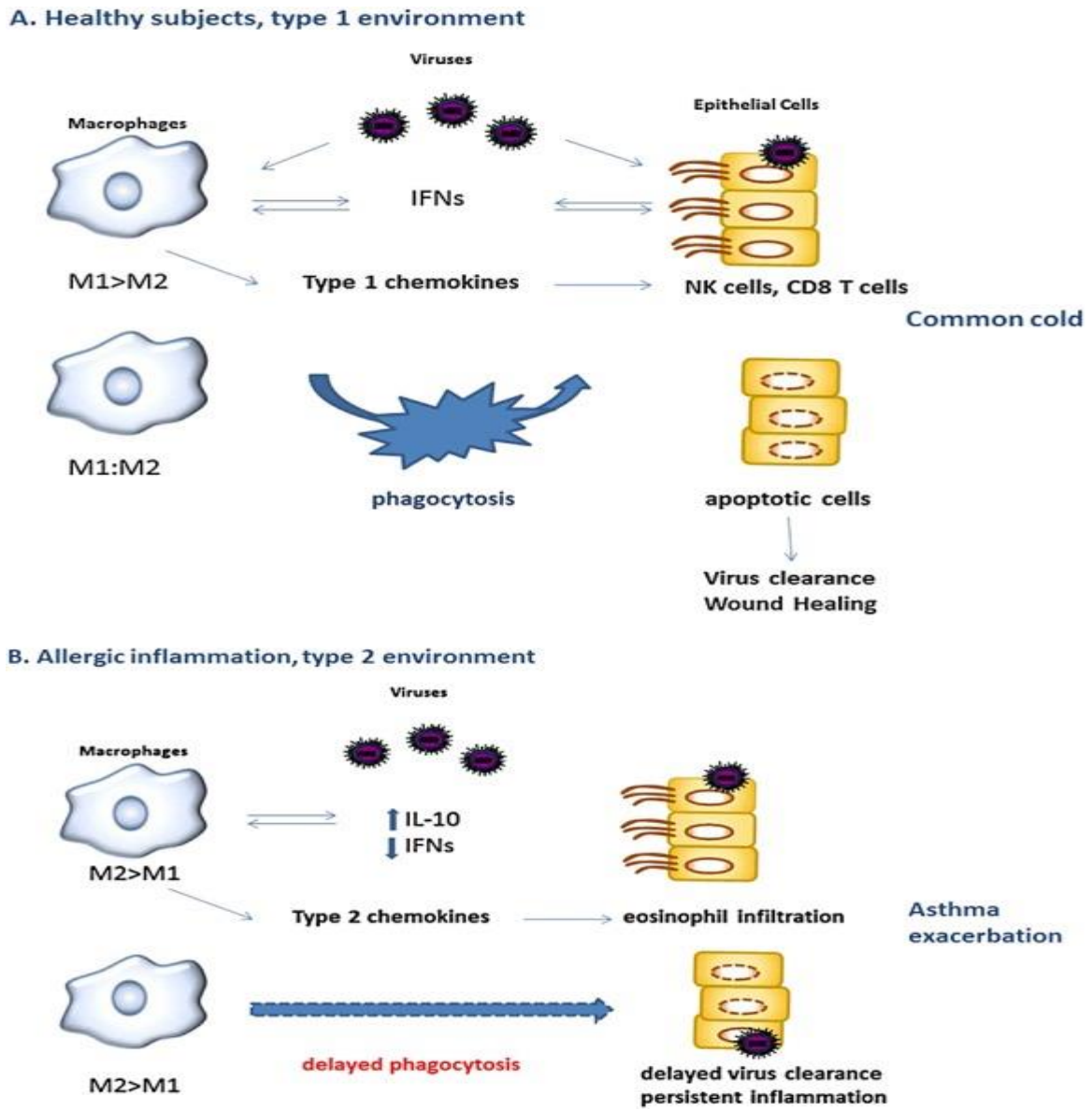


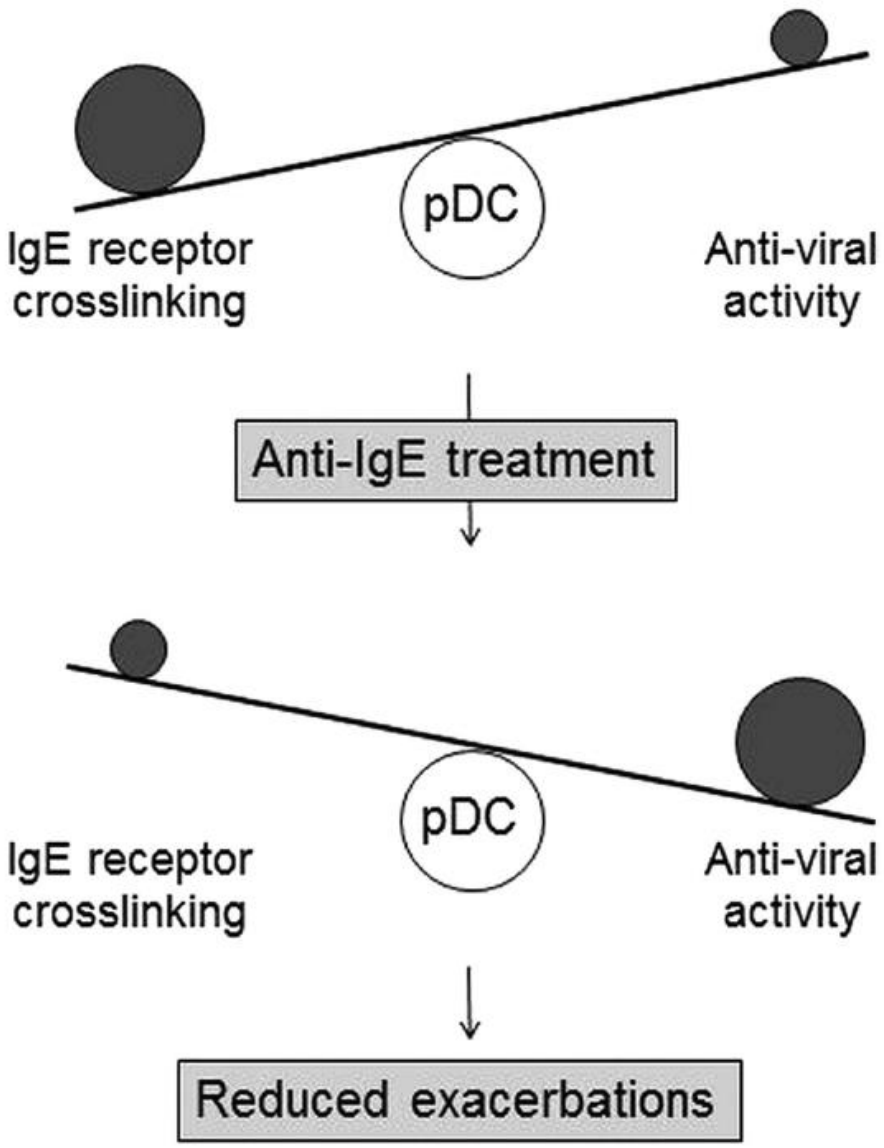




Busse WW et al. N Engl J Med 2011

Θα αλλάξουμε το δρόμο της αντι IgE?





Johnston S Rev med Vir 2015 & Lommatzsch M et al Thorax 2014

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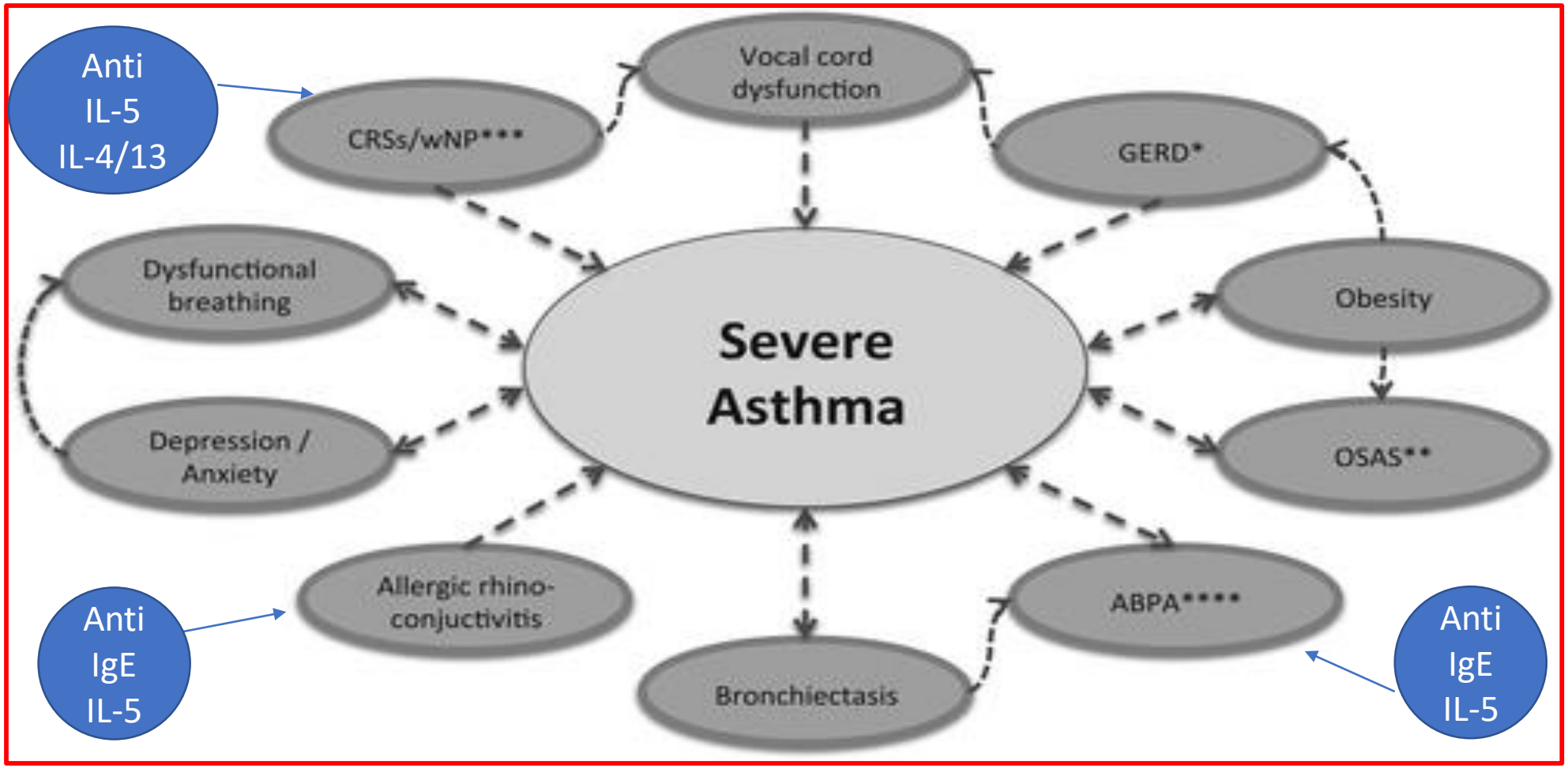
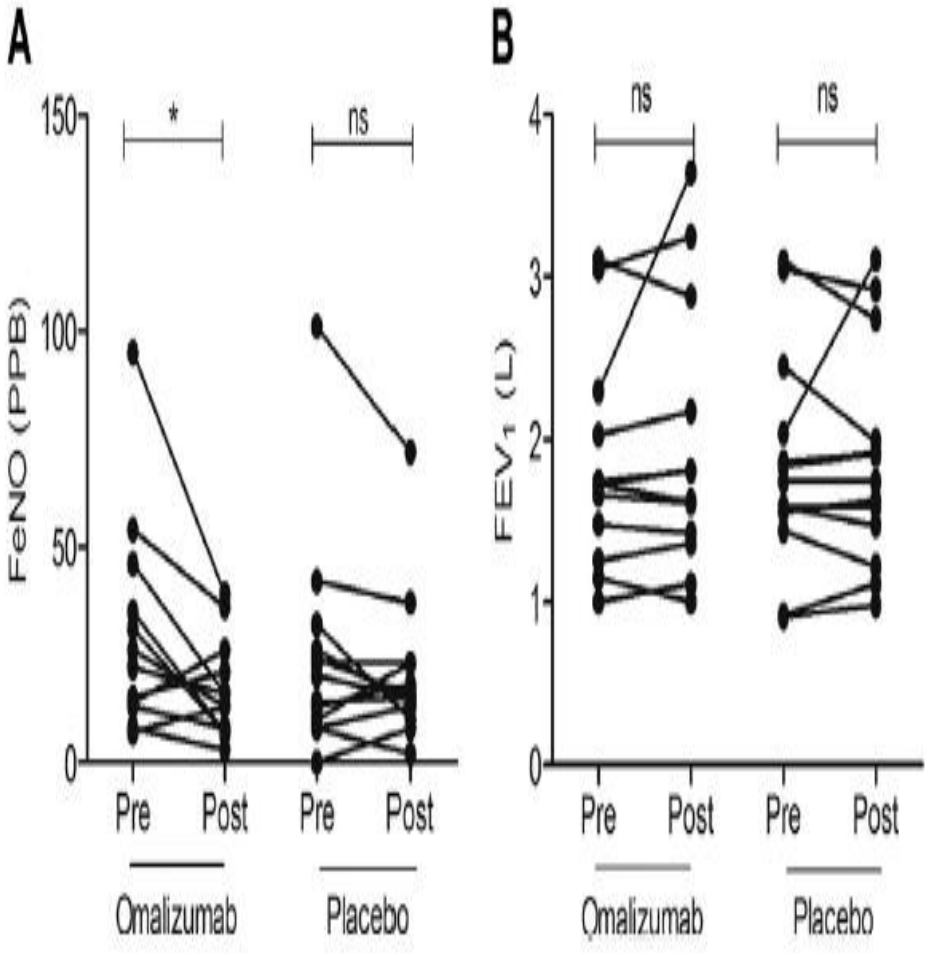
Συν-νοσηρότητες στο ΣΑ-Θεραπευτικός φαινότυπος με συγκεκριμένους ενδότυπους



Celeste Porsbjerg & Menzies Gow A Respirology 2017

Anti IgE [omalizumab] για ABPA



Voskamp AL et al JACI practice 2015

Anti IL-5-Churg Strauss

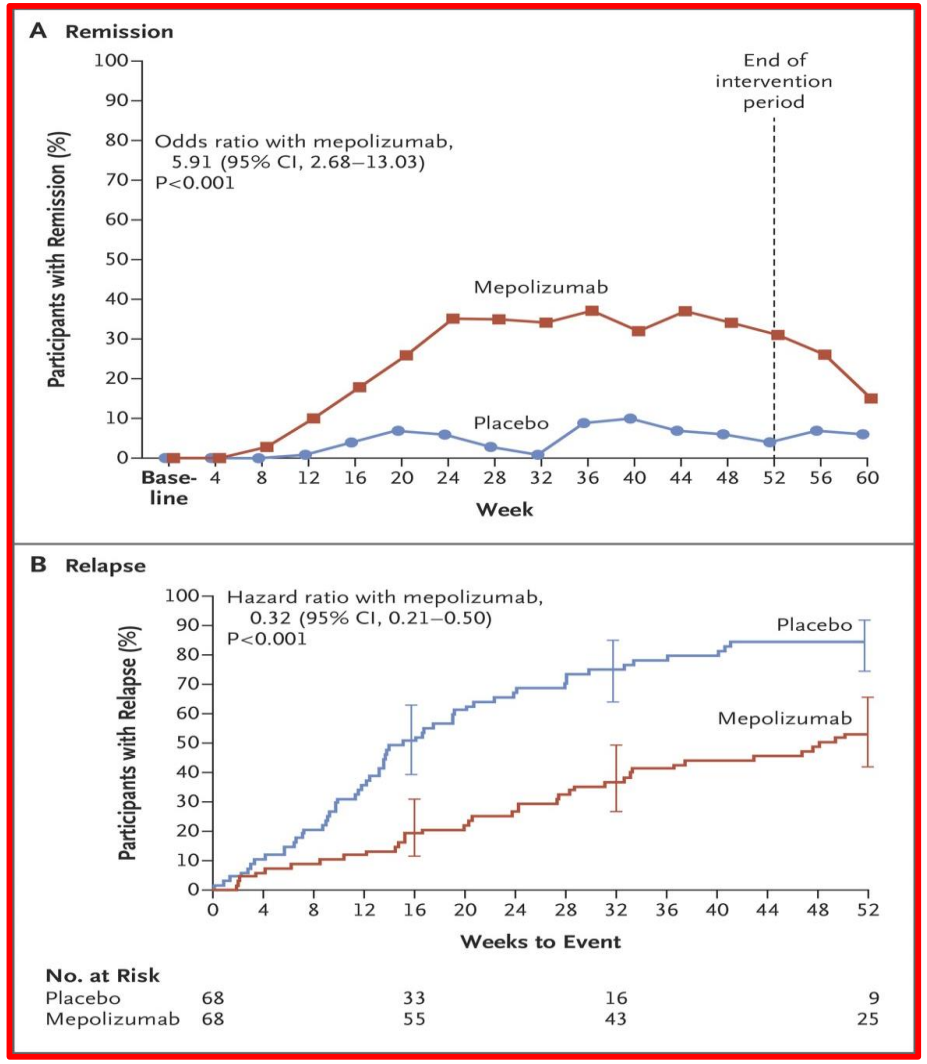


Table 2. Efficacy End Points in the Intention-to-Treat Population.*

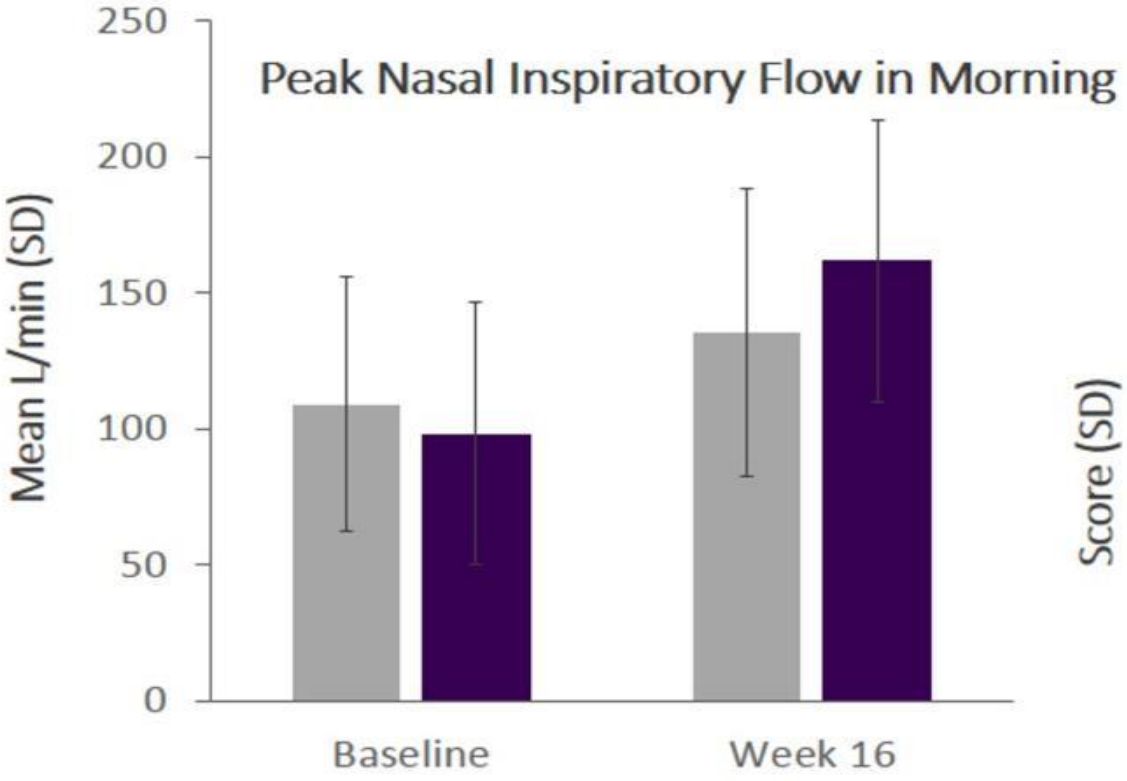
End Point	Mepolizumab (N=68)	Placebo (N=68)	Odds Ratio or Hazard Ratio (95% CI)	P Value
	no. of participants (%)			
Primary end points				
Accrued weeks of remission over 52-wk period			5.91 (2.68–13.03)	<0.001
0 wk	32 (47)	55 (81)		
>0 to <12 wk	8 (12)	8 (12)		
12 to <24 wk	9 (13)	3 (4)		
24 to <36 wk	10 (15)	0		
≥36 wk	9 (13)	2 (3)		
Remission at wk 36 and wk 48	22 (32)	2 (3)	16.74 (3.61–77.56)	<0.001
Other end points				
Remission within the first 24 wk that was sustained until wk 52	13 (19)	1 (1)	19.65 (2.30–167.93)	0.007
First EGPA relapse	38 (56)	56 (82)	0.32 (0.21–0.50)	<0.001

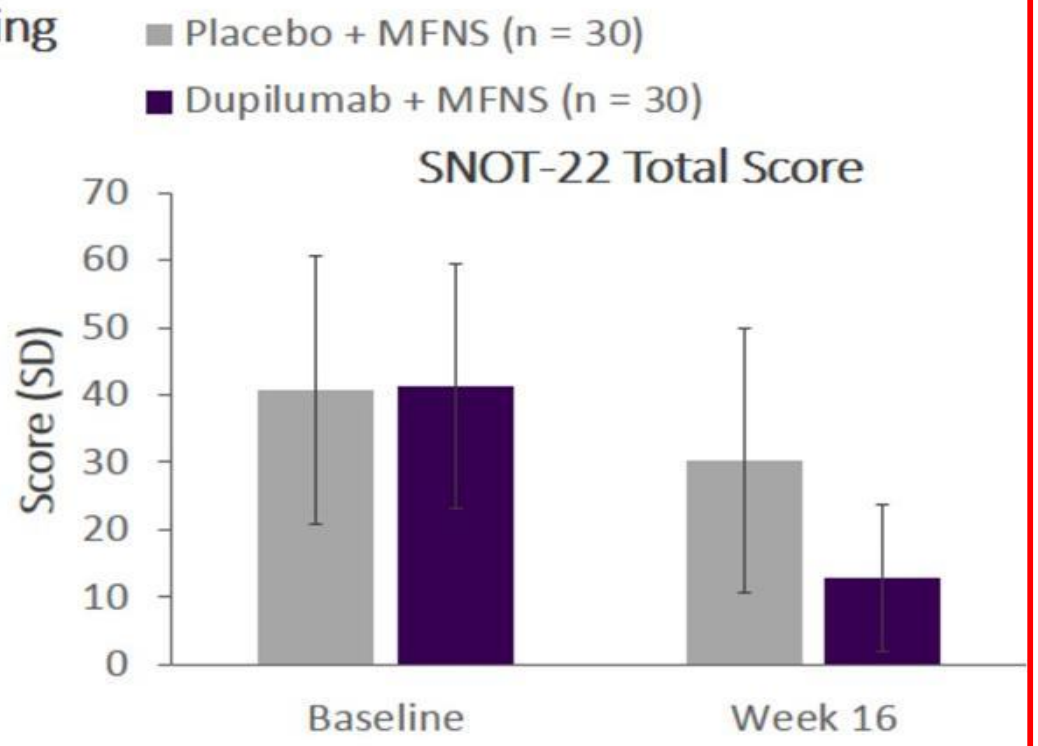
* Odds ratios are shown for the analyses of the two primary end points and for the secondary analysis of remission within the first 24 weeks that was sustained until week 52. For the analysis of accrued weeks in remission, the odds ratio is for 24 or more weeks of accrued remission. Remission was defined as a BVAS of 0 (on a scale from 0 to 63, with higher scores indicating greater disease activity) and a prednisolone or prednisone dose of 4.0 mg or less per day. For the time-to-event analysis of the first relapse of EPGA, the hazard ratio is shown. Participants with a first EGPA relapse were those who had a relapse before the completion of the planned trial period or who withdrew prematurely from the trial.

Wechsler ME et al. N Engl J Med 2017;376:1921-1932

The NEW ENGLAND JOURNAL of MEDICINE

Dupilumab σε πολύποδες- CRS

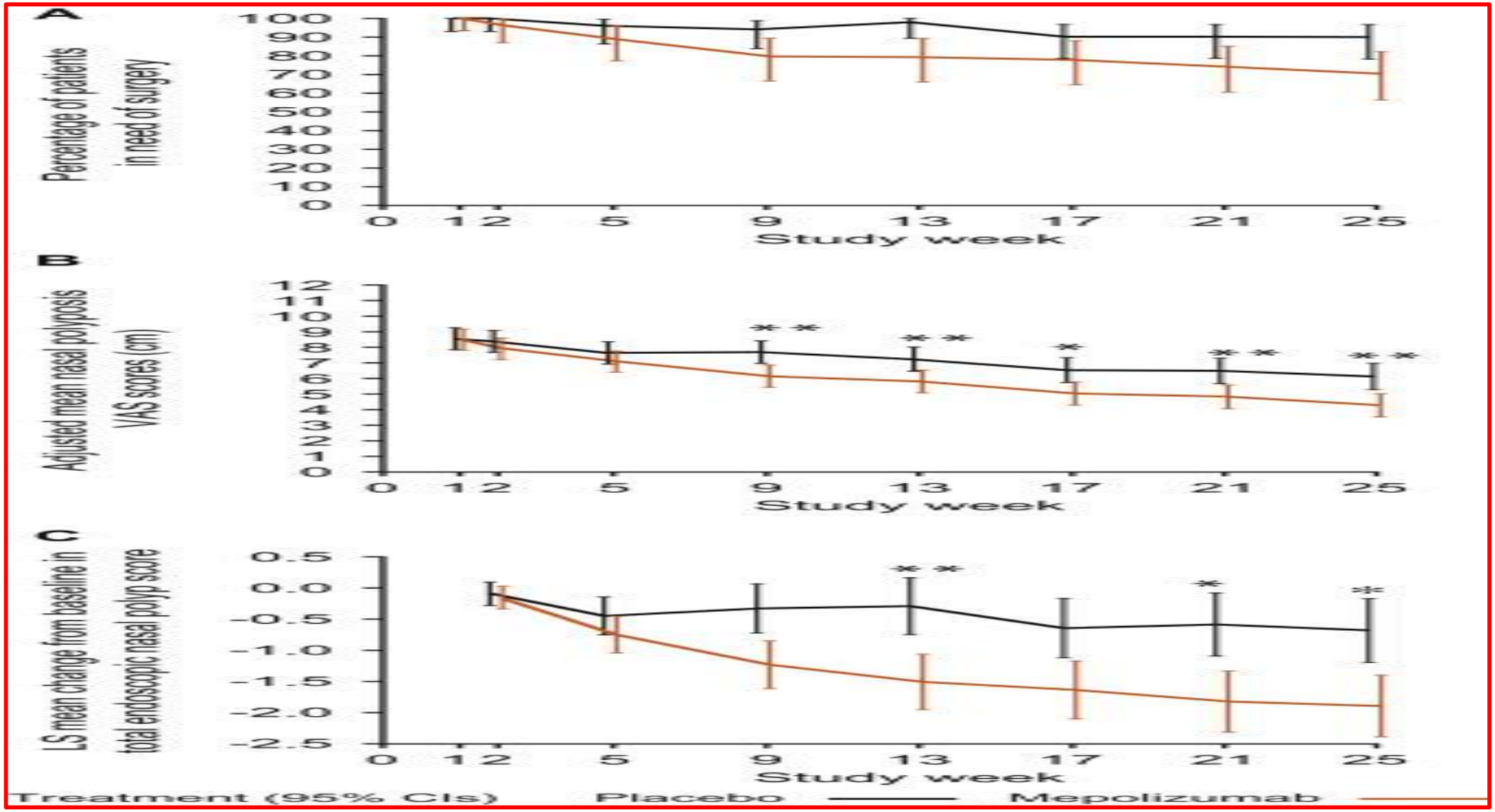




35 with asthma FEV1, ACQ-5

Bachert C, et al. *JAMA*. 2016;315:469-479.

Anti IL-5 σε πολύποδες



Bachert C et al JACI 2017

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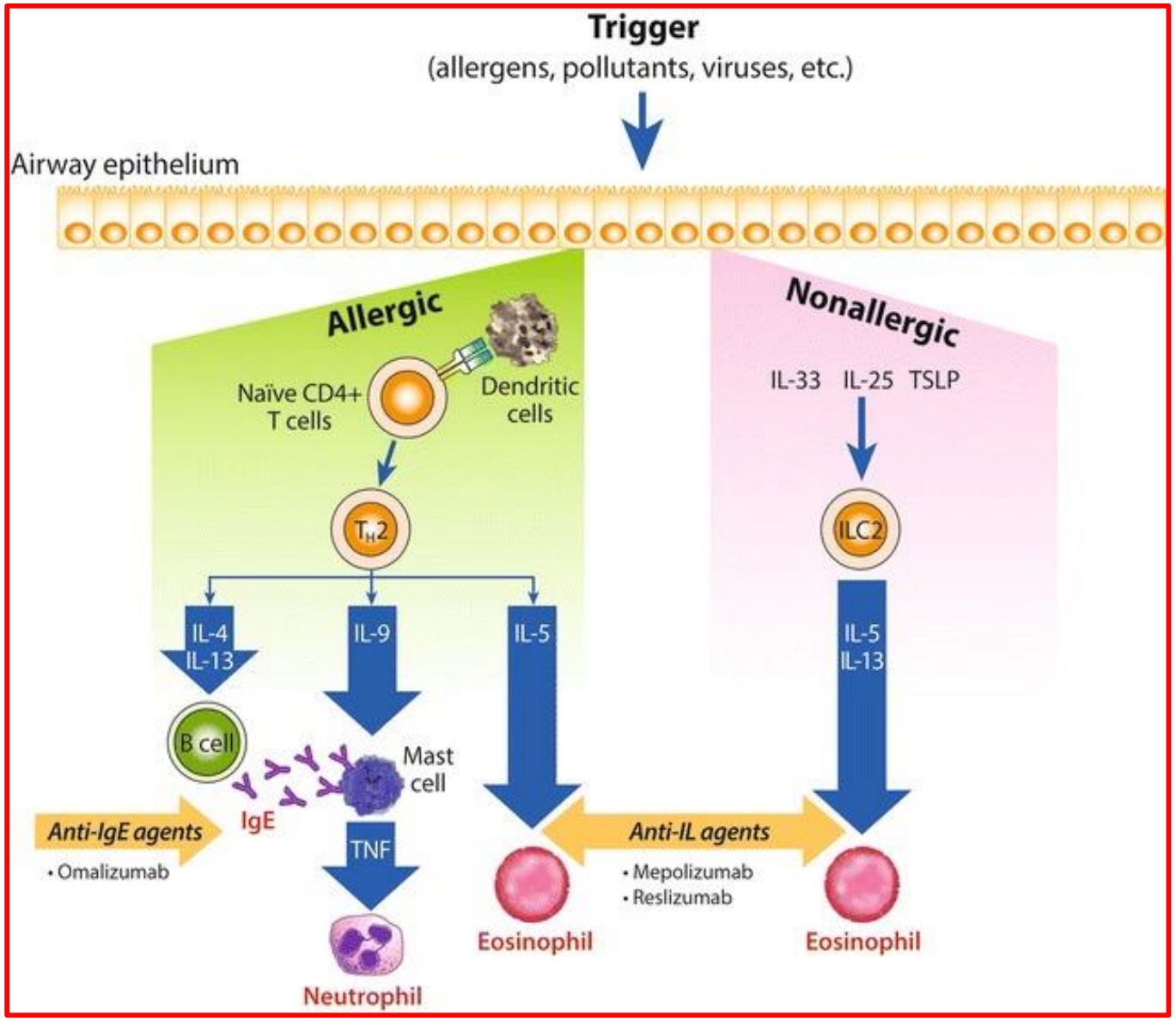
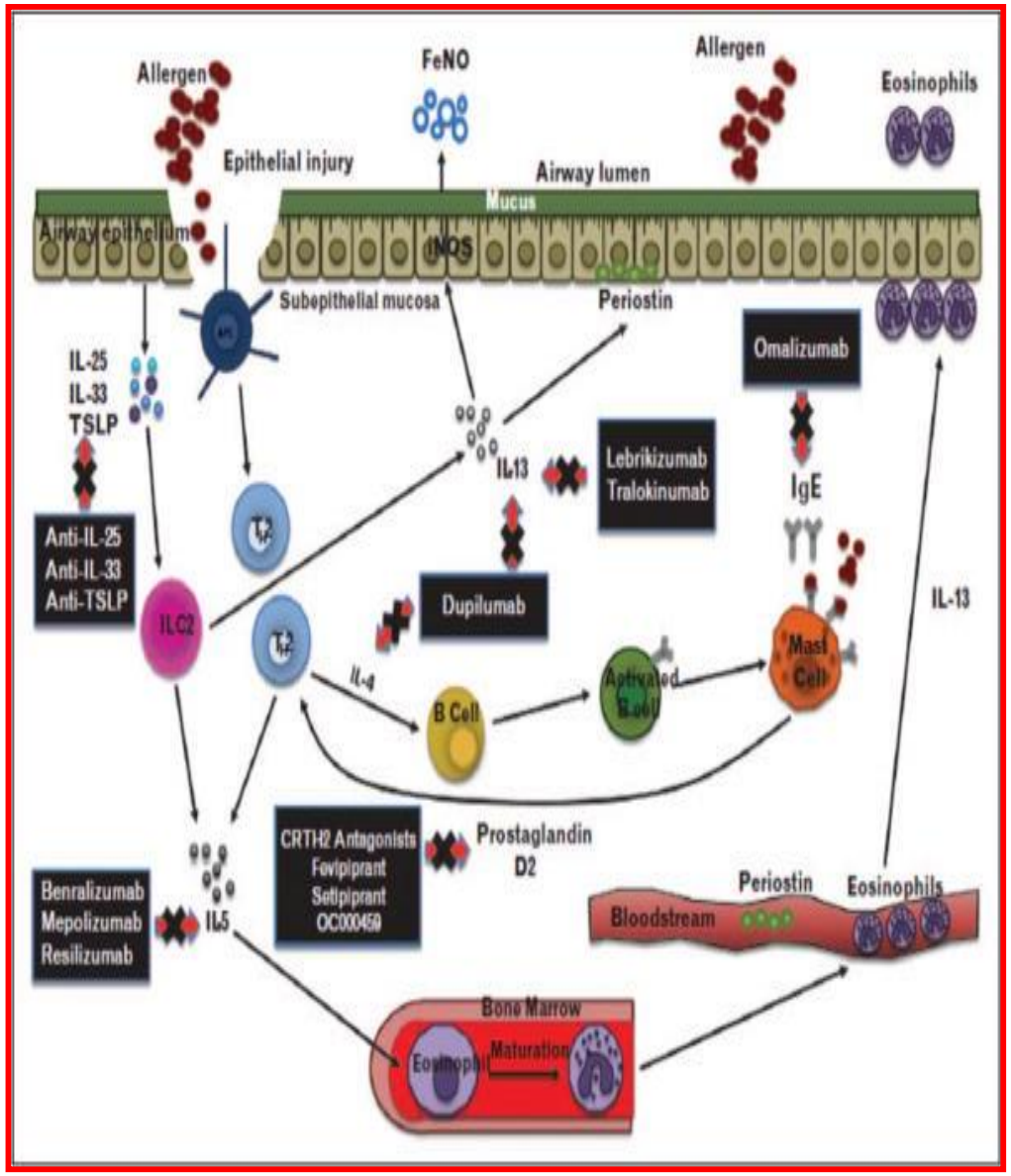
The endotyping mechanism

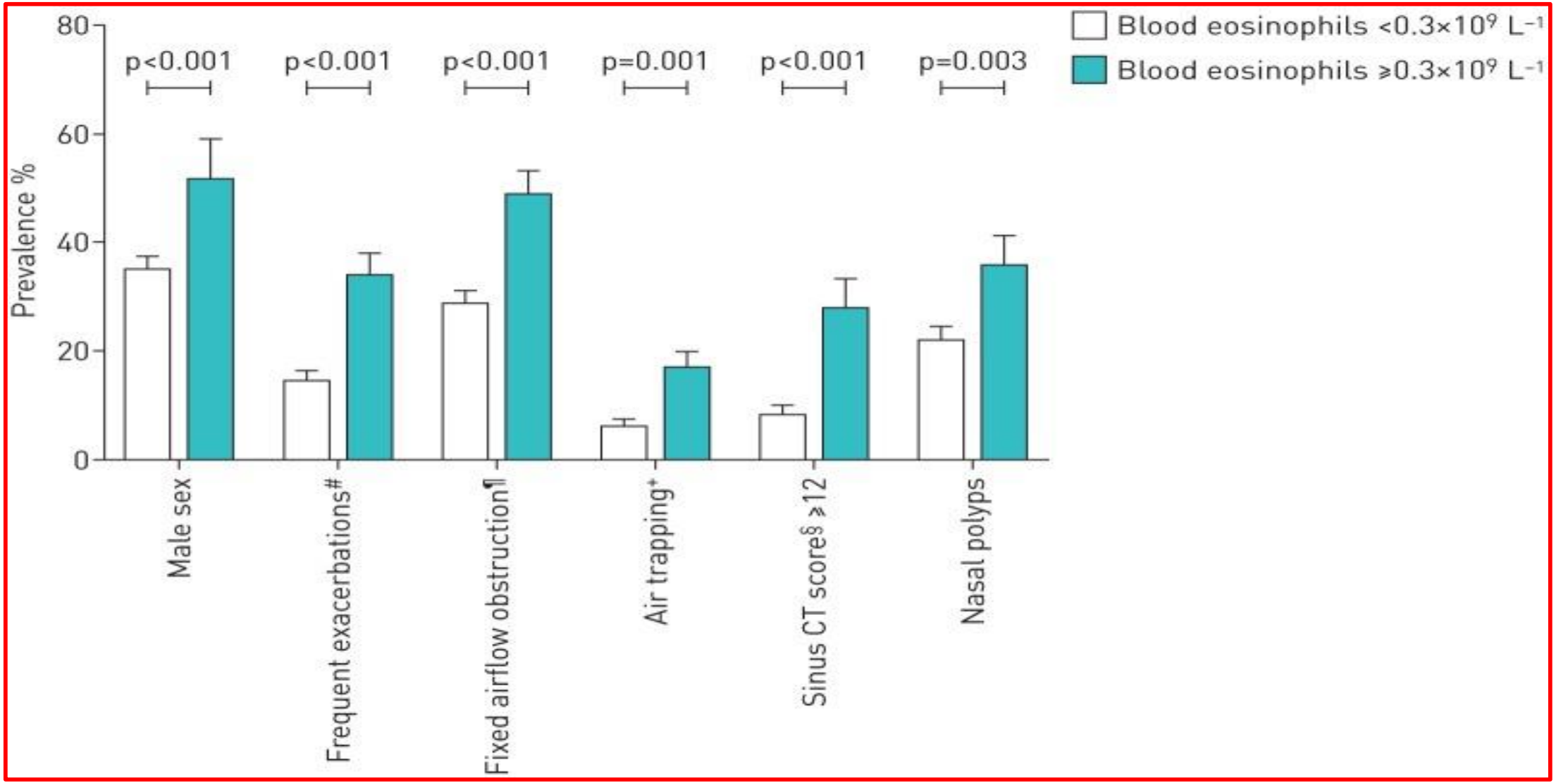


Kim H et al Allergy Asthma Clin Immunol 2017



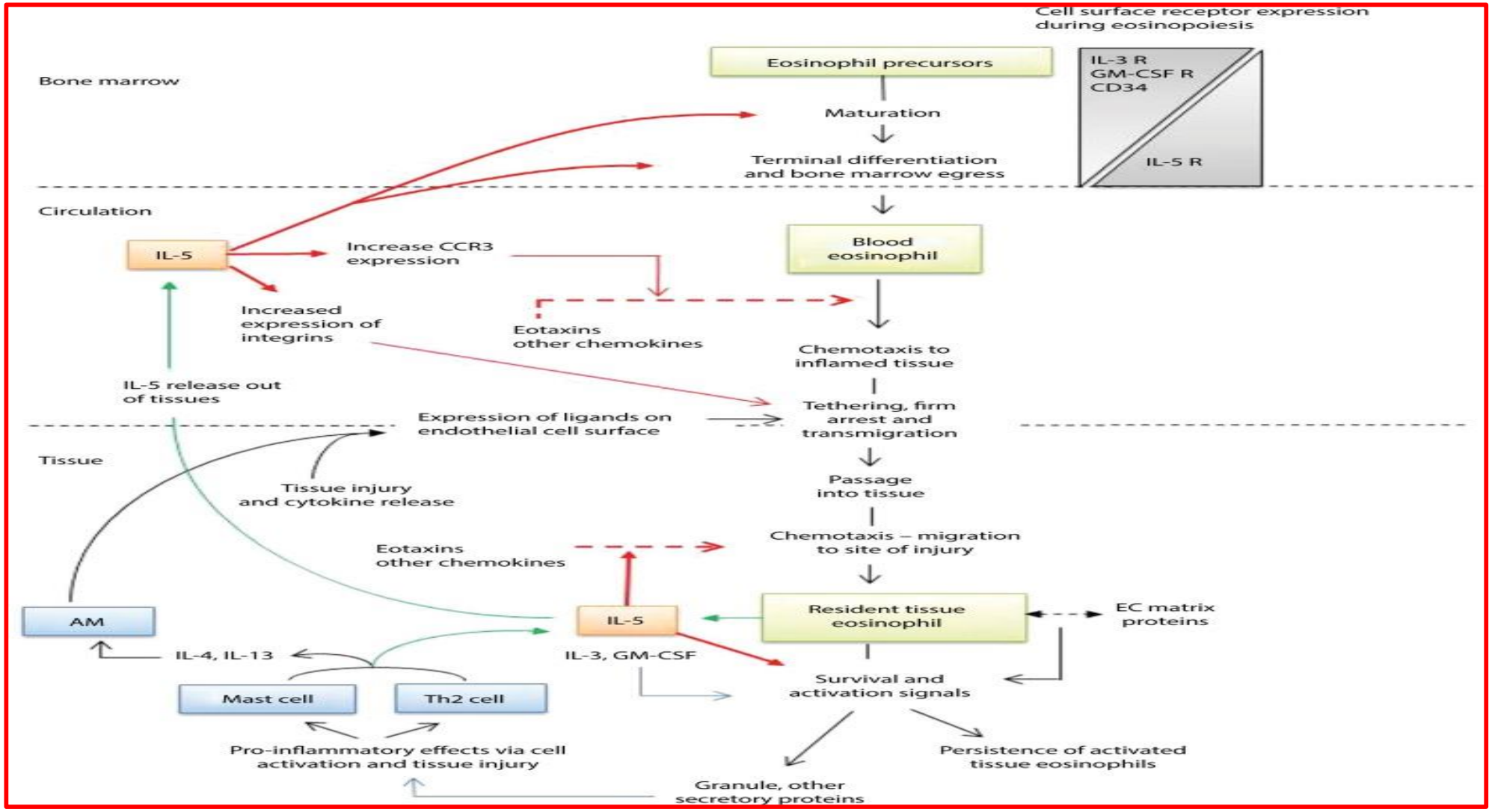
Humbert M et al Cur Opinion Pulm Med 2018

Ο ρόλος της συστηματικής ηωσινοφιλίας στο άσθμα ενηλίκων



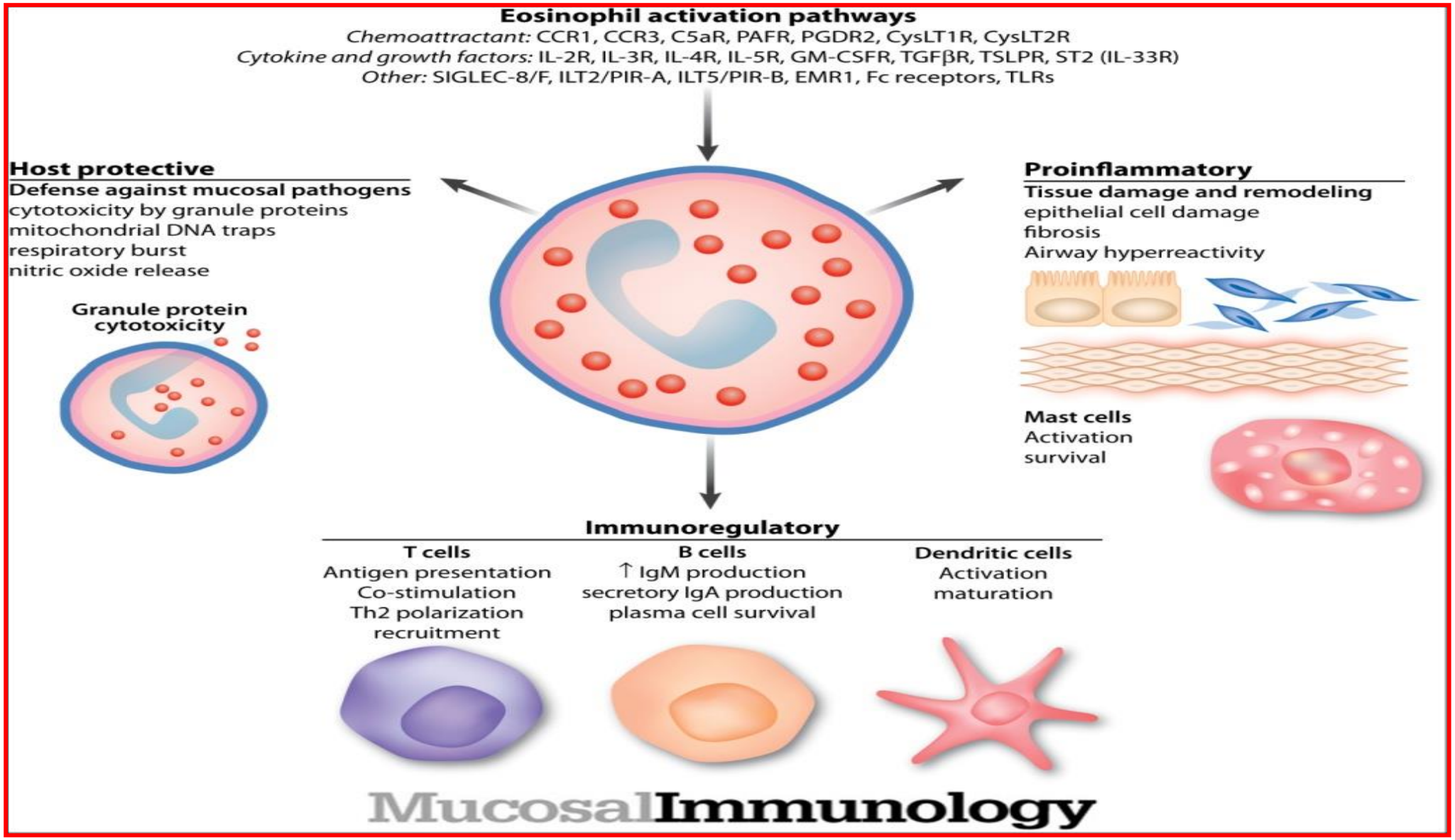
De Groot JC et al ERJ open2016

Eosinophilic Biology



Haldar P Biologics target & Therapy 2017

Eosinophil: A key regulatory cell



Travers J et al Mucosal Immunology (2015) 8, 464-475;

ERJ open research

An algorithmic approach for the treatment of severe uncontrolled asthma

Eleftherios Zervas[1], Konstantinos Samitas[1], Andriana I. Papaioannou[2], Petros Bakakos[3], Stelios Loukides[2] and Mina Gaga[1]

TABLE 2 Clinical features and biomarkers that can be used to differentiate between allergic and eosinophilic T2-high severe asthma

	A: allergic-predominant asthma	B: eosinophilic-predominant asthma
1	Early onset	Late onset
2	SPT/RAST+ with clinically significant allergies#	SPT/RAST– or + with no clinically significant allergies
3	IgE >100 IU·mL^{-1}	IgE <100 IU·mL^{-1}
4	Allergic rhinitis	Nasal polyps
5	High *F*ENO (30–50 ppb)	Very high *F*ENO (>50 ppb)
6	Blood eosinophils <300 cells·µL^{-1}	Blood eosinophils >300 cells·µL^{-1}#

SPT: skin prick test; RAST: radioallergosorbent test; *F*ENO: exhaled nitric oxide fraction. Check the number of relevant patient characteristics per column. If a patient has more features from column A or B it is more likely that he/she has allergic- or eosinophilic-predominant asthma, respectively. If the patient shares features from both columns, it is more likely that he/she suffers from eosinophilic/allergic overlap asthma. #: obligatory characteristics for allergic and/or eosinophilic asthma.

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- **Το ηωσινόφιλο**
- **Ο χαμηλός Τ2 φαινότυπος-ενδότυπος**

Βασικές διαφορές?

ERJ open research

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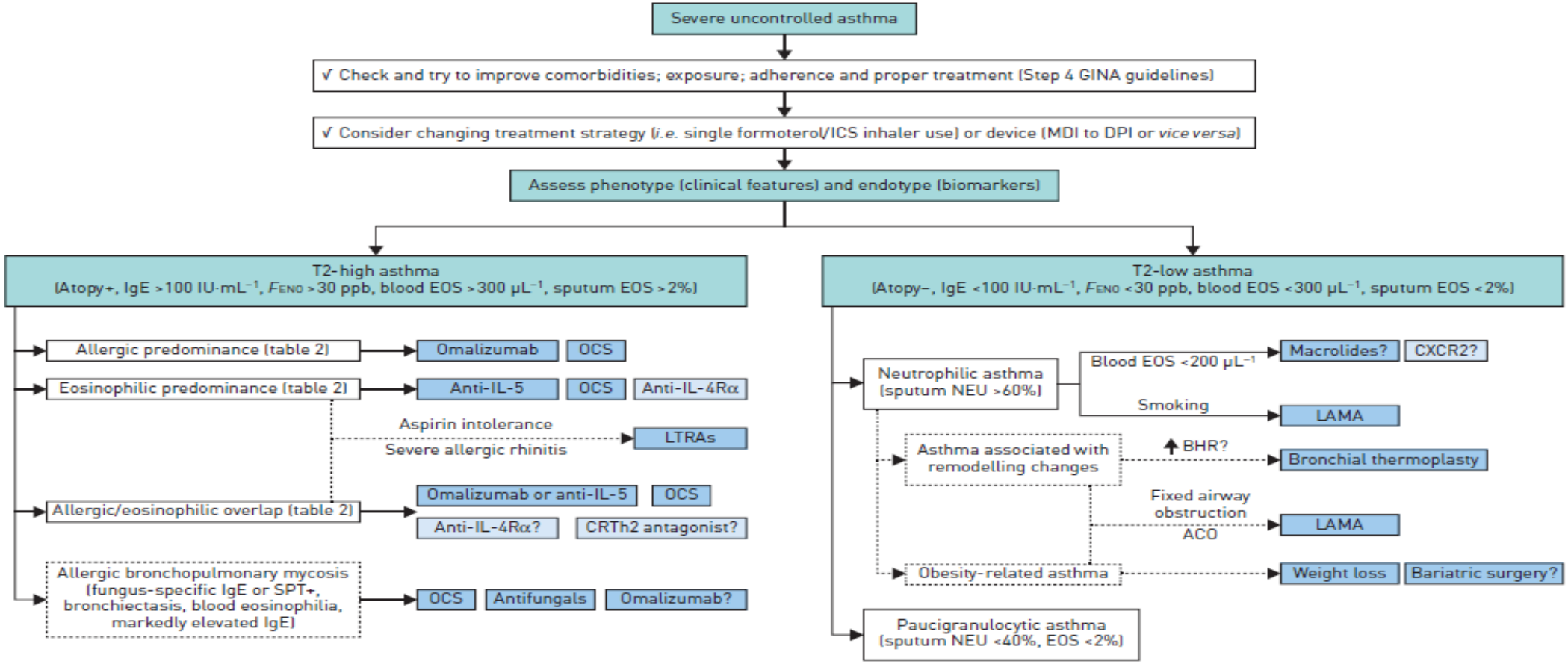
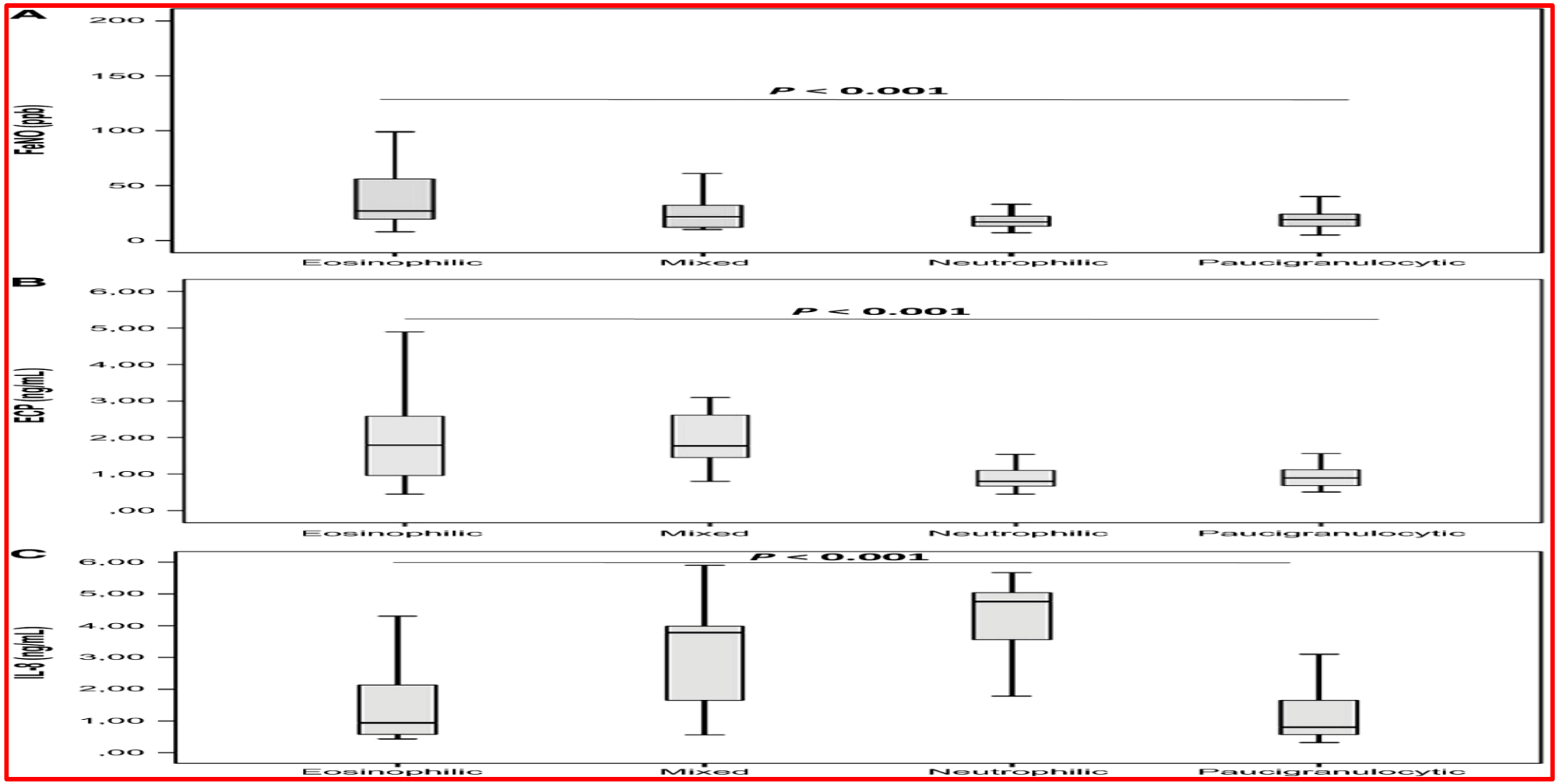
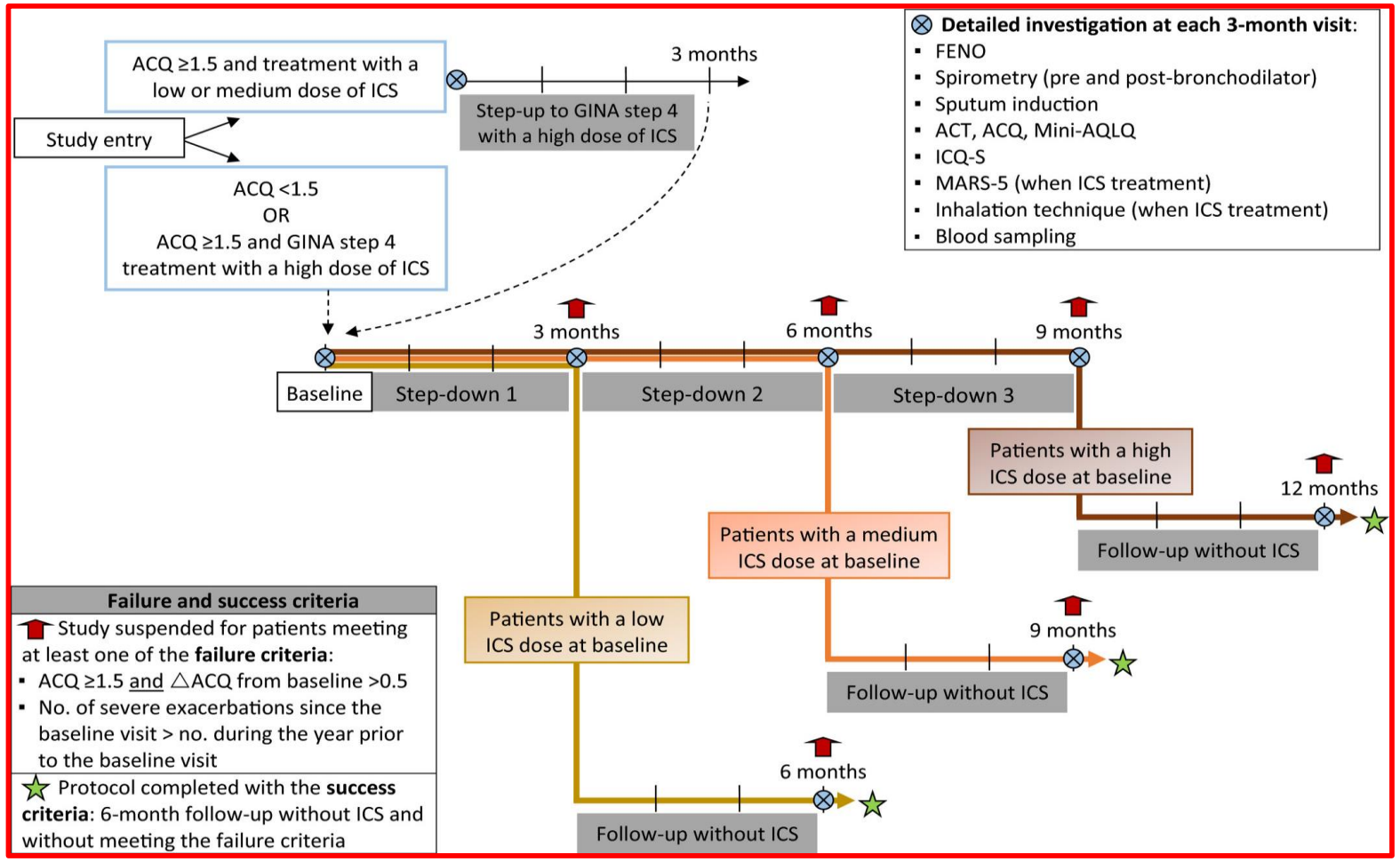


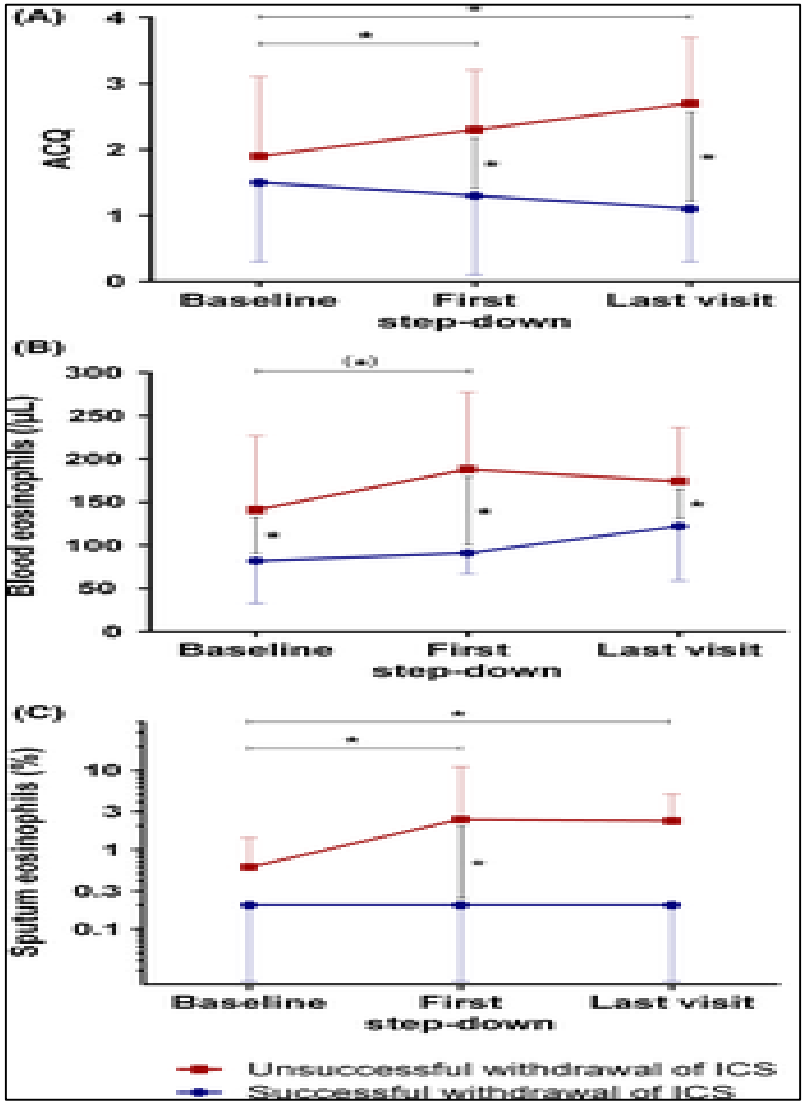
Η δύσκολη απόφαση



Ntontsi P et al Clinical, functional and inflammatory characteristics in patients with paucigranulocytic stable asthma: Comparison with different sputum phenotypes, Volume: 72, Issue: 11, Pages: 1761-1767, First published: 13 April 2017, DOI: (10.1111/all.13184)

Καιρός για LABA/LAMA?





S Dimarche et al Step-down of inhaled corticosteroids in non-eosinophilic asthma: A prospective trial in real life, Volume: 48, Issue: 5, Pages: 525-535, First published: 31 January 2018, DOI: (10.1111/cea.13106)

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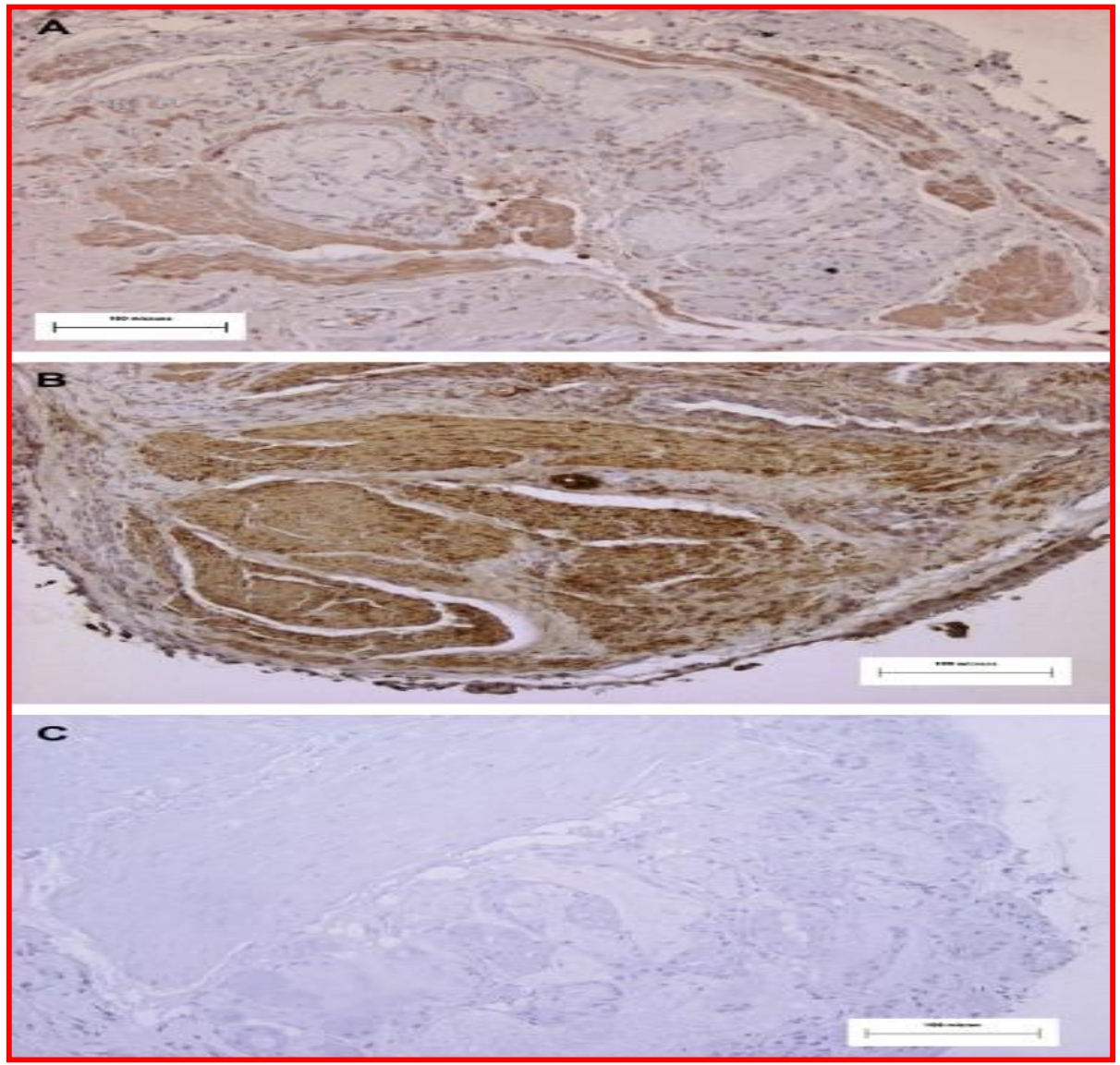
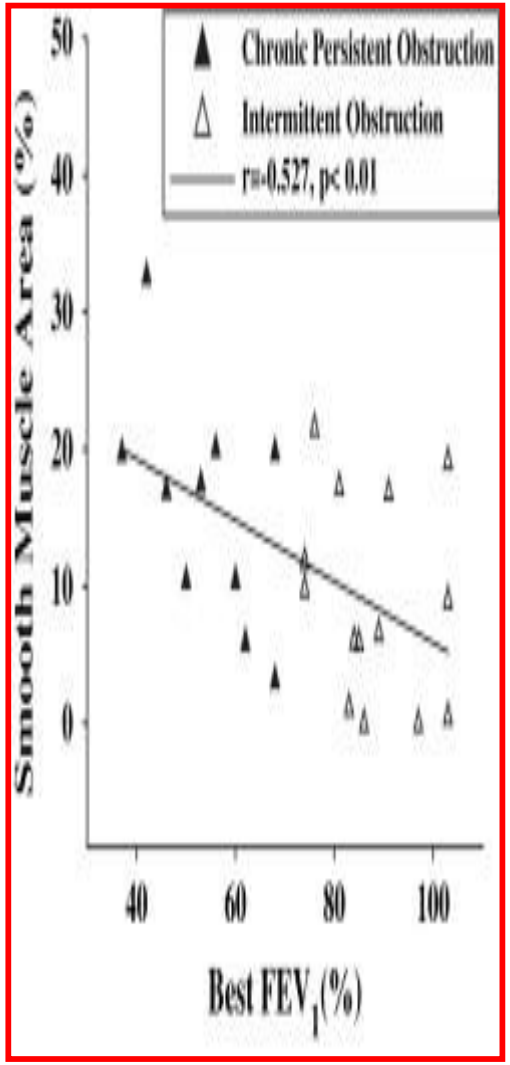
- **Η μόνιμη απόφραξη**

ASM & μόνιμη απόφραξη αεραγωγών





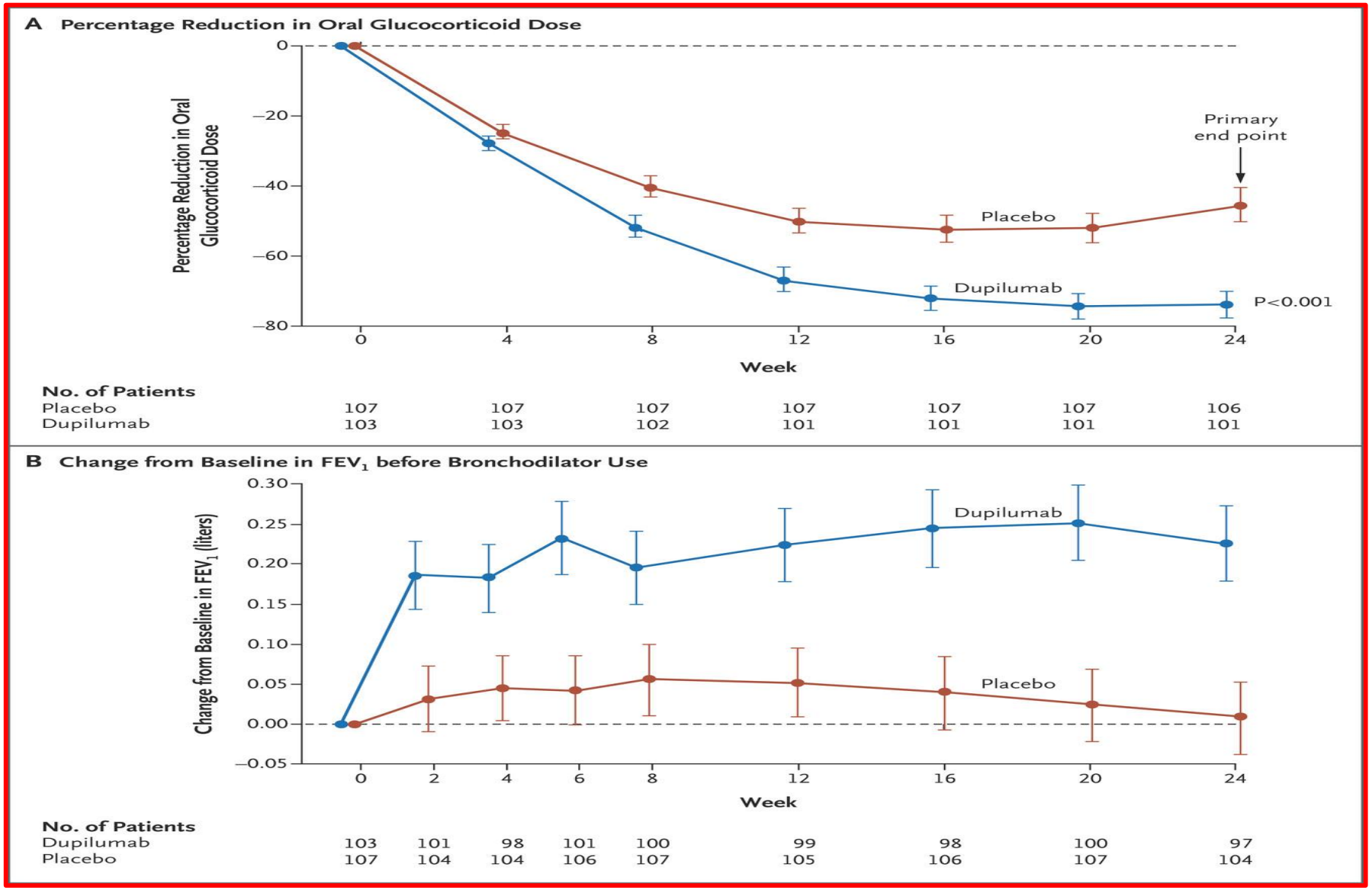
Marta Kaminska et al JACI 2009

Φαινότυπος SRA?

Cluster	Cluster 1	Cluster 2	Cluster 3
Size (%)	56 (32.9%)	53 (31.2%)	61 (35.9%)
Features	Low dose ICS (100%)	**High dose ICS (100%)**	Low dose ICS (100%)
	No criteria for SRA (100%)	**Criteria for SRA (90.6%)**	No criteria for SRA (100%)
	No atopy (100%)	**Atopy (54.7%)**	Atopy (100%)
	No oral CS (100%)	**Oral CS (64.2%)**	No oral CS (100%)
	No persistent airflow obstruction (85.7%)	**Persistent airflow obstruction (83%)**	No persistent airflow obstruction (86.9%)

Konstantellou E et al Resp Med 2015

PFts : IL-4/IL-13

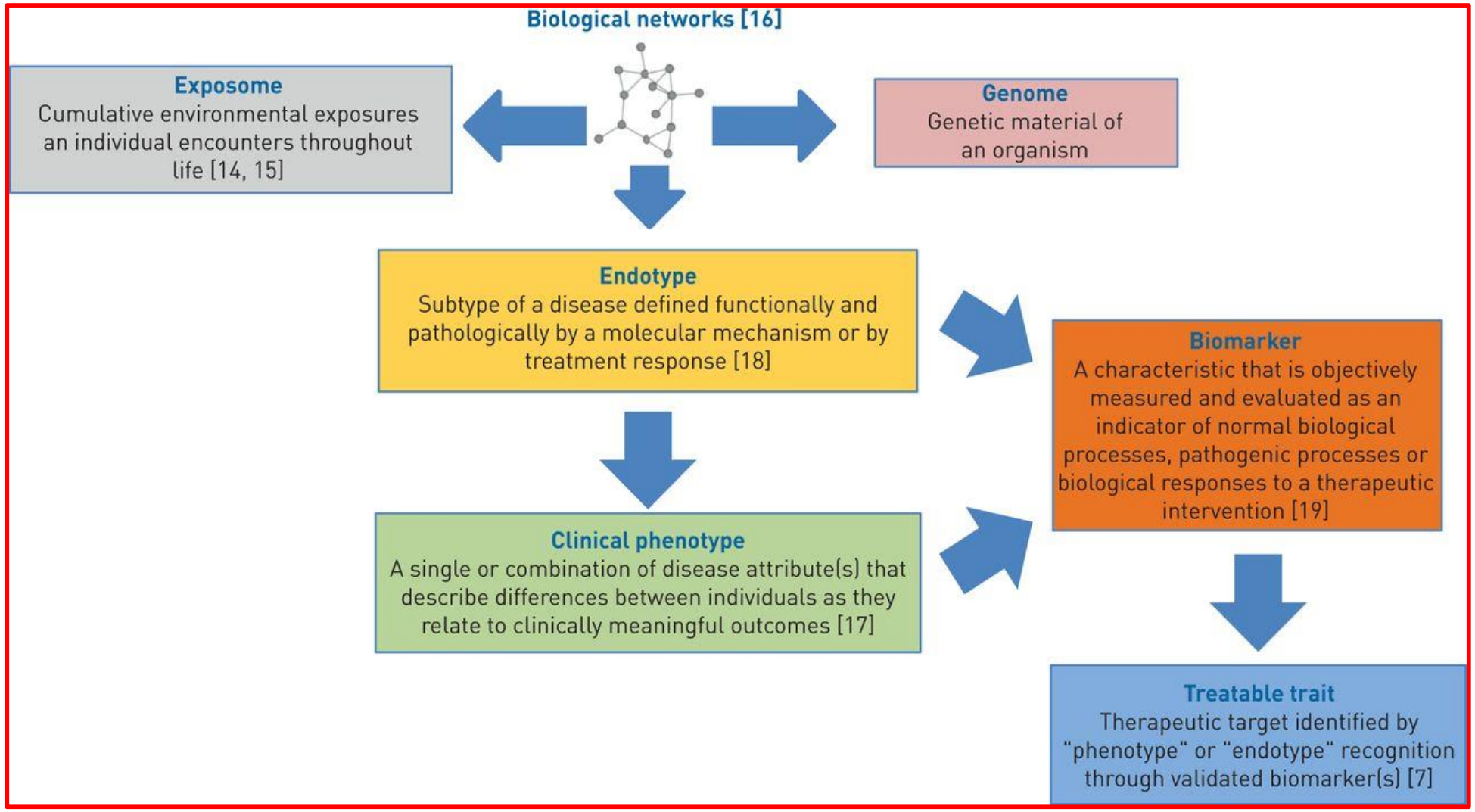


KF Rabe et al. N Engl J Med 2018. DOI: 10.1056/NEJMoa1804093

Σχεδιασμός

- **10 χρόνια πριν & εισαγωγικά σχόλια**
- **Ξεκινώντας από τη παιδική ηλικία**
- **Οι συν-νοσηρότητες**
- **Το ηωσινόφιλο**
- **Ο χαμηλός Τ2 φαινότυπος-ενδότυπος**
- **Η μόνιμη απόφραξη**
- **Επίλογος**

Η προσωποποιημένη θεραπεία στην επόμενη δεκαετία



Alvar Agustí et al. Eur Respir J 2017;50:1701655

GINA 2027
Θεραπευτικά βήματα

Μείωση ← → **Αύξηση**

Βήμα 1	Βήμα 2	Βήμα 3	Βήμα 4	Βήμα 5
SABA κατ' επίκληση	β_2-διεγέρτης βραχείας δράσης κατ' επίκληση			
	ICS& φορμοτερόλη			
	Επιλέξτε ένα	*Επιλέξτε ένα*	*Προσθέστε ένα ή περισσότερα*	*Προσθέστε ένα ή και τα δύο*
Επιλογές ρυθμιστικών φαρμάκων	Χαμηλή δόση ICS	Χαμηλή δόση ICS + LABA	Μέτρια ή Υψηλή δόση ICS + LABA +LAMA	Ένα Μονοκλωνικό Ή και συνδυασμός
	LTRA	Μέτρια ή Υψηλή δόση ICS Χαμηλή δόση ICS + LTRA LAMA& LABA ~~Χαμηλή δόση ICS + Θεοφυλλίνη SR~~	~~Τιοτρόπιο~~ LTRA? ~~Θεοφυλλίνη SR~~ Ένα Μονοκλωνικό Ή και συνδυασμός	~~CS από το στόμα (ελάχιστη δόση)~~ Αναστολέας CRTH2 Μακρολίδες σε low Th2? ?