

# Asthma State Of The Art

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UNIVERSITY of  
ROCHESTER

# Disclosures

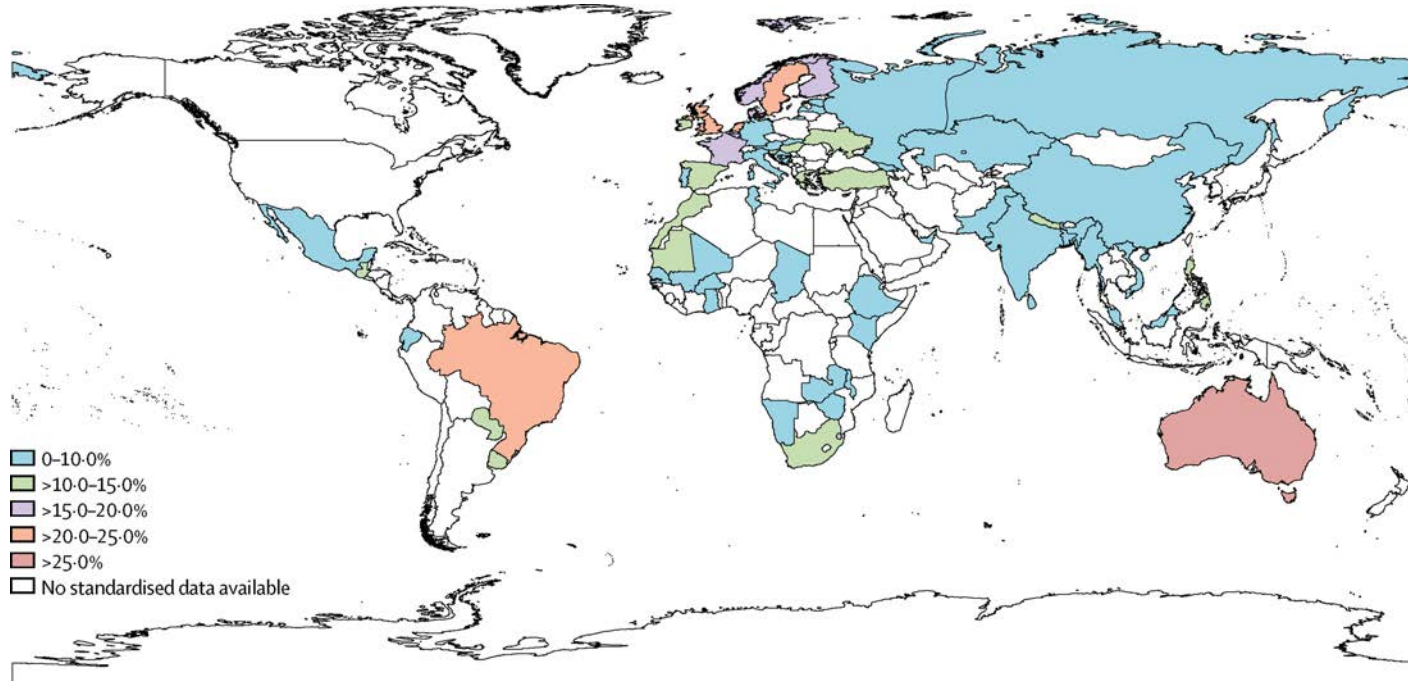
Grant support – GSK

I will not be discussing off-label use for any drugs or devices

# Objectives

- Describe recent advances in our understanding of asthma
- Identify factors contributing to poor control of asthma
- Discuss a systematic approach to phenotyping asthma, and applying traditional & advanced therapies

# Prevalence of symptoms of asthma worldwide (World Health Survey 2002–03)



# Asthma definitions over time...

**Corpus Hippocraticum, 4th century BC**  
Ailments characterised by spasms of  
breathlessness occurring more frequently  
in anglers, tailors, and metal workers.



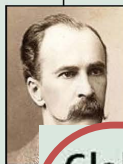
**Sir John Floyer, 1698<sup>33</sup>**

"When the Muscles labour much for Inspiration and Expiration thro' some Obstruction, or Compression of the Bronchia, etc. we properly call this a Difficulty of Breath: but if this Difficulty be by the Constriction of the Bronchia, 'tis properly the Periodic Asthma: And if the Constriction be great, it is with Wheezing; but if less, the Wheezing is not so evident."



**Sir William Osler, 1894<sup>35</sup>**

Osler highlighted the following features: spasm of the bronchial muscles; swelling of the bronchial mucous membrane; a special form of inflammation of the smaller bronchioles; similarities with hay fever; running in families; often beginning in childhood and sometimes lasting into old age; symptoms occurring in a variety of circumstances which at times induce a paroxysm; a relationship with climate, atmosphere (ie, hay, dust, cat), violent emotion, diet, and colds; and distinctive sputum containing rounded gelatinous masses (perles), Curschmann spirals, and octahedral crystals of Leyden.



**Global Initiative for Asthma, 2002<sup>36</sup>**

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These episodes are usually associated with widespread airflow obstruction that is typically reversible either spontaneously or with treatment.

**Global Initiative for Asthma 2017<sup>37</sup>**

Asthma is a heterogeneous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation.



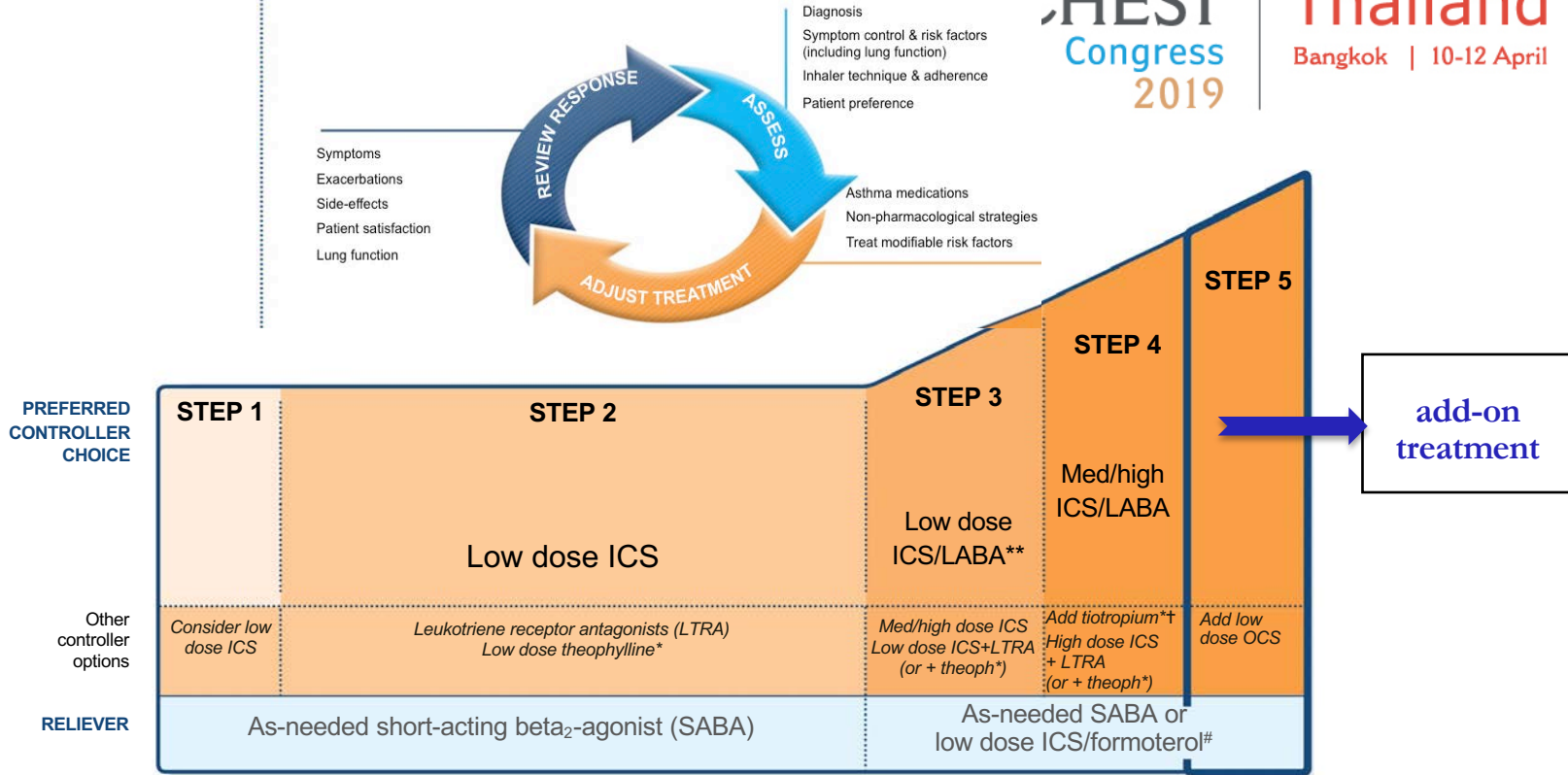
**Maimonides, 12th century AD**

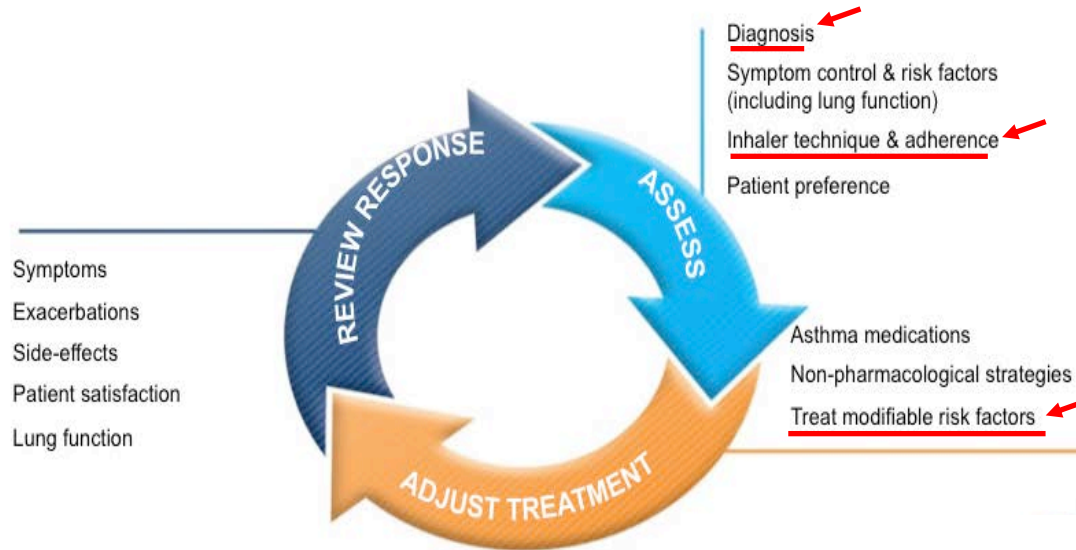
Patient's symptoms often started as a common cold during the wet months. Eventually the patient gasped for air and coughed until phlegm was expelled. Maimonides noted that the dry months of Egypt helped asthma sufferers.



**Henry Hyde Salter, 1860<sup>34</sup>**

"Paroxysmal dyspnoea of a peculiar character with intervals of healthy respiration between attacks."





# Question

What percentage of patients with doctor-diagnosed asthma may not have current asthma?

- A. Less than 10 percent
- B. Less than 20 percent
- C. 30-40%
- D. Greater than 60%



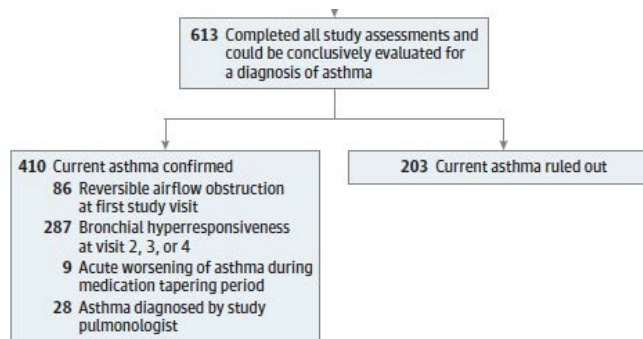
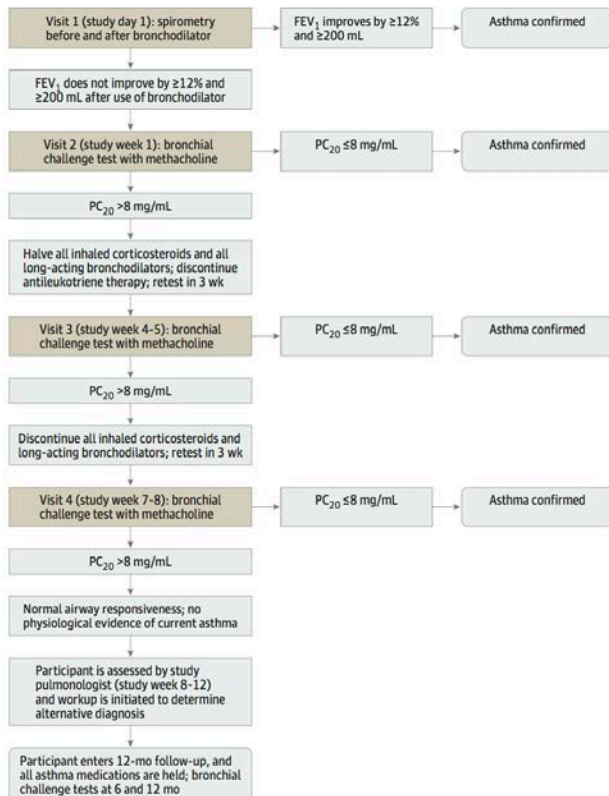
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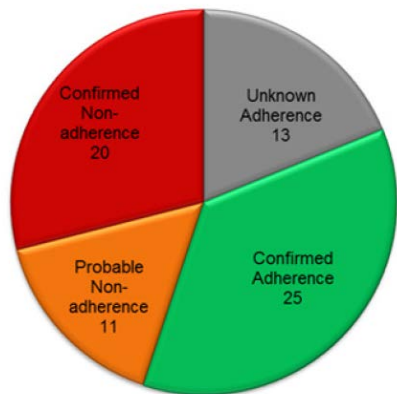
# Reevaluation of Diagnosis in Adults With Physician-Diagnosed Asthma

Shawn D. Aaron, MD; Katherine L. Vandemheen, MScN; J. Mark FitzGerald, MD; Martha Ainslie, MD; Samir Gupta, MD; Catherine Lemière, MD; Stephen K. Field, MD; R. Andrew McIvor, MD; Paul Hernandez, MD; Irvin Mayers, MD; Sunita Mulpuru, MD; Gonzalo G. Alvarez, MD; Smita Pakhale, MD; Ranjeeta Mallick, PhD; Louis-Philippe Boulet, MD; for the Canadian Respiratory Research Network

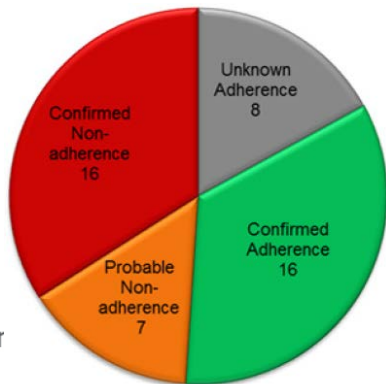


**Current Asthma ruled-out in 33%!**

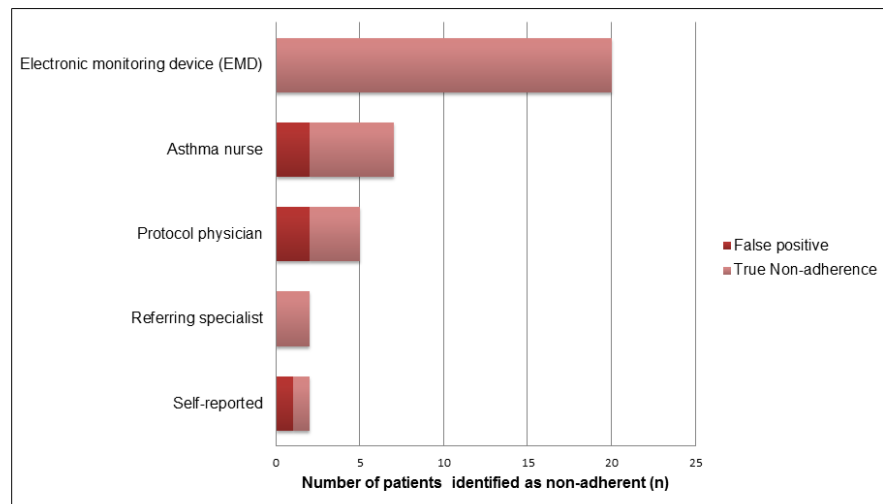
# Nonadherence in the era of expensive advanced therapies



All patients  
n=69



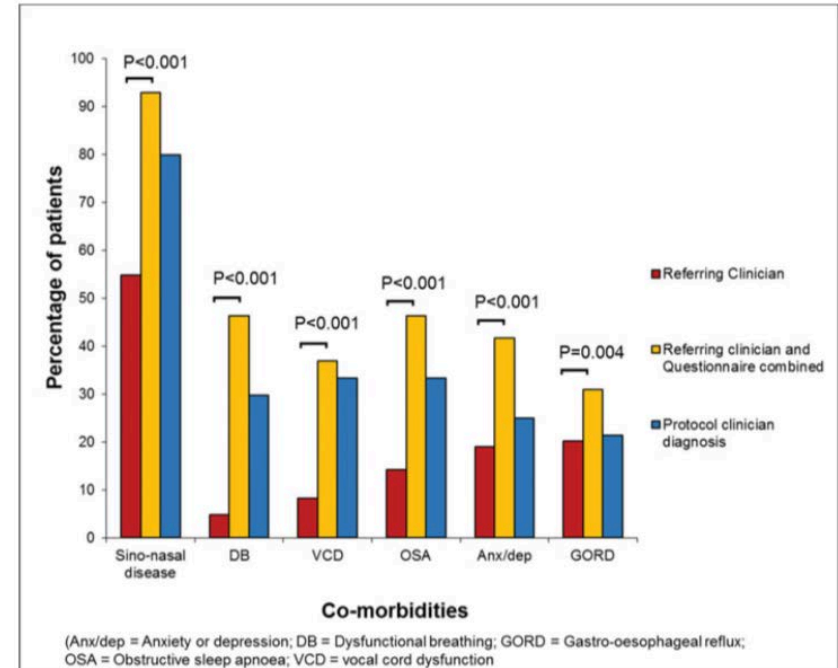
Patients eligible for  
novel therapy n=47



# Validated questionnaires can improve detection of comorbidities in difficult asthma. N=86

| Questionnaires    | Comorbidity        | Items | Sensitivity (%) | Specificity (%) |
|-------------------|--------------------|-------|-----------------|-----------------|
| SNQ [32,33]       | Sino-nasal disease | 5     | 90              | 94              |
| SFAR [34]         | AR                 | 8     | 74              | 83              |
| NIJMEGEN [3,5,26] | DB                 | 16    | 91              | 95              |
| PVCDI [37]        | VCD                | 4     | 83              | 95              |
| BERLIN [38,39]    | OSA                | 10    | 86              | 77              |
| HADS [40]         | Anx/Dep            | 14    | 80              | 80              |
| GERD-Q [41,42]    | GORD               | 6     | 65              | 71              |

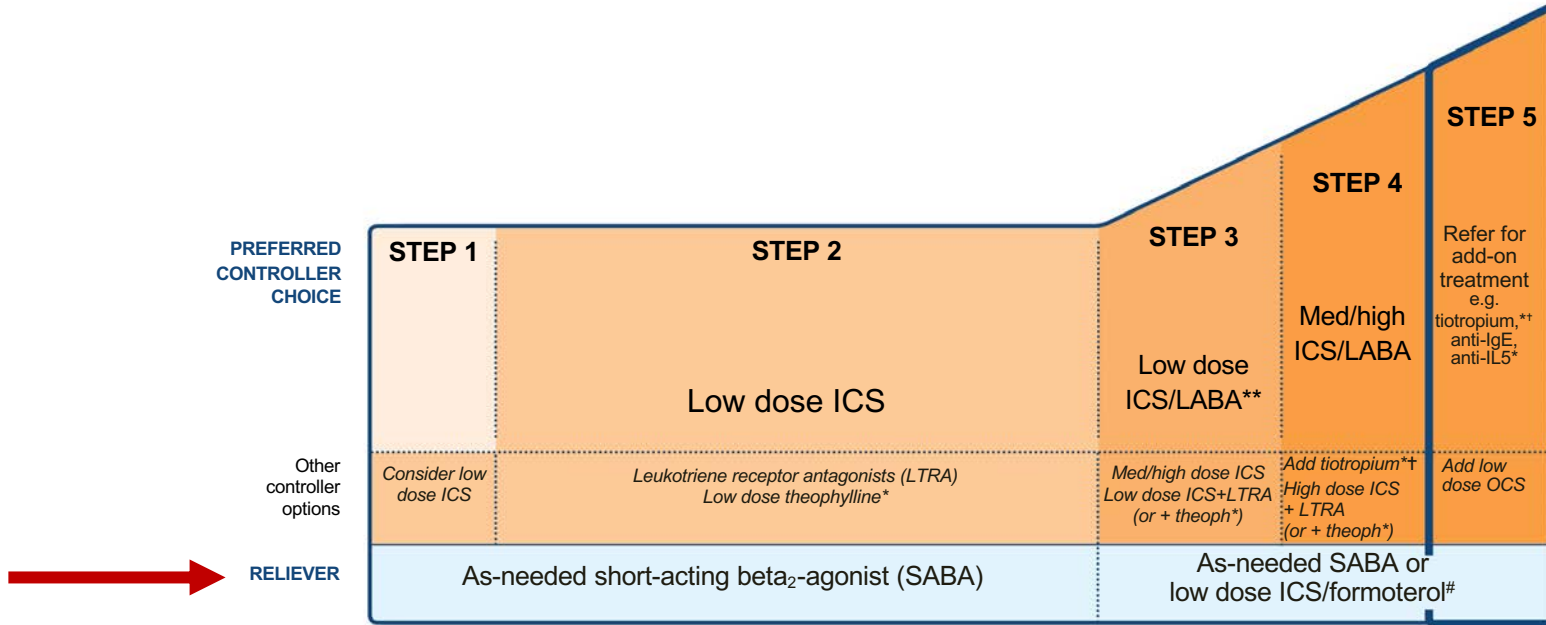
The average time for questionnaire administration was approximately **40 minutes**.



# Association, prevalence and treatment outcomes of comorbidities in difficult asthma

| Comorbidity            | Associated with asthma? | Prevalence in asthma | Does treatment improve asthma? |
|------------------------|-------------------------|----------------------|--------------------------------|
| Sino-nasal disease AR  | Yes                     | 80% #                | Yes                            |
| Sino-nasal disease CRS | Yes                     | 70-74% *             | Yes                            |
| GERD                   | Yes                     | 59% #                | Inconsistent                   |
| OSA                    | Yes                     | 75-95% *             | Yes                            |
| VCD                    | Yes                     | 75% *                | Inconsistent                   |
| DB                     | Yes                     | 29% #                | Yes                            |
| Anx/Dep                | Yes                     | 49% *                | Yes                            |

# Suggested stepwise approach to mitigate impairment and risk



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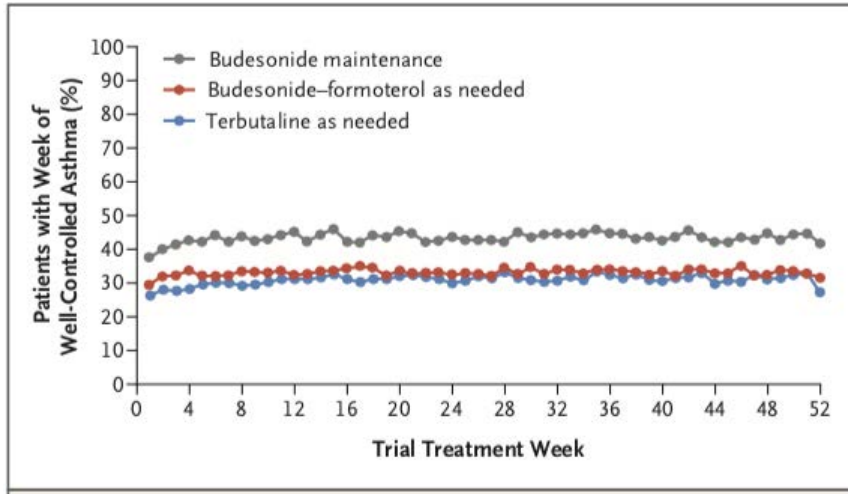
MAY 17, 2018

VOL. 378 NO. 20

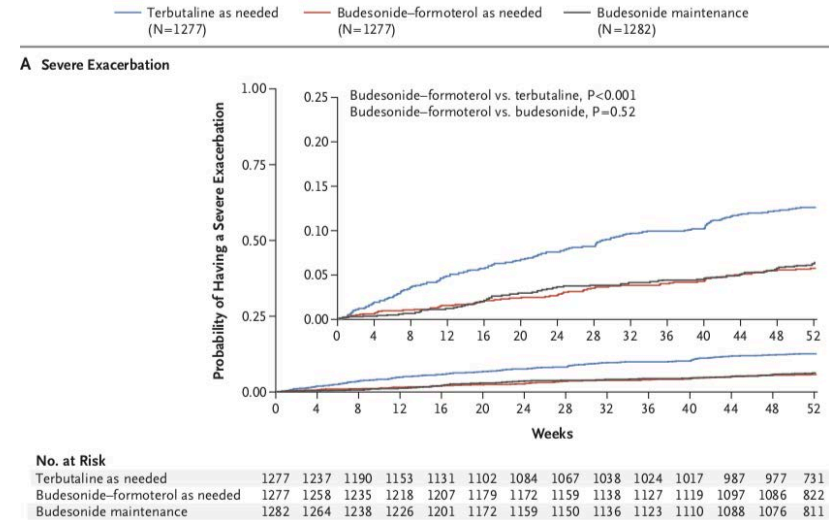
Inhaled Combined Budesonide–Formoterol as Needed  
in Mild Asthma

Paul M. O'Byrne, M.B., J. Mark FitzGerald, M.D., Eric D. Bateman, M.D., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D.,  
Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D., Stefan Ivanov, M.D., Ph.D., and Helen K. Reddel, M.B., B.S., Ph.D.

# SYGMA 1: Budesonide/Formoterol given as needed in mild asthma



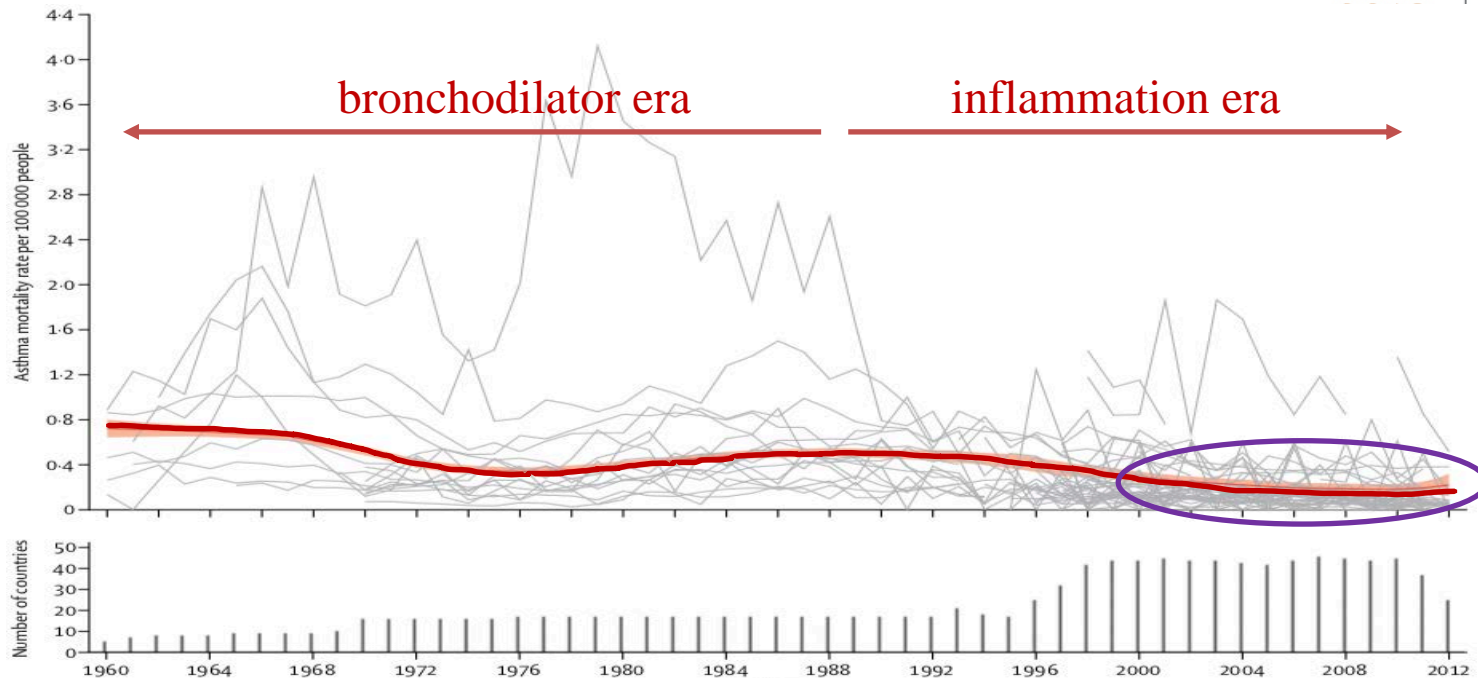
In terms of weeks of well controlled asthma, budesonide-formoterol was:  
Superior to as needed terbutaline  
Inferior to Budesonide maintenance



In terms of exacerbations:  
 As-needed budesonide/formoterol was non-inferior to maintenance ICS  
 with 1/5<sup>th</sup> of the ICS dose



# Global Asthma Mortality Rates 1960-2012



Trends in international asthma mortality: analysis of data from the WHO Mortality Database from 46 countries (1993-2012)

Stefan Ebmeier, Damiga Thayabaran, Irene Braithwaite, Clément Bénamara, Mark Weatherall, Richard Beasley

Register now at [congress.chestnet.org](http://congress.chestnet.org)

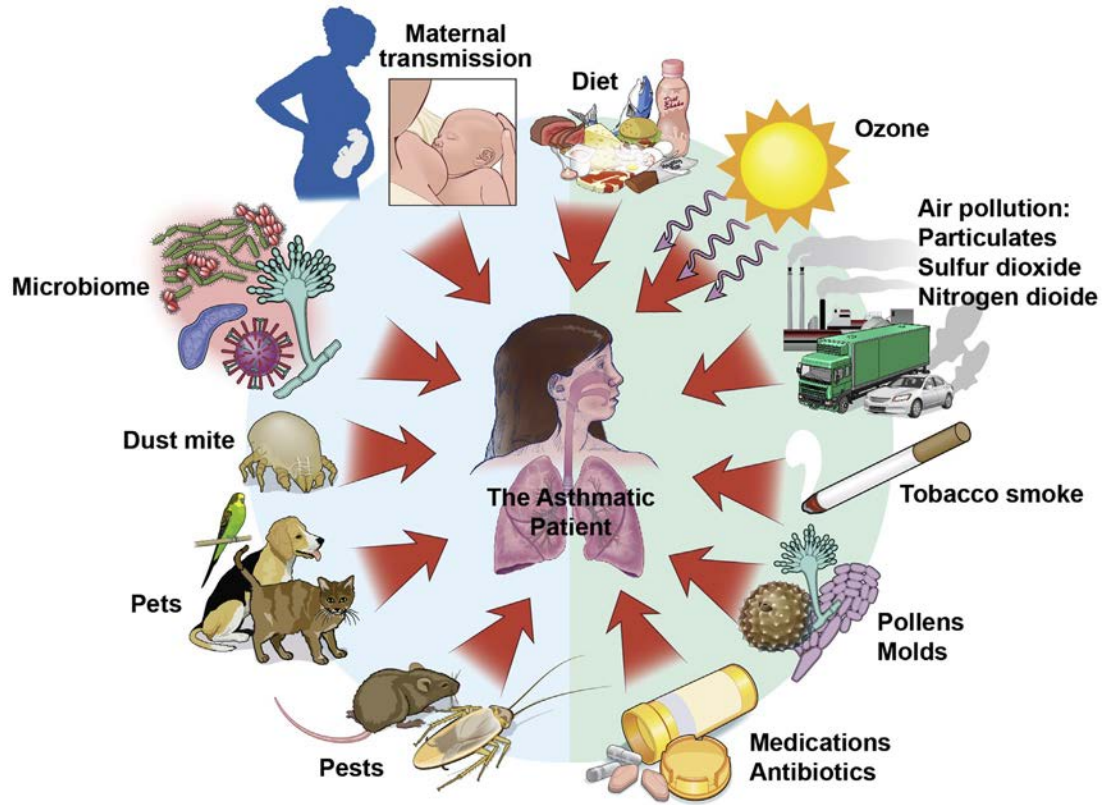
# Time for change?

- Progress against key outcomes has stalled
- Pitfalls in diagnosis...absent 'gold standard'
- Better understanding of complex pathophysiology
- Identification of different treatable traits
- Management guided by these traits appears more effective

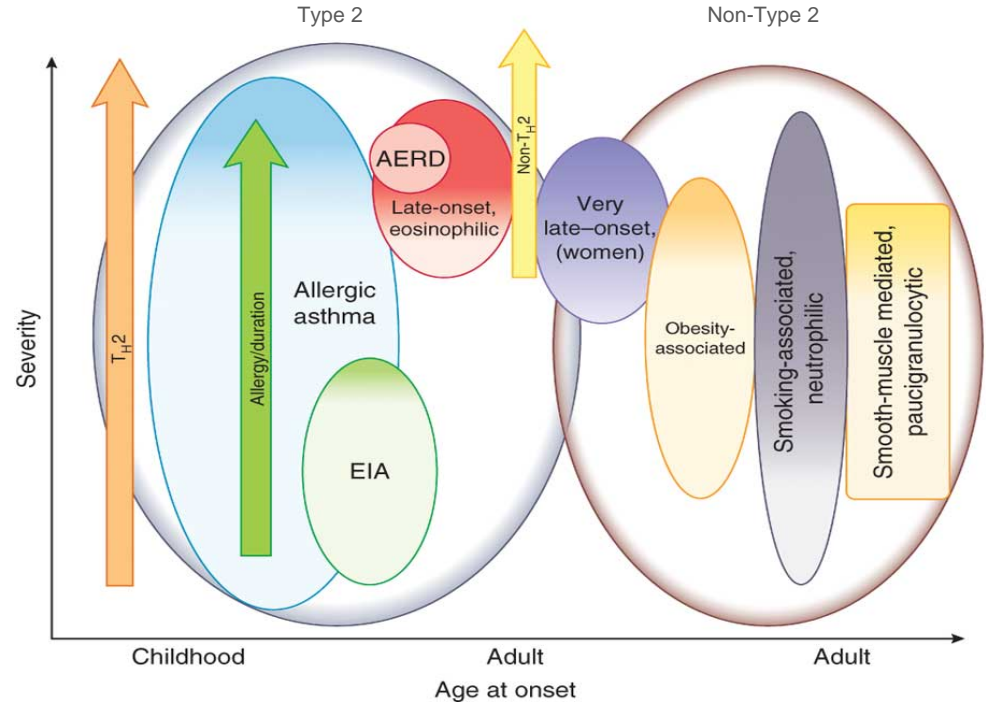
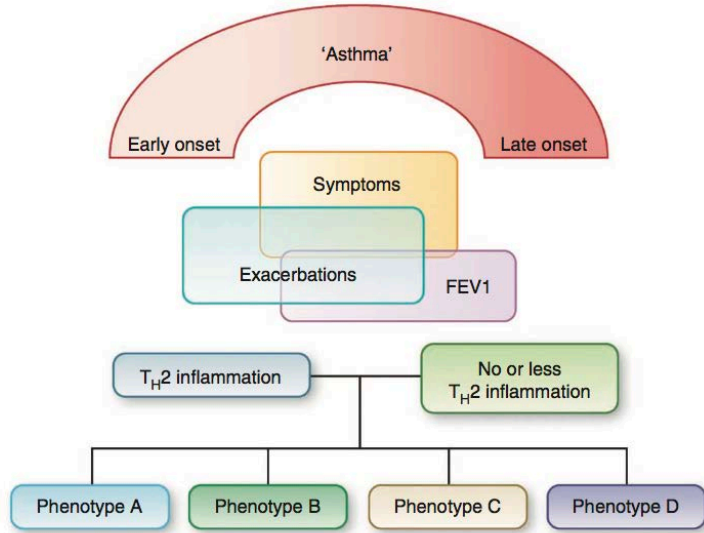
Francis Rackemann did a detailed longitudinal clinical study of asthma in the first half of the 20th century and was the first to highlight the heterogeneity of asthma.

*“surely it is hard to believe that the wheeze that comes to the young school girl for a day or two in the ragweed season is the same disease as that which develops suddenly in the tired business man or in the harassed housewife and pushes them down to the depths of depletion and despair. The problem is still wide open: the approach is not at all clear”*

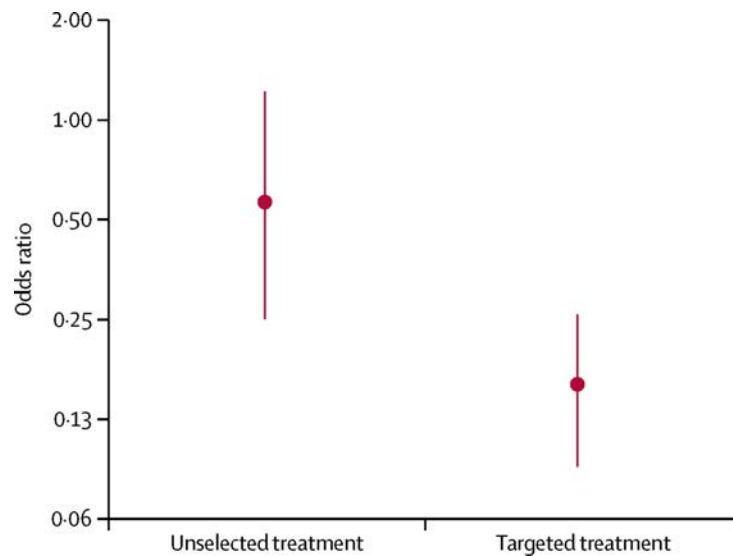
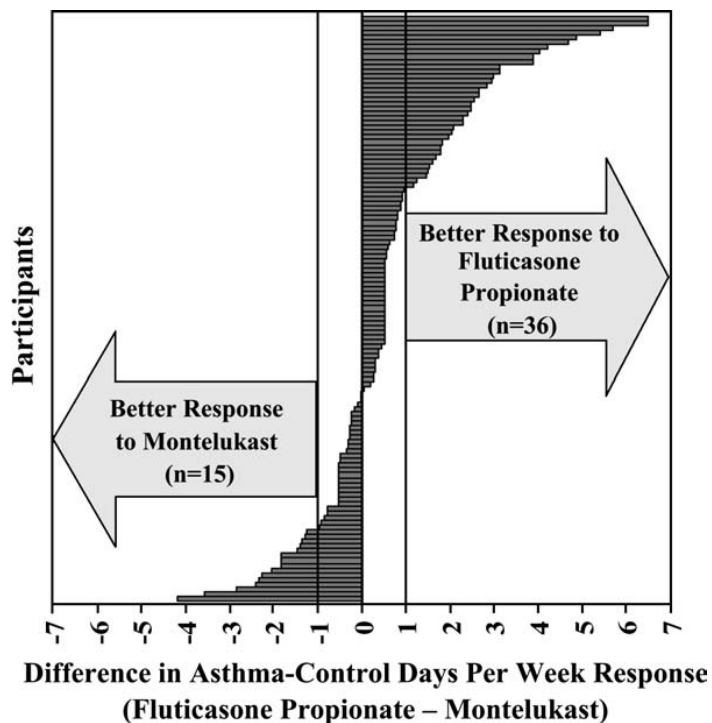
# Complex gene/environment interactions...



...result in different clinical expressions

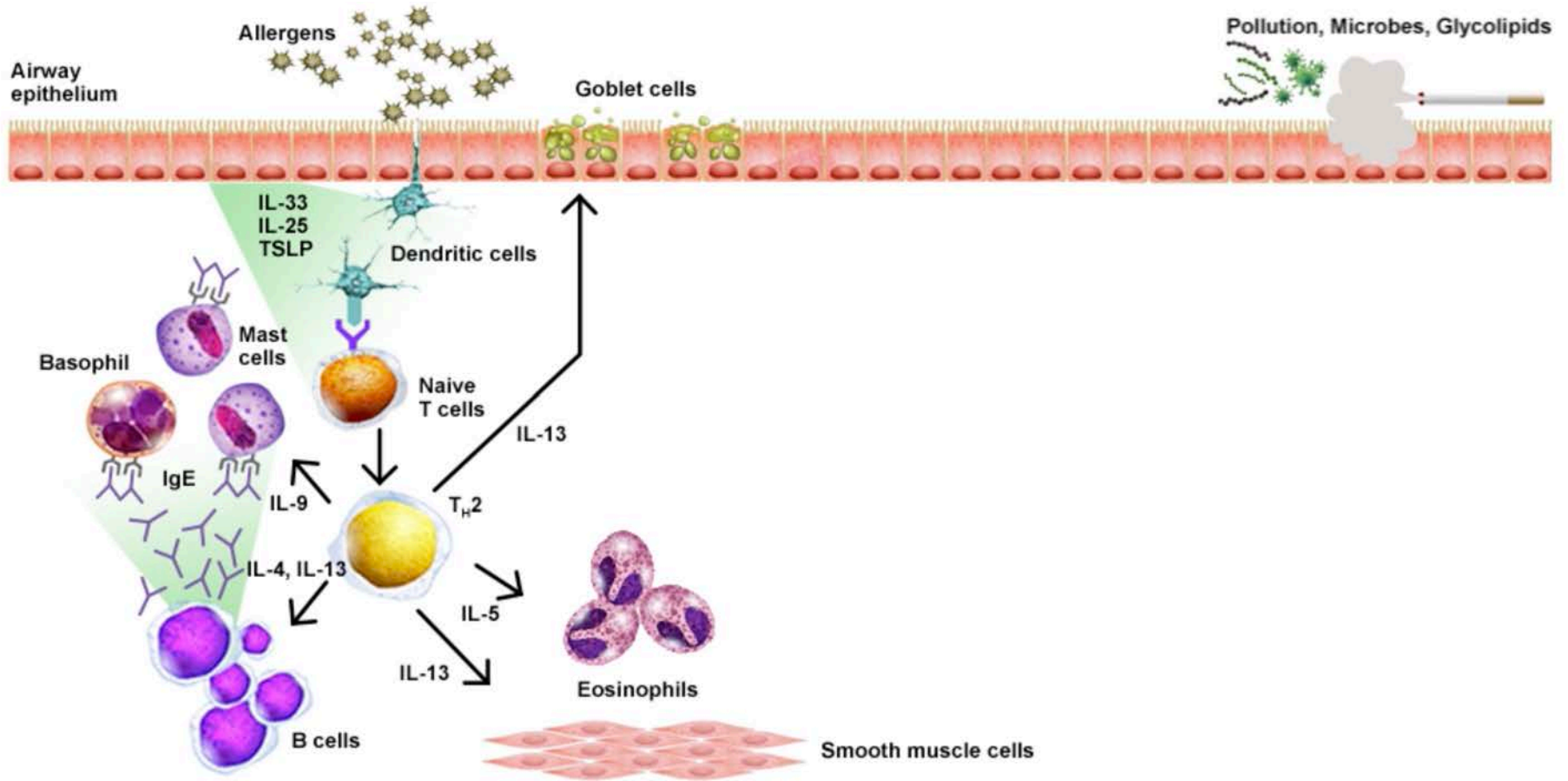


# And variable treatment responses

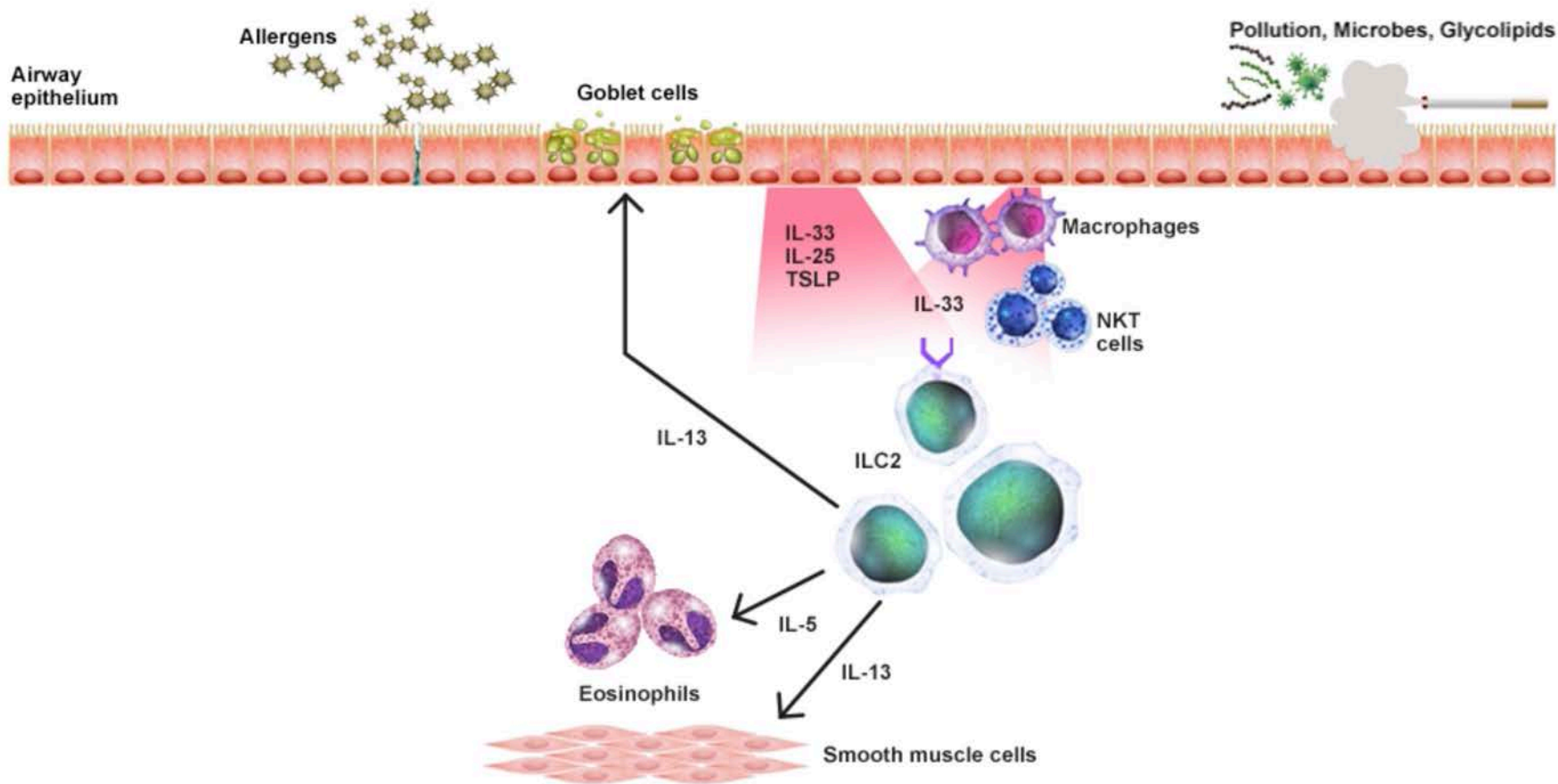


Comparative effect sizes for exacerbation rates (Mepolizumab)

# Allergic Eosinophilic

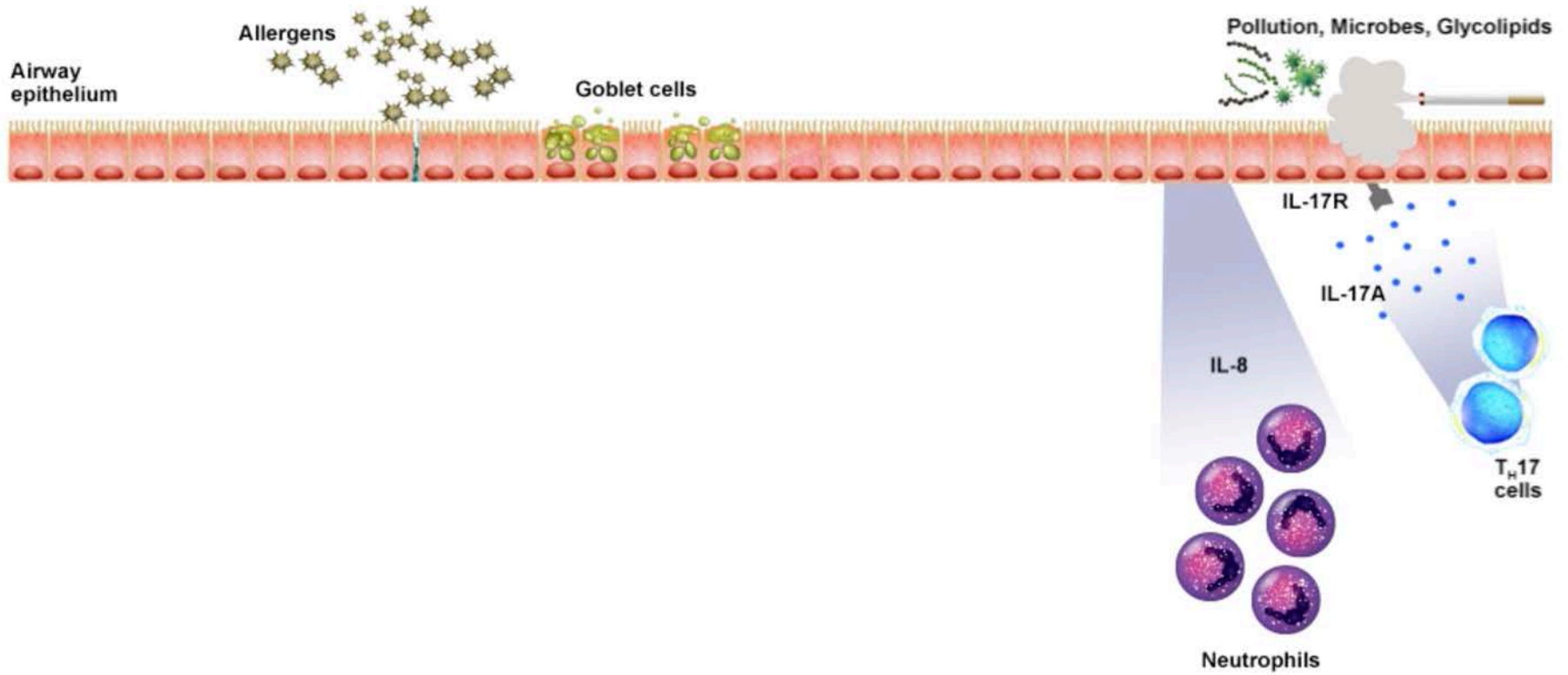


# Nonallergic Eosinophilic





# Neutrophilic



# Question

Currently available biologic therapies DO NOT target

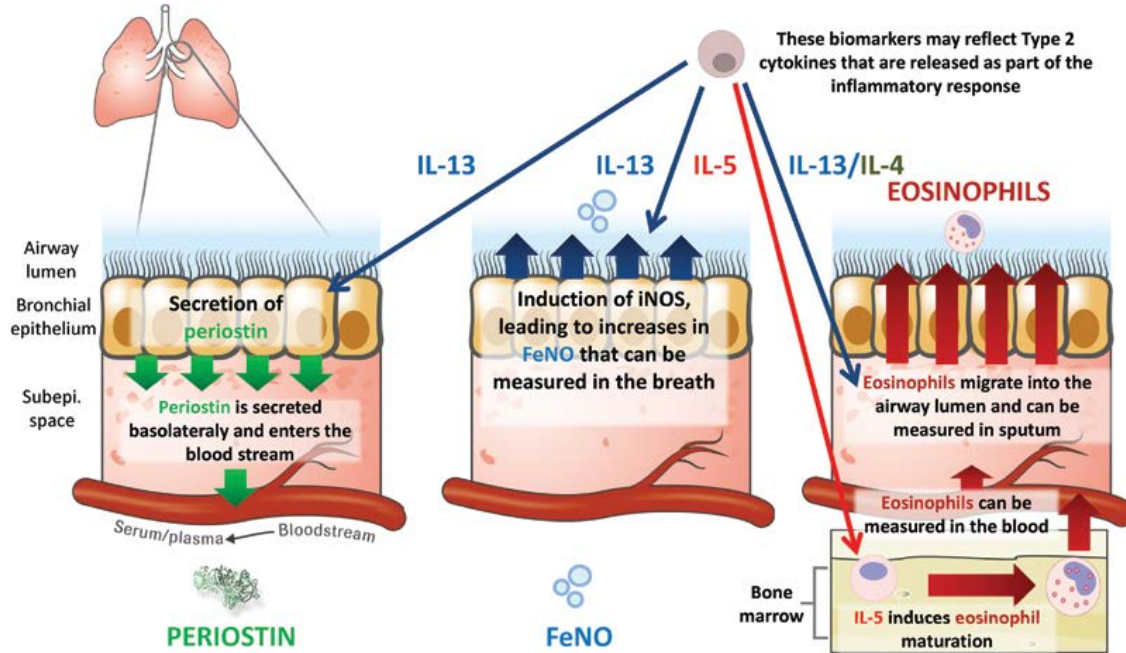
- A. Eosinophilic asthma
- B. Allergic Asthma
- C. T2 low asthma
- D. All of the above

# Question

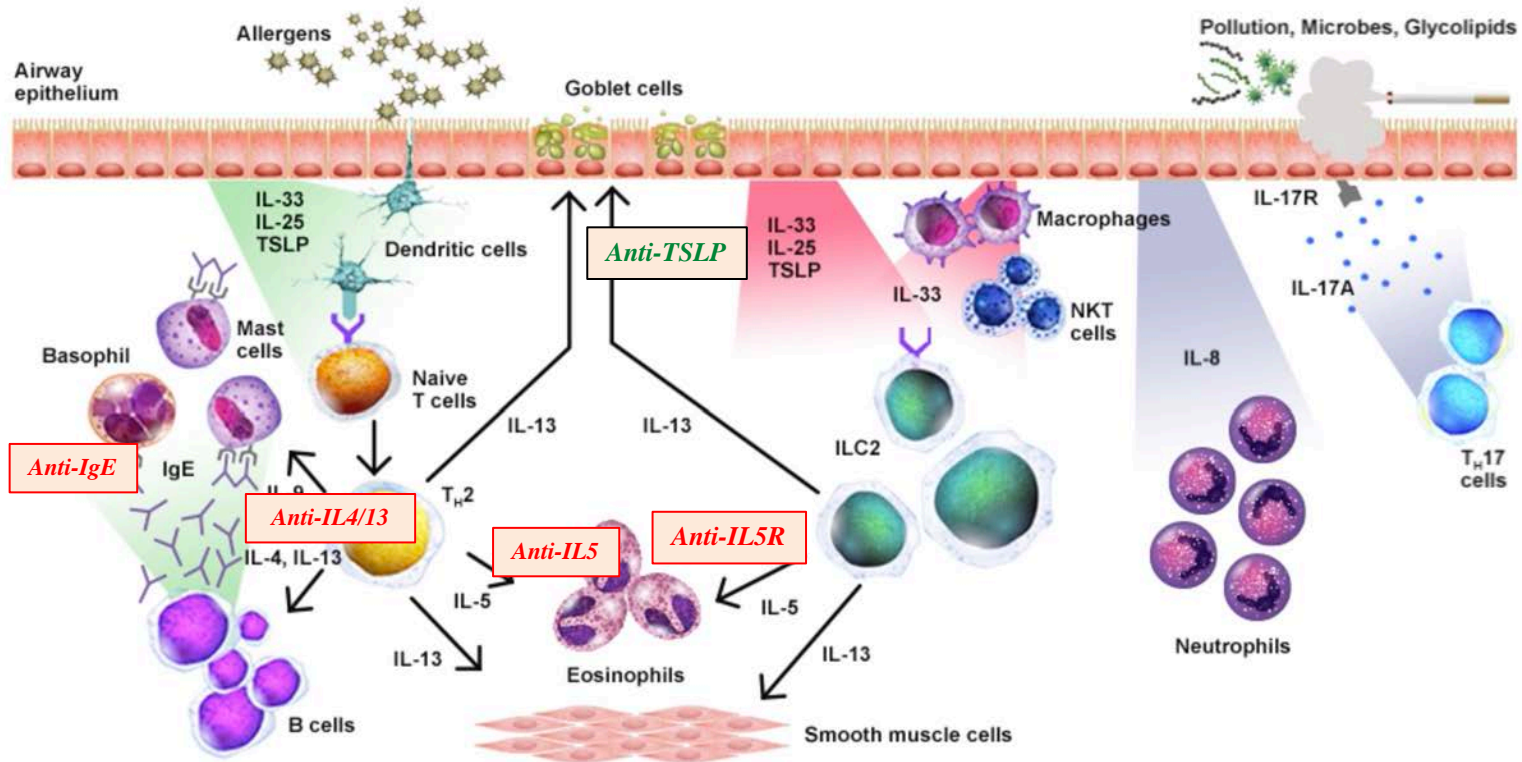
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- A. Eosinophilic asthma
- B. Allergic Asthma
- C. T2 low asthma
- D. All of the above

# Type 2 Biomarkers



# Type 2 asthma and therapeutic targets



Re: **Allergic Eosinophilic**

**Nonallergic Eosinophilic**

**Neutrophilic**

# Biologics for Type 2 Asthma

| Drug                                    | Dosing                                     | Mechanism   | FDA Indication  |
|---|--|-------------|---|
| Omalizumab (Xolair®, Genentech)         | 75-375 mg SC Q 2-4 weeks                   | Anti-IgE    | Age ≥ 6 years with moderate to severe persistent asthma who test positive for year-round allergens <sup>7</sup>                         |
| Mepolizumab (Nucala®, GlaxoSmithKline)  | 100 mg SC Q 4 weeks                        | Anti-IL-5   | Age ≥ 12 years with severe asthma and eosinophilic phenotype <sup>8</sup>   |
| Reslizumab (Cinqair®, Teva)             | 3 mg/kg IV Q 4 weeks                       | Anti-IL-5   | Age ≥ 18 years with severe asthma and eosinophilic phenotype <sup>9</sup>   |
| Benralizumab (Fasenra™, AstraZeneca)    | 30 mg SC Q 4 weeks x 3, then Q 8 weeks     | Anti-IL-5Rα | Age ≥ 12 years with severe asthma and eosinophilic phenotype <sup>10</sup>  |
| Dupilumab (Dupixent®, Sanofi/Regeneron) | 200 mg SC Q 2 weeks<br>300 mg SC Q 2 weeks | Anti-IL-4Rα | Age ≥ 12 years with moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma <sup>11</sup> |

# Biologics for Type 2 Asthma - Efficacy

| Treatment        | Rate Ratio (95% CI) |
|------------------|---------------------|
| Omalizumab       | 0.52 (0.37-0.73)    |
| Mepolizumab      | 0.45 (0.36-0.55)    |
| Reslizumab       | 0.43 (0.33-0.55)    |
| Benralizumab     | 0.59 (0.51-0.68)    |
| Dupilumab 200 mg | 0.44 (0.34-0.58)    |
| Dupilumab 300 mg | 0.40 (0.31-0.53)    |

Rate Ratio for exacerbations

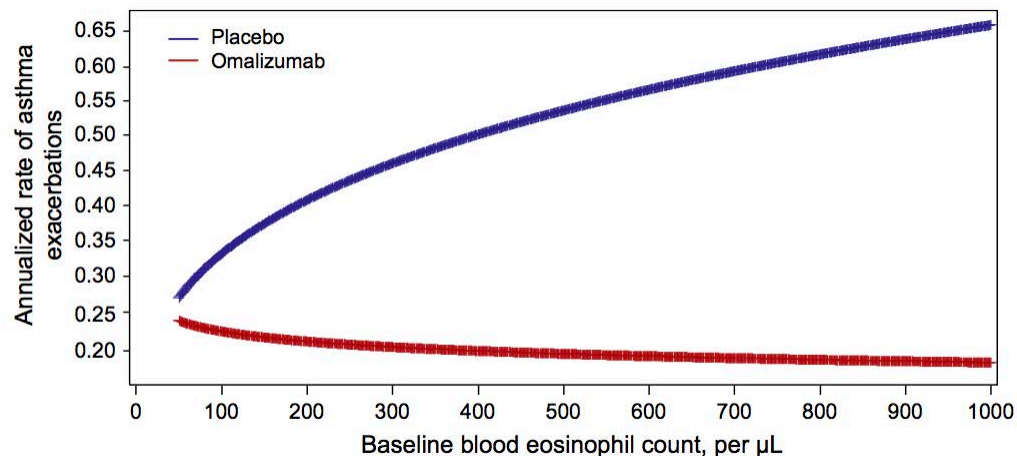
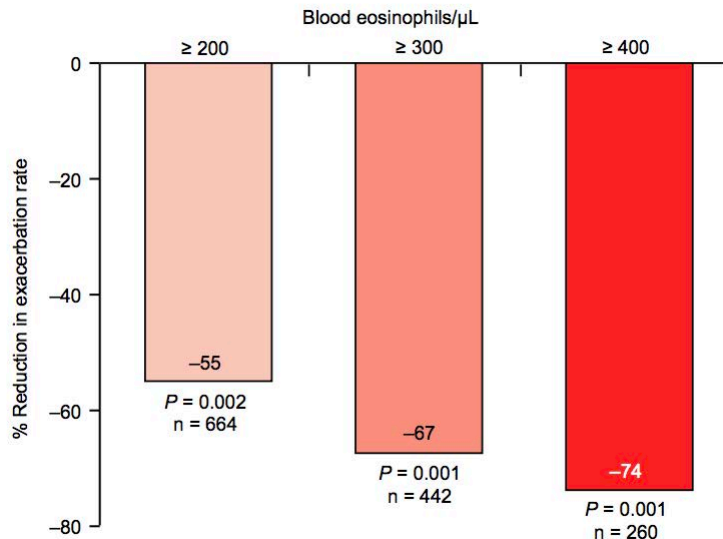
## Mean Difference AQLQ

| Treatment        | Difference (95% CI) |
|------------------|---------------------|
| Omalizumab       | 0.26 (0.05-0.47)    |
| Mepolizumab      | NR                  |
| Reslizumab       | 0.28 (0.17-0.39)    |
| Benralizumab     | 0.23 (0.11-0.35)    |
| Dupilumab 200 mg | 0.29 (0.15-0.44)    |
| Dupilumab 300 mg | 0.26 (0.12-0.40)    |

| Treatment        | Difference (95% CI)    |
|------------------|------------------------|
| Omalizumab       | NR                     |
| Mepolizumab      | -0.42 (-0.56 to -0.28) |
| Reslizumab       | -0.27 (-0.36 to -0.19) |
| Benralizumab     | -0.23 (-0.34 to -0.12) |
| Dupilumab 200 mg | -0.39 (-0.53 to -0.25) |
| Dupilumab 300 mg | -0.22 (-0.36 to -0.08) |

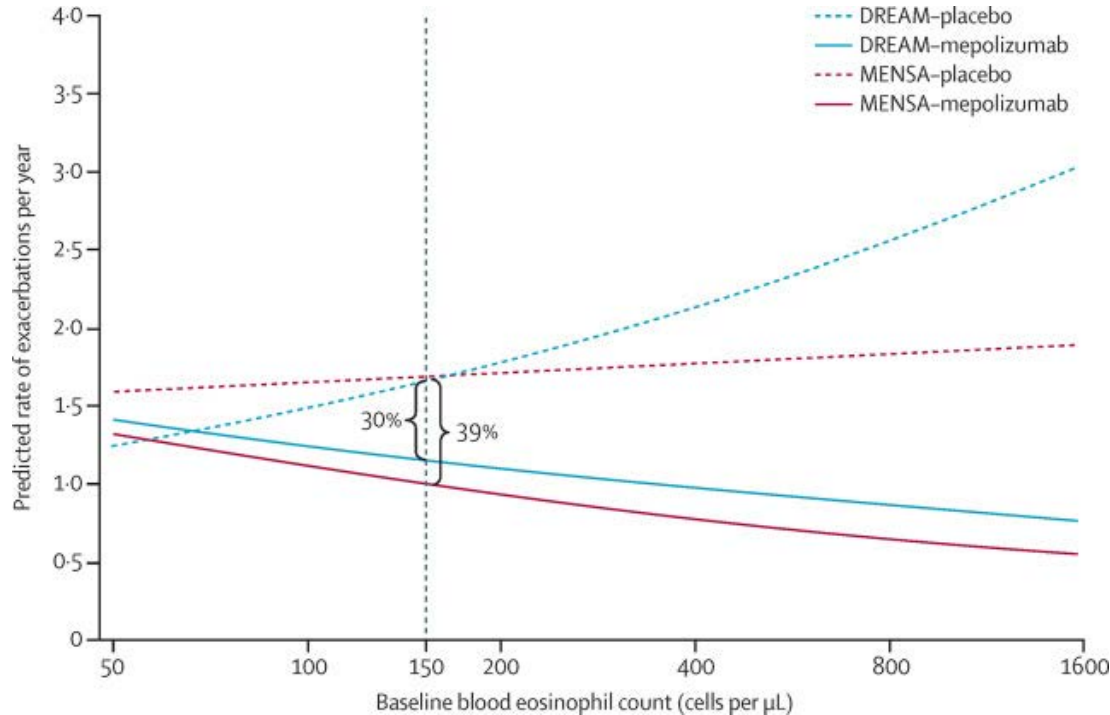
Mean Difference ACQ

# Blood eosinophil count predicts response to omalizumab

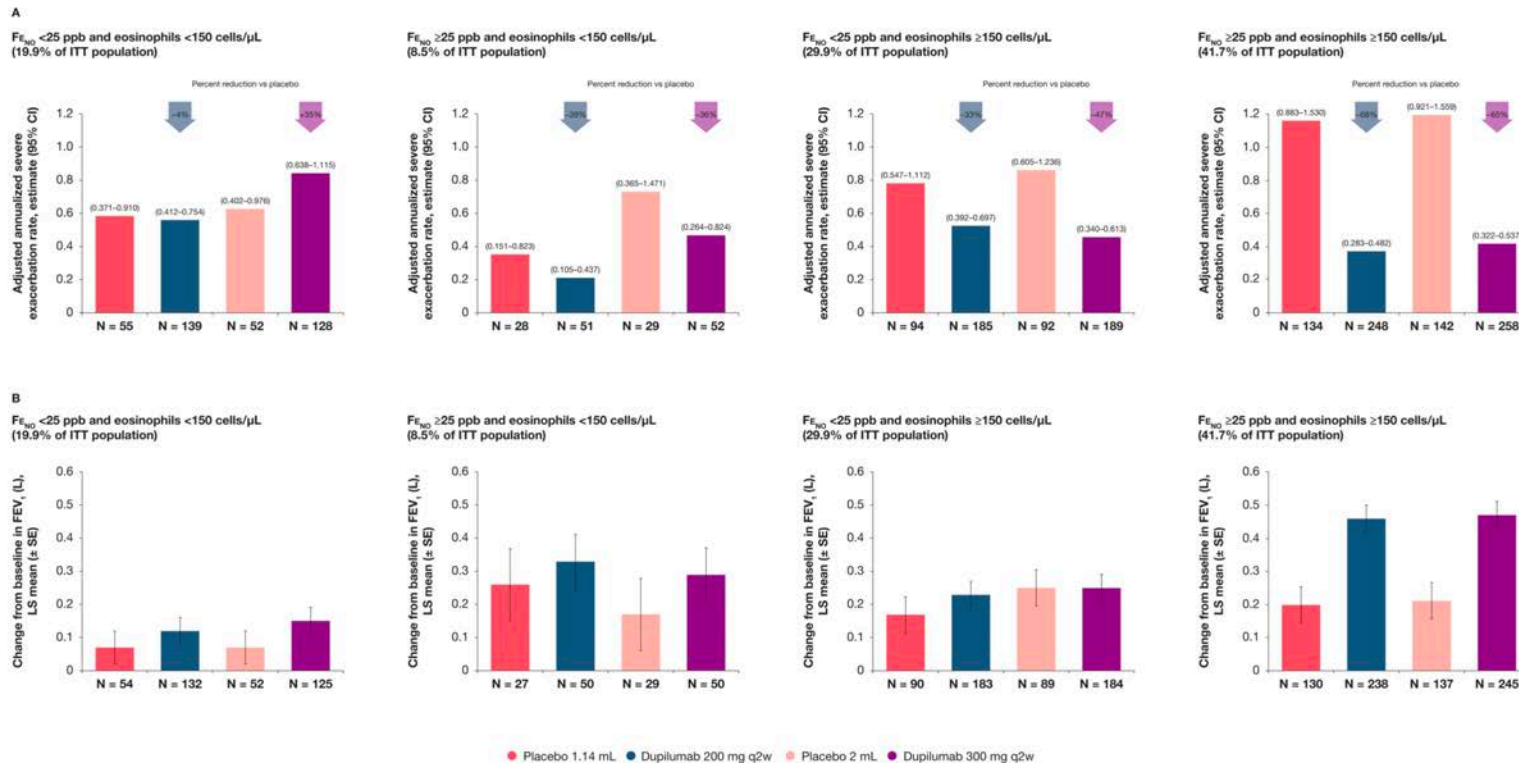




# Blood eosinophil count predicts response to mepolizumab



# Effect of dupilumab on exacerbation and lung function by baseline Eos and FeNO



# Question

Which of the following biologics has NOT been studied for steroid sparing efficacy?

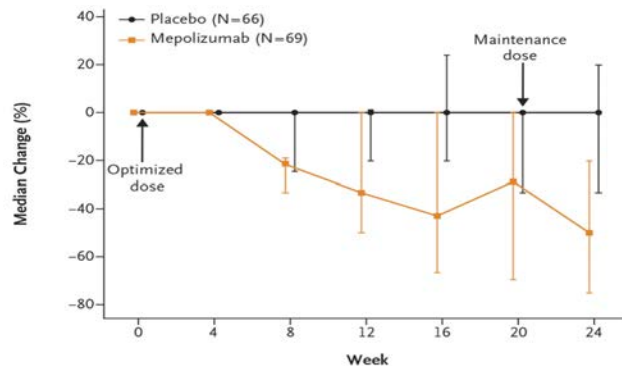
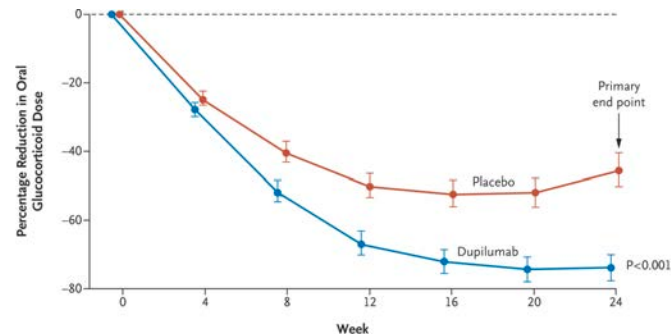
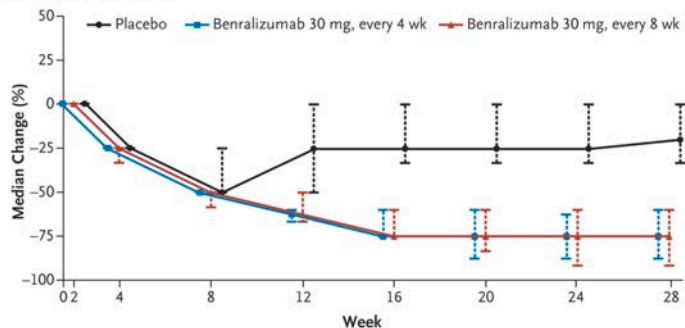
- A. Mepolizumab
- B. Reslizumab
- C. Benralizumab
- D. Dupilumab

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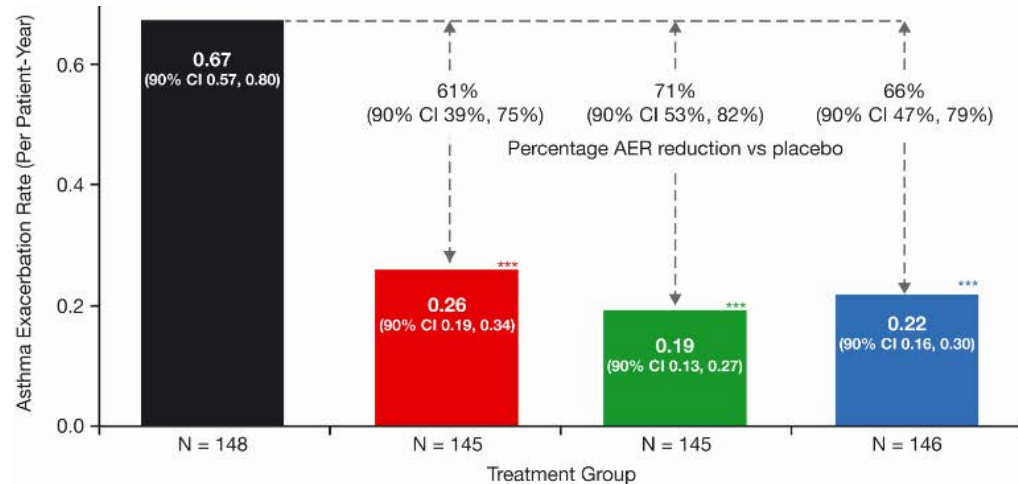
- A. Mepolizumab
- B. Reslizumab
- C. Benralizumab
- D. Dupilumab

# Steroid-sparing effect of biologics

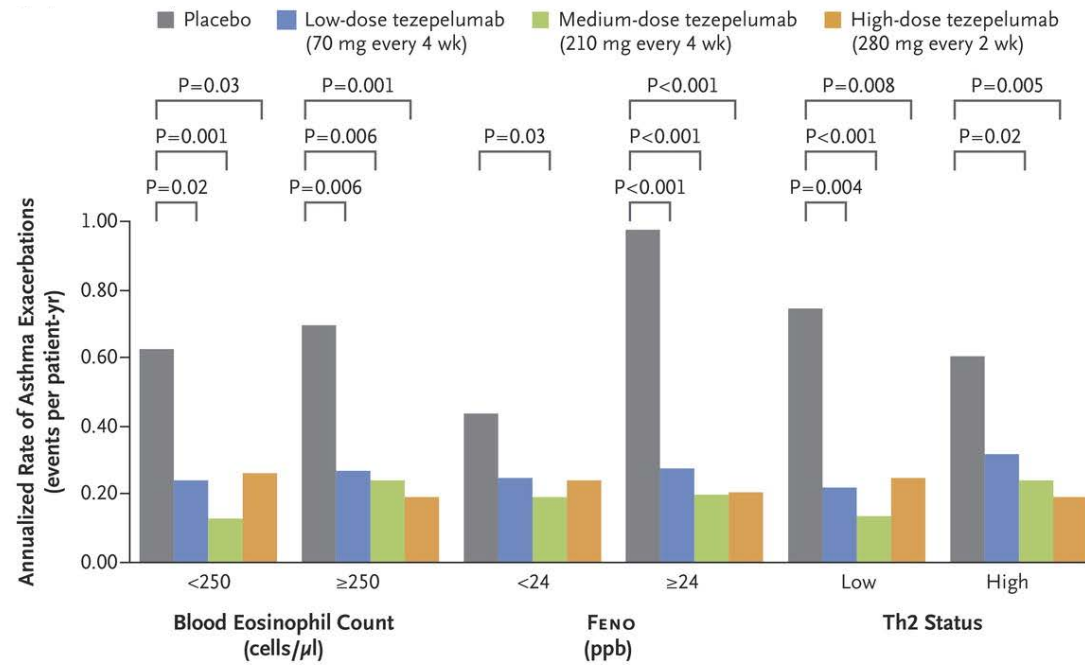


# Tezepelumab in Adults with Uncontrolled Asthma

- Placebo (N = 148)
- Tezepelumab 70 mg Q4W (low-dose) (N = 145)
- Tezepelumab 210 mg Q4W (medium-dose) (N = 145)
- Tezepelumab 280 mg Q2W (high-dose) (N = 146)



# Anti-TSLP: Effect by Th2 status

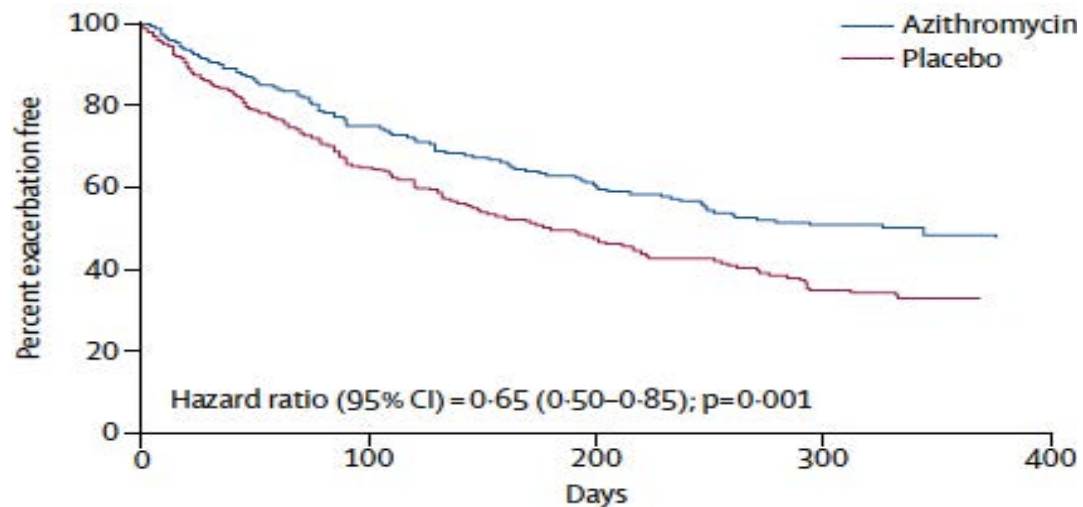


# Azithromycin & Asthma

N=420

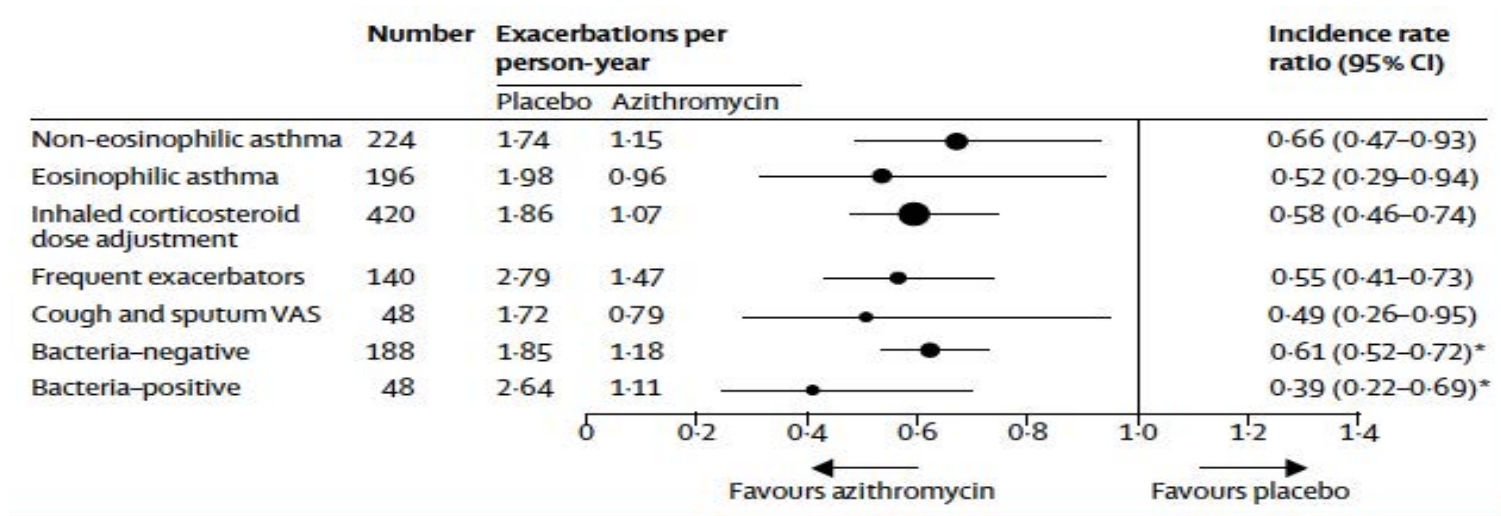
Symptomatic asthma despite  
ICS/LABA

Azithromycin 500 mg thrice  
weekly vs placebo for 48 weeks

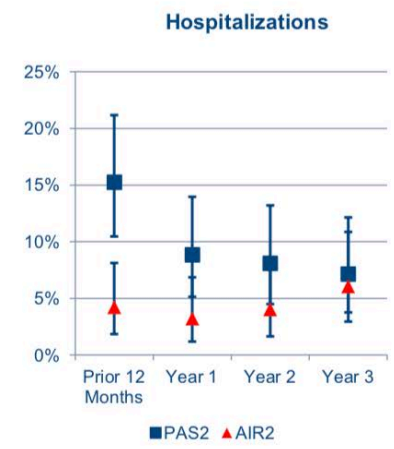
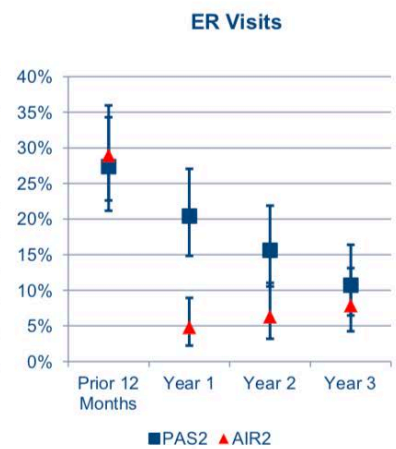
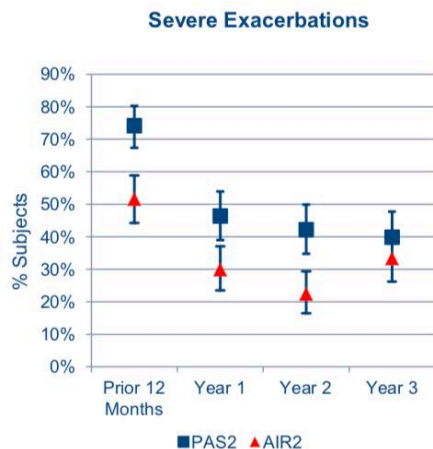




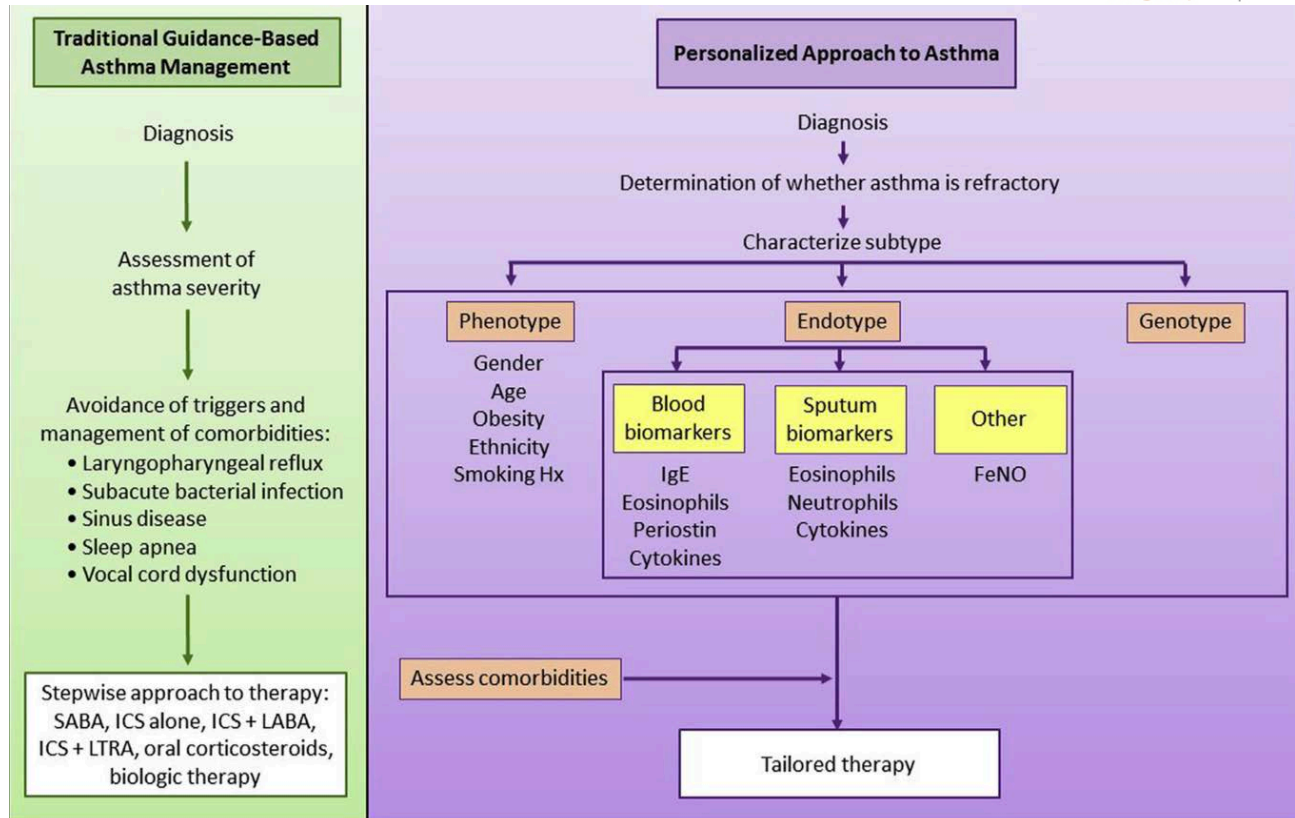
# Azithromycin asthma AMAZES



# Bronchial Thermoplasty PAS 2 Study Real world effectiveness – 3 year follow-up



# 'Traditional' vs. 'Personalized'



# Summary

- Burden of asthma remains high and mortality rates have stalled
- Heterogeneity and complex pathophysiology increasingly recognized. Multiple mechanisms in play. Therefore, a ‘one-size’ approach is no longer appropriate.
- Before pursuing advanced therapies, a systematic assessment is critical to evaluate correct diagnosis and address modifiable risk factors
- Recent studies suggest a role for as needed ICS/fast acting LABA for mild asthma
- Several biologics targeting type 2 pathways are effective in reducing exacerbations and steroid dependence. Limited options for non-eosinophilic asthma.

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