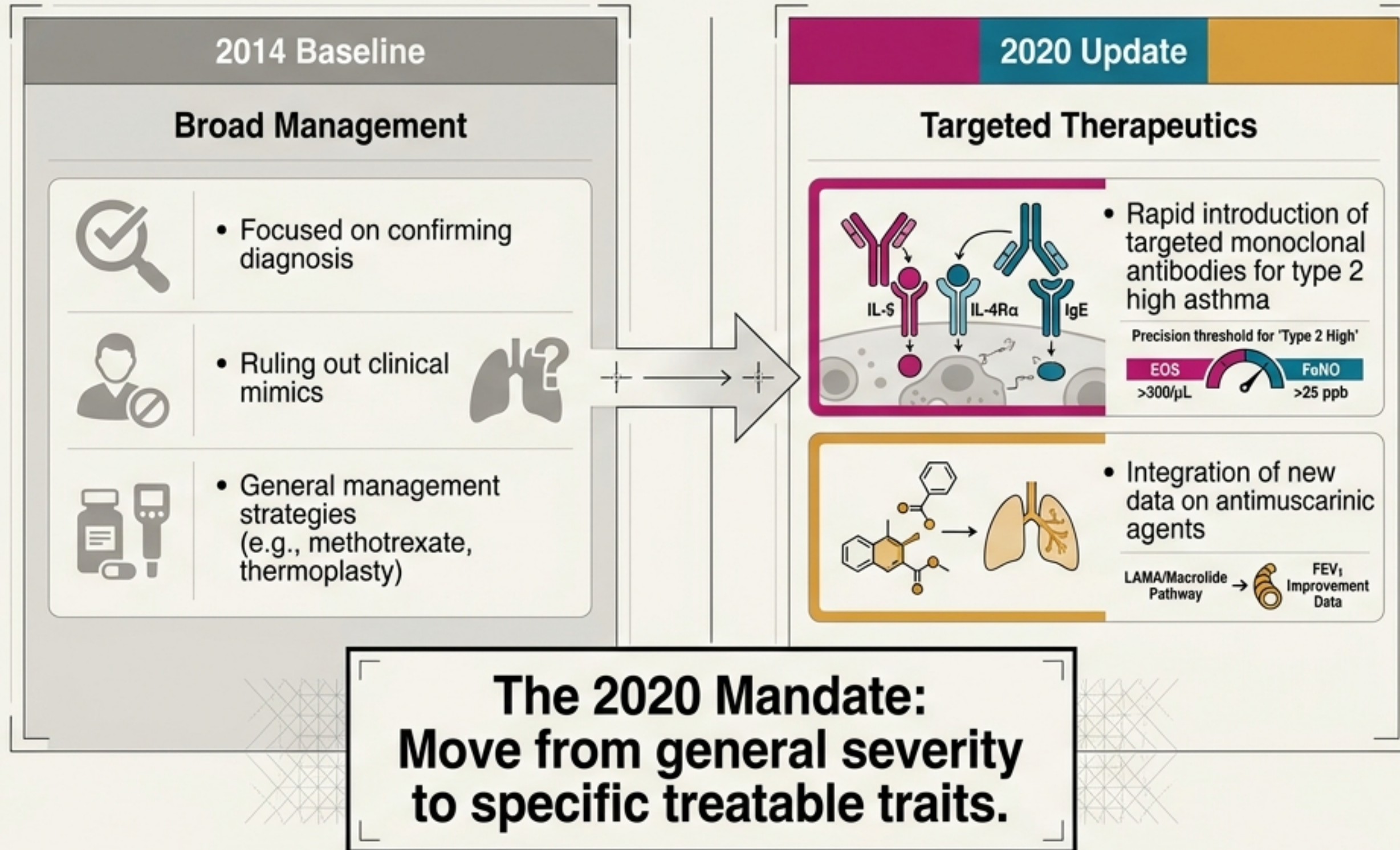




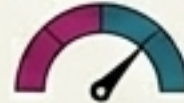
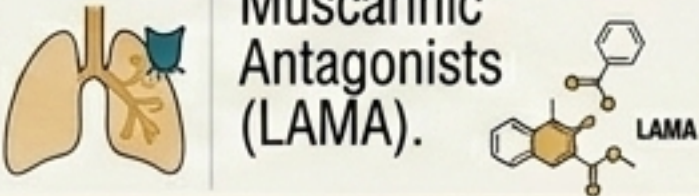
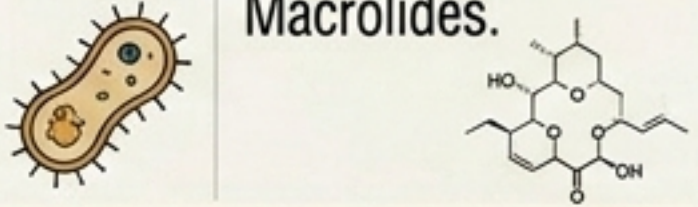
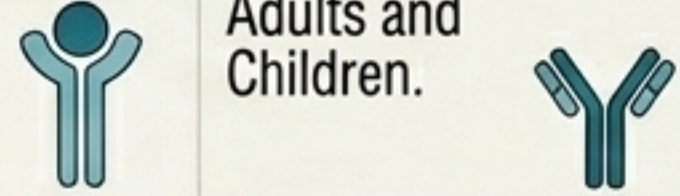


# The Rapid Evolution of Severe Asthma Care

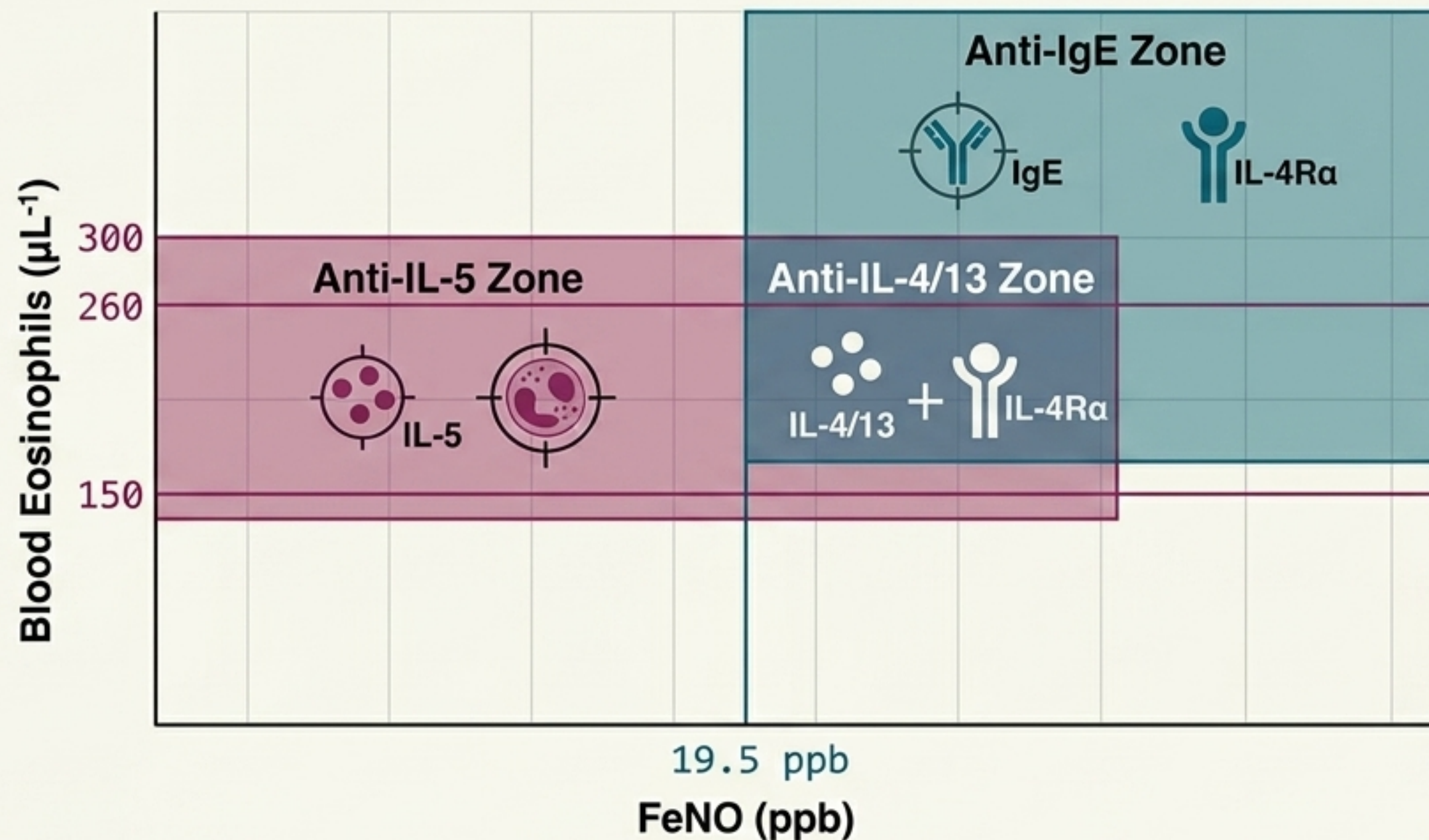


# Six Targeted Clinical Questions Drive the 2020 Framework

TABLE 1 European Respiratory Society (ERS)/American Thoracic Society (ATS) Severe Asthma Task Force questions

<p><b>1</b></p> <p><b>System Status</b></p> <p><b>Biologics:</b> Role of Anti-IL-5 in Adults and Children.</p> 	<p><b>2</b></p> <p><b>System Status</b></p> <p><b>Biomarkers:</b> Guiding Anti-IL-5 initiation.</p> 	<p><b>3</b></p> <p><b>System Status</b></p> <p><b>Biomarkers:</b> Guiding Anti-IgE initiation.</p> <p>IgE</p> 
<p><b>4</b></p> <p><b>System Status</b></p> <p><b>Adjuncts:</b> Role of Long-Acting Muscarinic Antagonists (LAMA).</p> 	<p><b>5</b></p> <p><b>System Status</b></p> <p><b>Adjuncts:</b> Role of chronic Macrolides.</p> 	<p><b>6</b></p> <p><b>System Status</b></p> <p><b>Biologics:</b> Role of Anti-IL-4R<math>\alpha</math> in Adults and Children.</p> <p>IL-4R<math>\alpha</math></p> 

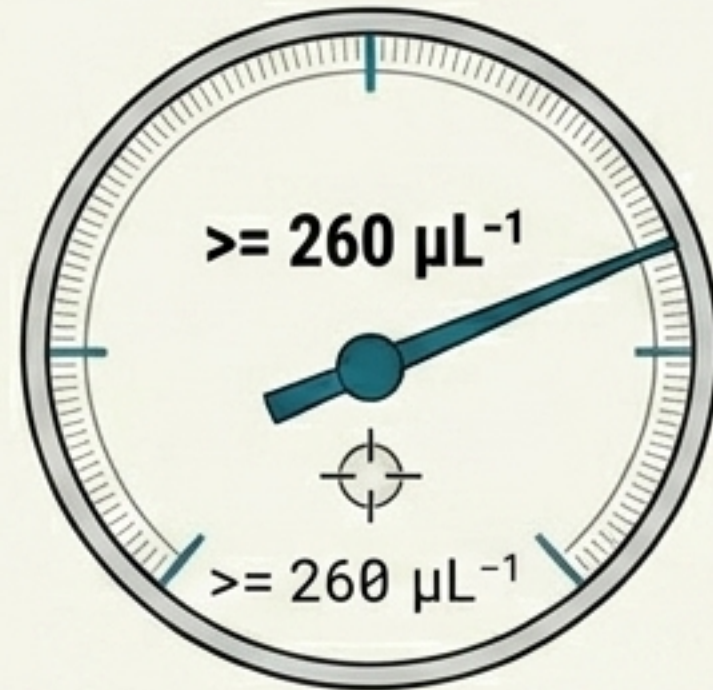
## The Biomarker Compass: Quantifying Type 2 Inflammation



Measuring disease traits precedes treating them. Corticosteroid-dependent patients require specific baseline testing prior to optimization.

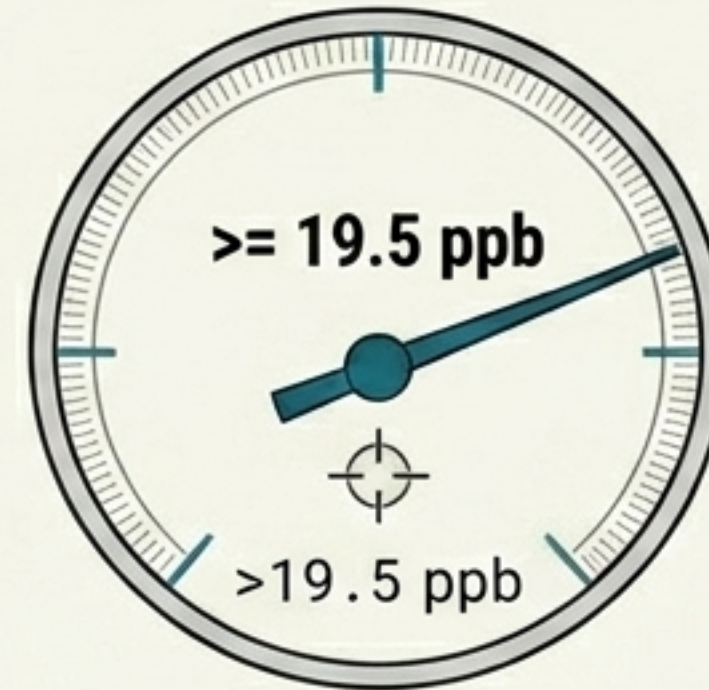
# Biomarker Predictors for Anti-IgE Efficacy

## Blood Eosinophils



Patients above this threshold show significantly longer time to first exacerbation (Hazard Ratio 0.64) and improved FEV1.

## FeNO

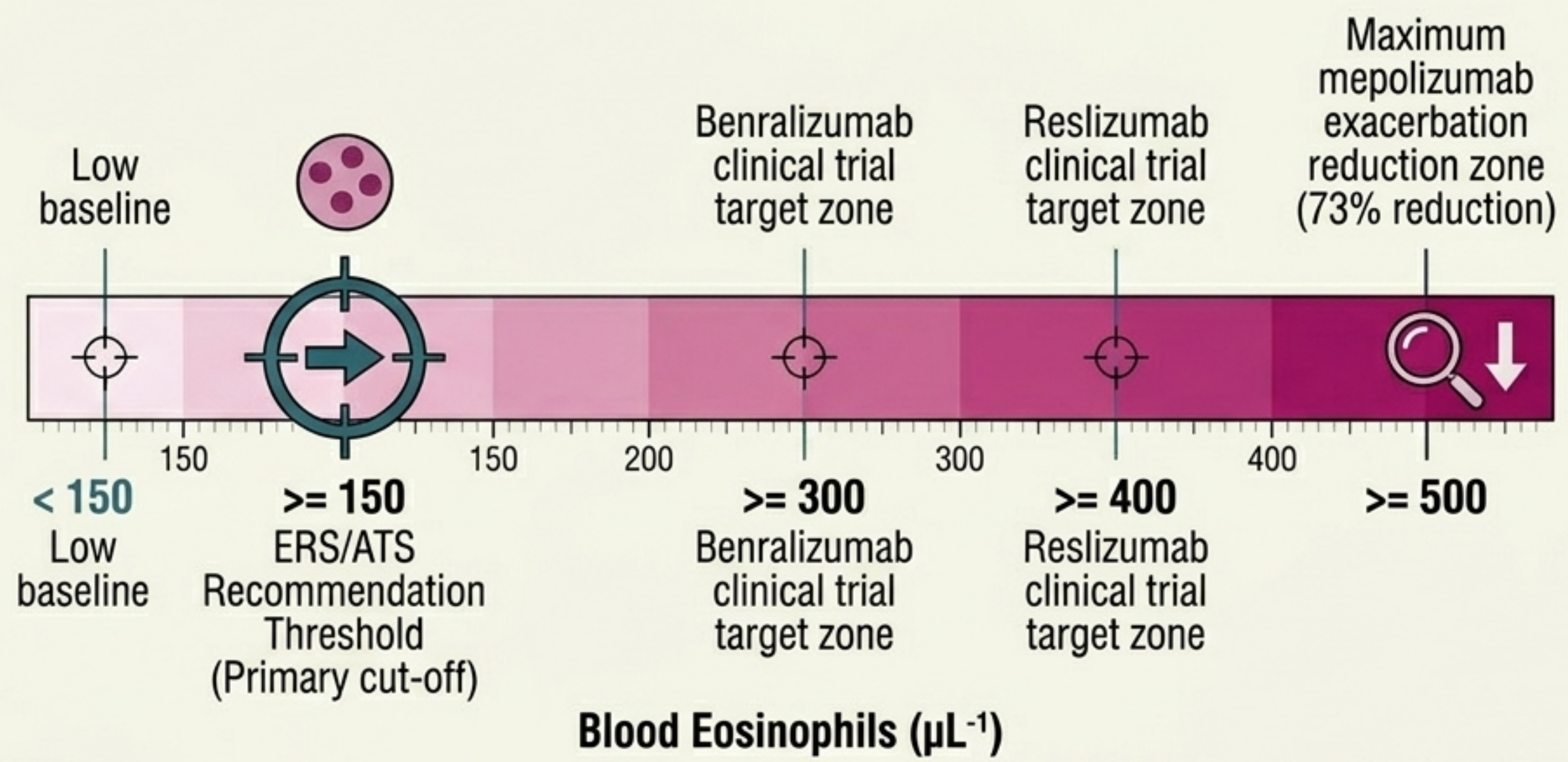


Patients above this threshold show a 53% relative reduction in exacerbation rates vs. 16% for those below.

### Clinical Caveat:

Patients with values below cut-offs may still benefit; periostin is not recommended clinically due to skeletal growth interference in children.

# Establishing Eosinophil Thresholds for Anti-IL-5 Initiation



**Clinical benefit is a gradient, not an absolute switch.**  
The guideline anchors at  $150 \mu\text{L}^{-1}$  for adults with prior exacerbations, though higher counts correlate with stronger responses.

# Pathway Blockade: Anti-IL-5 and Anti-IL-5R $\alpha$

## Recommendation Card

### Intervention

Mepolizumab, Reslizumab,  
Benralizumab

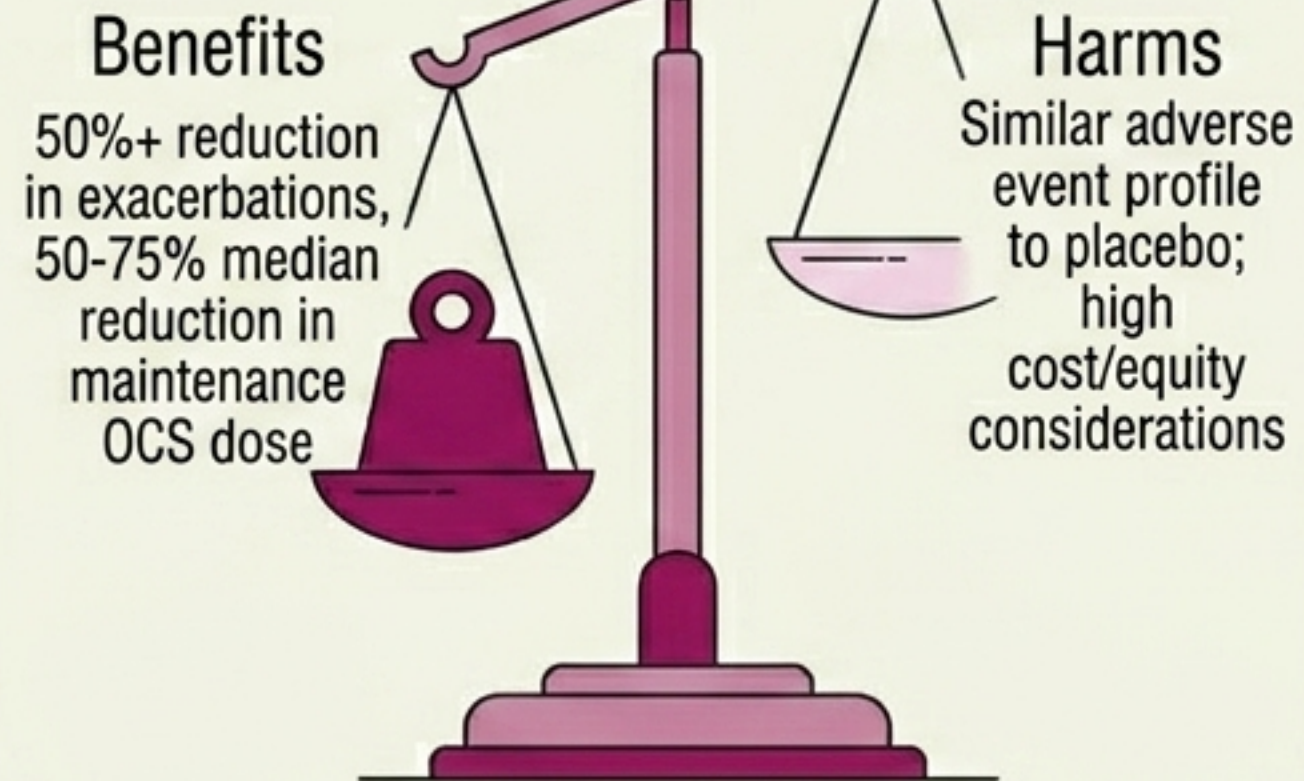
### Target Population

Severe uncontrolled adult  
eosinophilic asthma & severe  
OCS-dependent asthma

### GRADE Rating

Conditional Recommendation /  
Low Quality of Evidence

### Balance of Effects



# Dual Cytokine Blockade: Anti-IL-4R $\alpha$

## Recommendation Card

### Intervention

Dupilumab.

### Target Population

Adult severe eosinophilic asthma OR severe OCS-dependent asthma (regardless of baseline eosinophils).

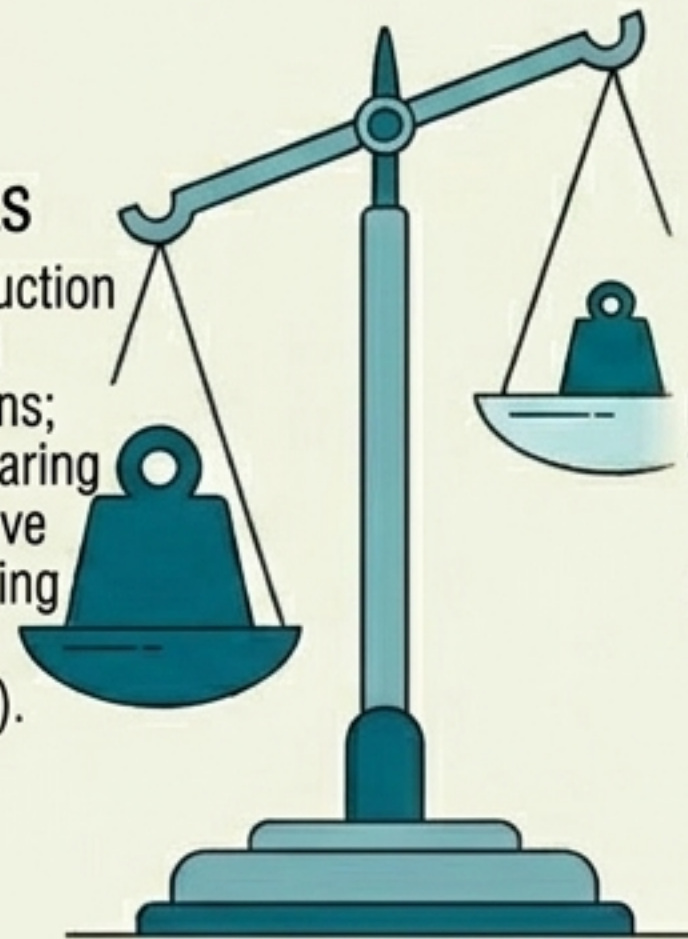
### GRADE Rating

Conditional Recommendation / Low Quality of Evidence.

### Balance of Effects

#### Benefits

46–70.5% reduction in annual exacerbations; robust OCS sparing (1.92x relative risk of reducing OCS to <5 mg/day).



#### Harms

Injection site reactions; mechanisms of transient blood eosinophilia require further elucidation.

# The Biologics Master Matrix




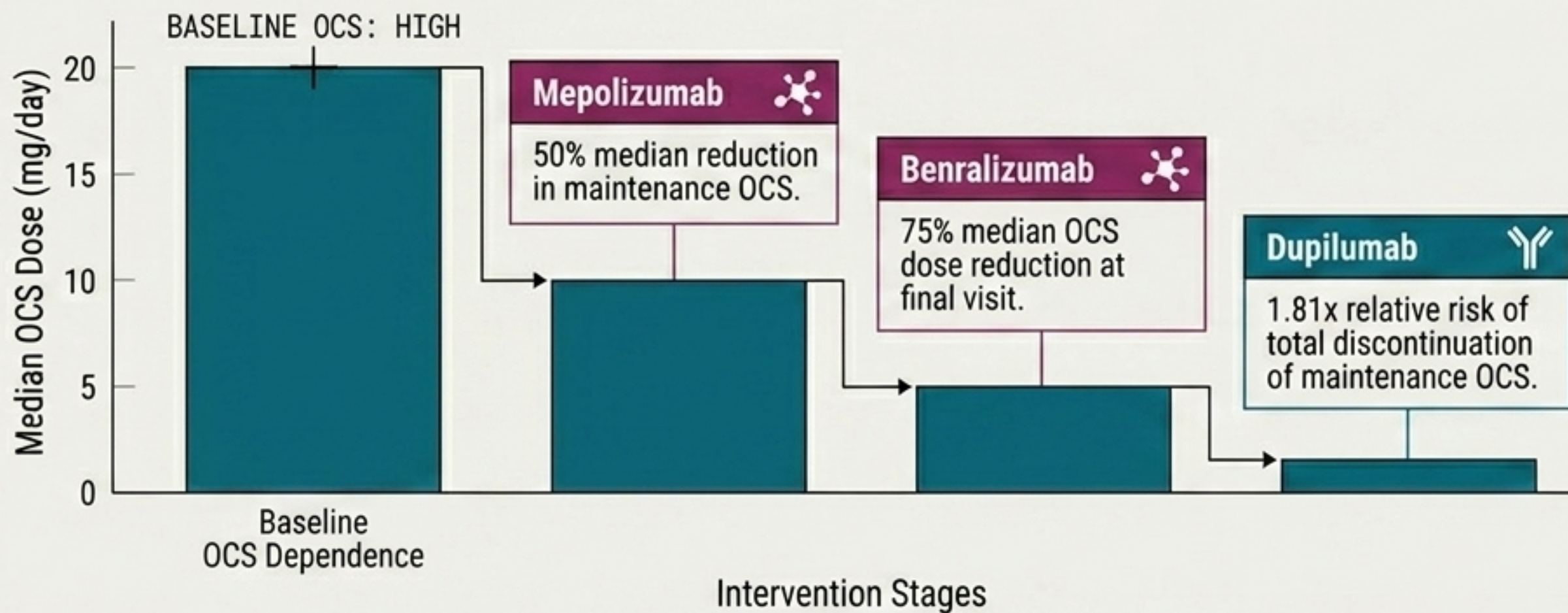
	Pathway & Drug	Target Population	Predictors of Response	Key Efficacy
	Anti-IL-5 (Mepolizumab, Reslizumab, Benralizumab)	Eosinophilic / OCS-dependent	Blood Eos $\geq 150 \mu\text{L}^{-1}$	42-54% exacerbation drop
	Anti-IgE (Omalizumab)	Severe Allergic	Eos $\geq 260 \mu\text{L}^{-1}$ , FeNO $\geq 19.5$ ppb	Extended time to exacerbation
	Anti-IL-4R $\alpha$ (Dupilumab)	Eosinophilic / OCS-dependent	Blood Eos $\geq 150 \mu\text{L}^{-1}$ , FeNO $\geq 25$ ppb	46-70% exacerbation drop

TABLE 2 European Respiratory Society (ERS)/American Thoracic Society (ATS) Severe Asthma Task Force recommendations for the management of severe asthma

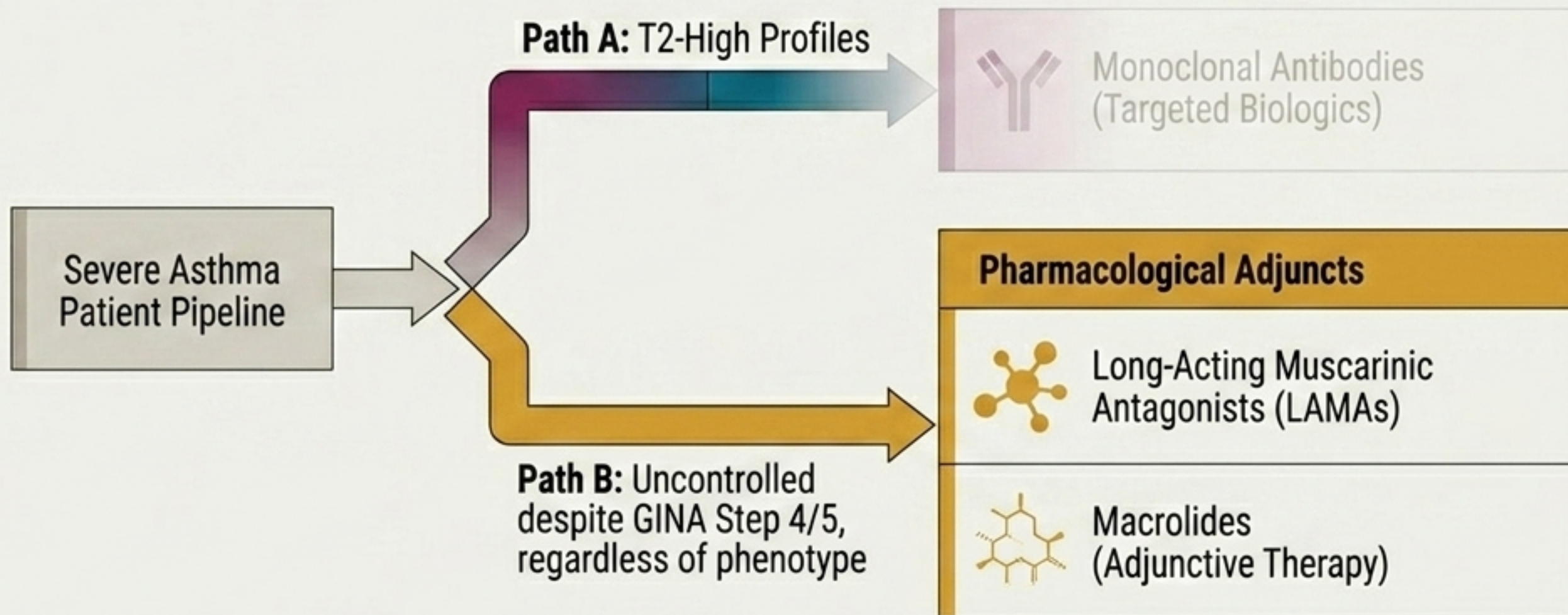
# The Corticosteroid-Dependent Phenotype

## OCS Reduction Staircase



**Clinical Remark:** Both anti-IL-5 and anti-IL-4/13 pathways are explicitly recommended for severe corticosteroid-dependent asthma, prioritizing the rapid reduction of systemic steroid toxicity.

## Expanding the Arsenal: Beyond Targeted Biologics



**Not all** severe asthma exhibits clear type 2 inflammation. For persistently symptomatic populations, the guidelines evaluate the addition of Long-Acting Muscarinic Antagonists (LAMAs) and Macrolides.

# Bronchodilator Adjuncts: Inhaled Tiotropium

## Intervention



LAMA (Tiotropium 5 µg)

## Target Population

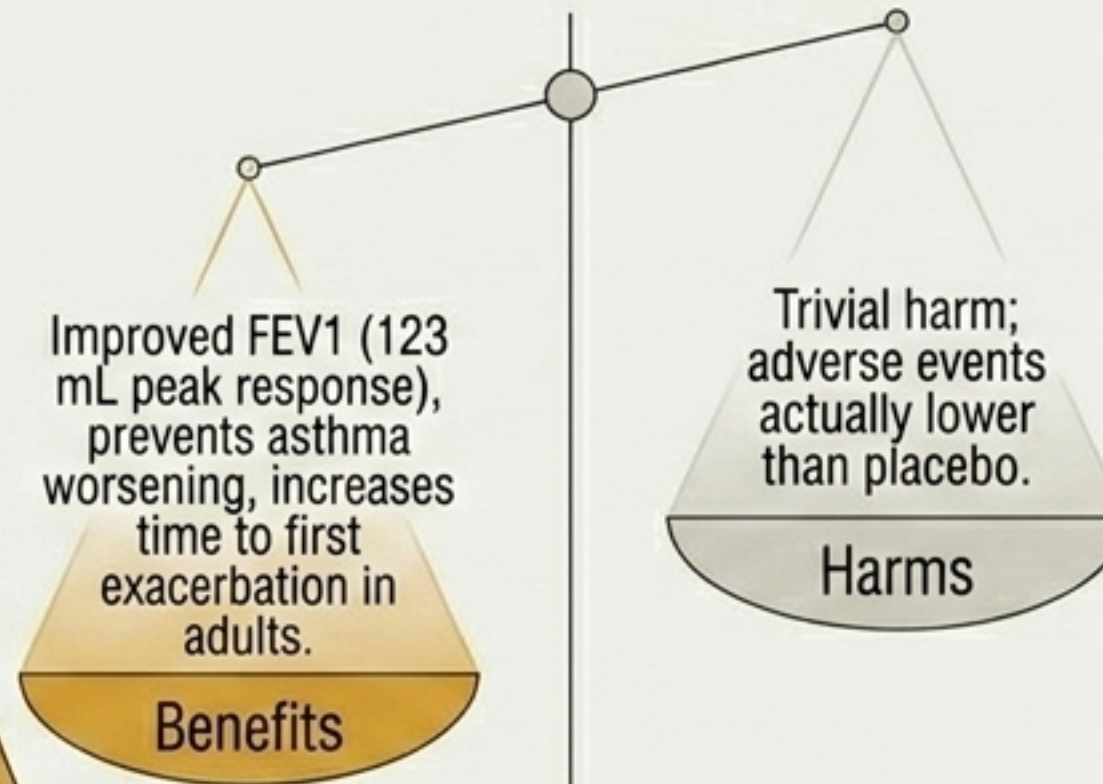
Children, adolescents, and adults uncontrolled despite GINA Step 4-5.

## GRADE Rating

**STRONG** Recommendation / Moderate Quality of Evidence.

**The Only Strong Recommendation** in the 2020 Guidelines.



## Balance of Effects



# Antimicrobial Adjuncts: Chronic Macrolide Therapy

Recommendation Card			
	Intervention	Target Population	GRADE Rating
	Azithromycin / Clarithromycin.	Adult subjects on GINA Step 5 remaining persistently symptomatic.	Conditional Recommendation / Low Quality of Evidence.

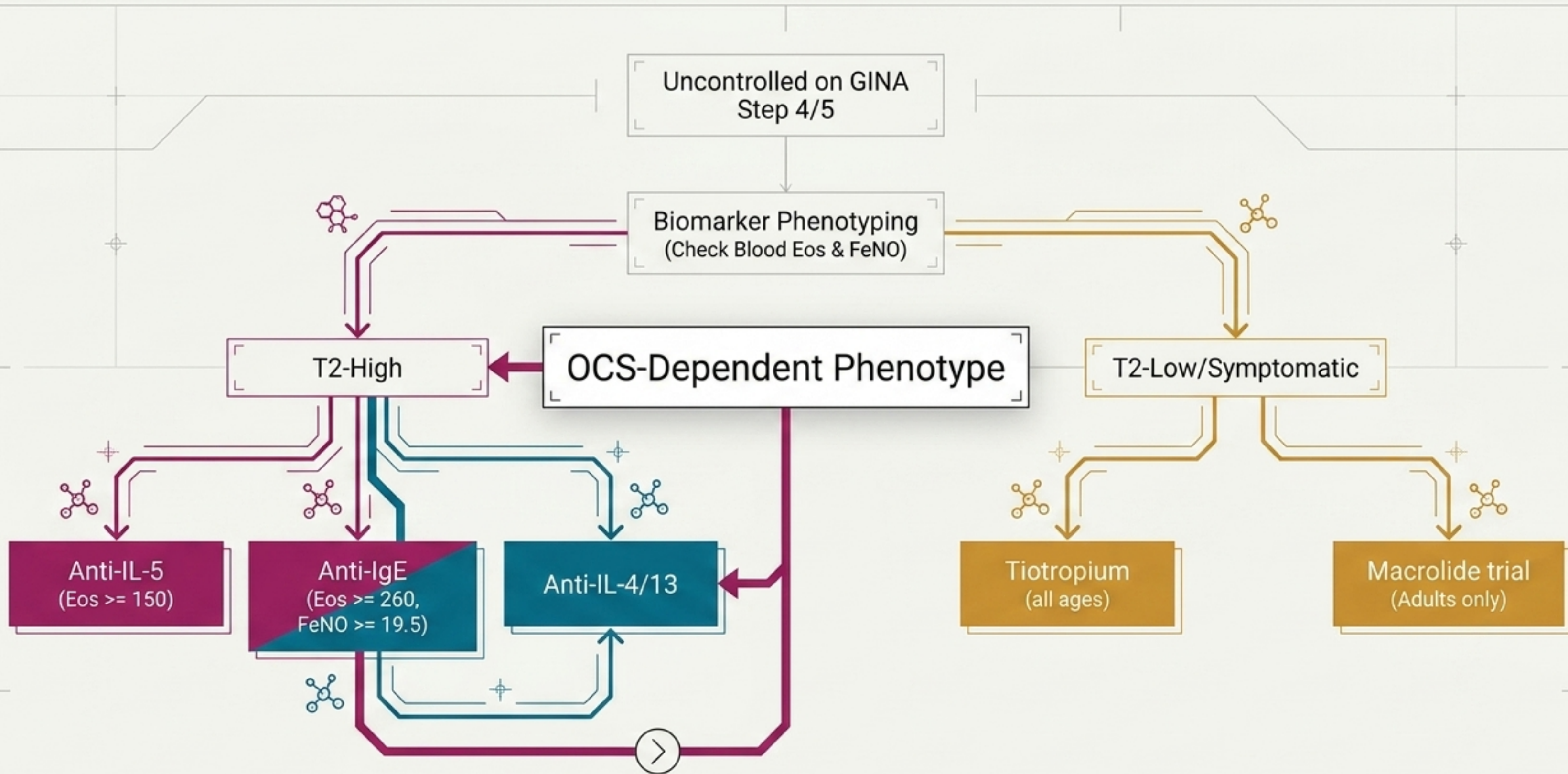
Split Population Rule	
 <b>Adults</b> Trial suggested to reduce exacerbations (Risk ratio 0.59).	 <b>Children/Adolescents</b> Recommended AGAINST use.

 <b>Balance of Effects</b> 	Benefits in exacerbation reduction weighed heavily against the public health threat of antimicrobial resistance.
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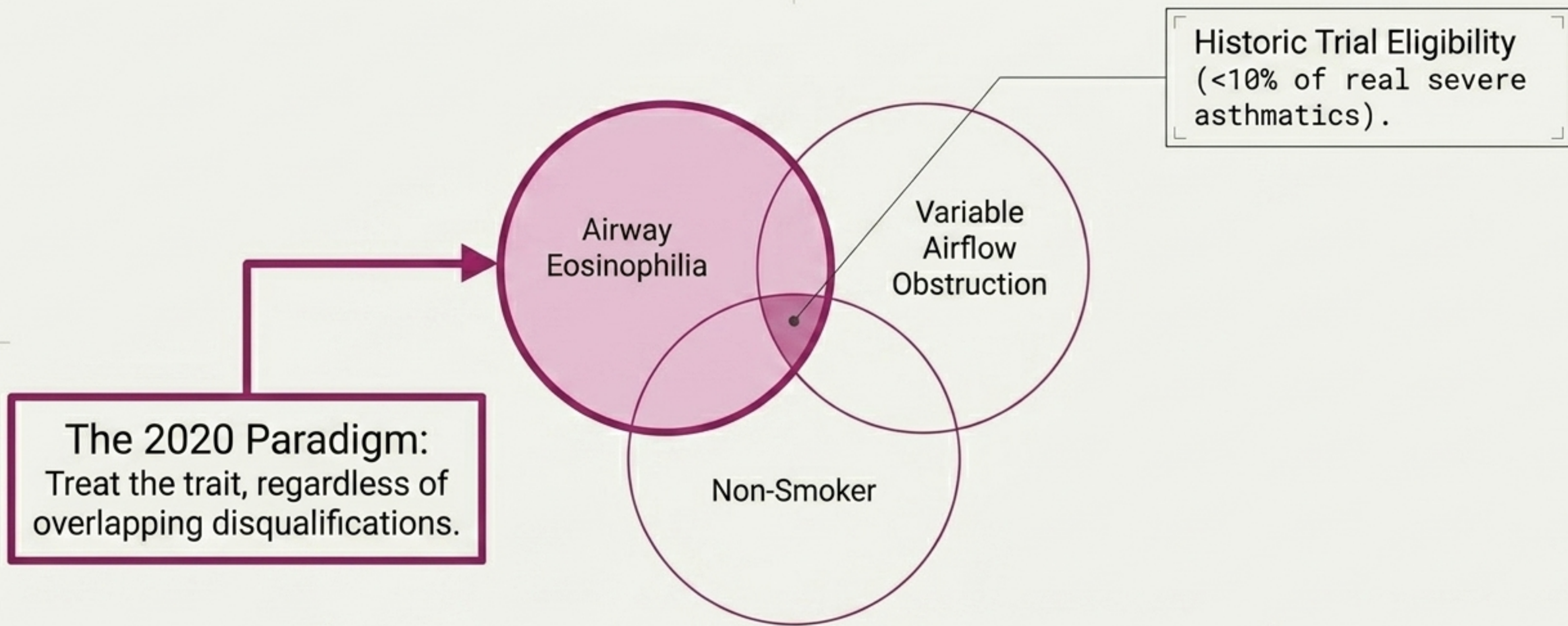
# The Adjunct Therapy Matrix

Comparison Parameters	LAMA (Tiotropium)	Macrolide (Azithromycin / Clarithromycin)
Primary Effect	Lung function & symptom control	Exacerbation reduction
Phenotype Dependence	Efficacy independent of phenotype	Efficacy independent of phenotype
Safety / Harms	Low adverse events	Antimicrobial resistance / GI issues
Pediatric Approval	Approved for children/adolescents ✓	Explicitly recommended against in children ✗

# The 2020 Clinical Decision Flowchart

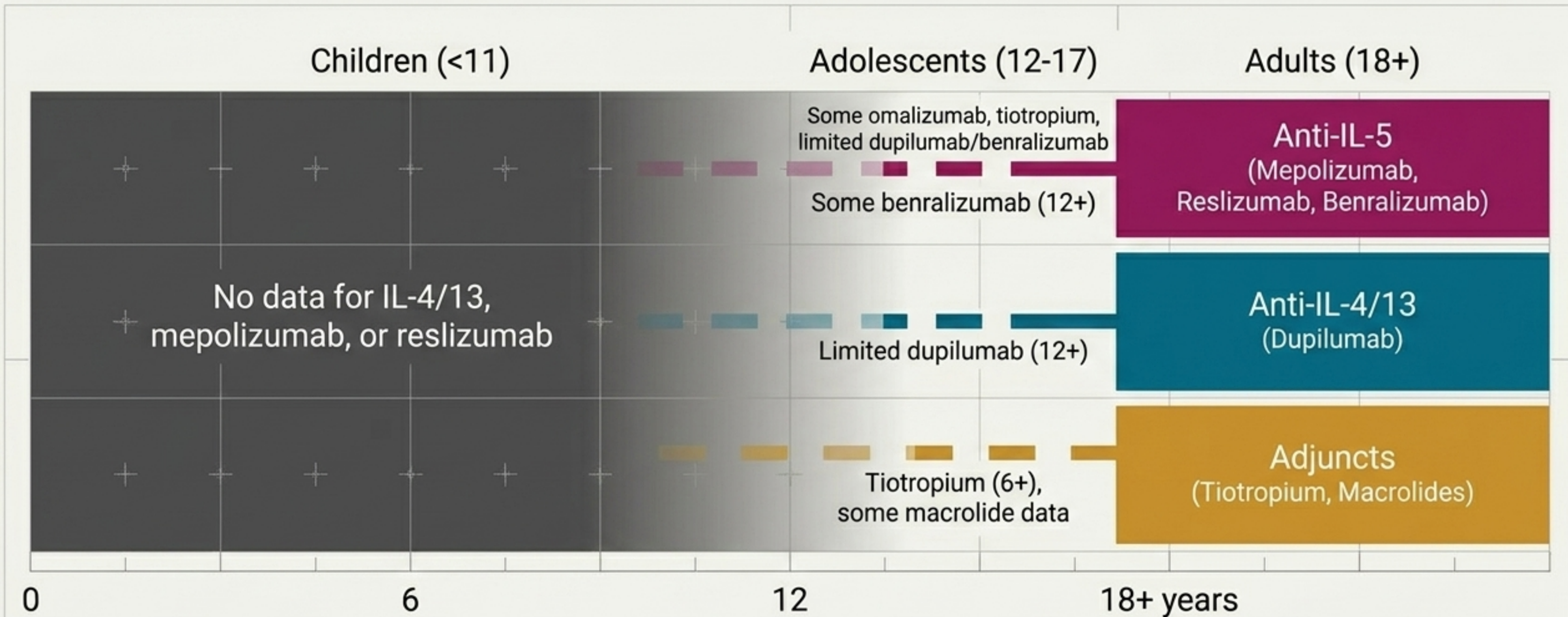


# The Real-World Mismatch: Targeting Traits over Stereotypes



*Excluding adult smokers with asthma to avoid a COPD misdiagnosis is illogical... those who smoke may be more steroid resistant and thus more likely to profit from biologics."*

# The Pediatric Evidence Gap



*Clear phenotypic differences exist between pediatric and adult asthma. The absence of safety and efficacy data in pre-school/childhood asthma remains the largest blind spot in the 2020 guidelines.*

# The Unfinished Blueprint: Directing Future Research

## Biomarker Evolution

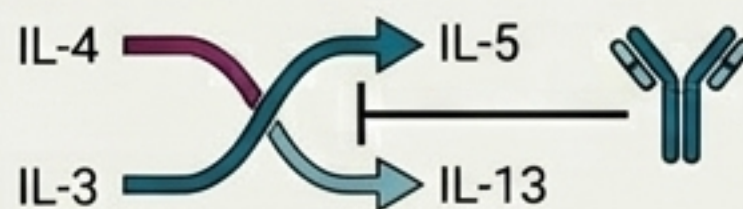
Need for point-of-care, non-invasive biomarkers beyond blood eosinophils (which are suppressed by OCS) to identify specific sub-endotypes.



## Biologic Combinations



The theoretical potential of combining dupilumab with anti-IL-5 to abrogate all signature type 2 cytokines (IL-4, IL-5, IL-13) simultaneously.



## Refractory Non-Adherence



The ethical debate: Should non-adherent patients with treatable traits receive hospital-observed biologicals to prevent fatal exacerbations?



*Before adopting targeted approaches, standard medications must be deployed to maximum benefit. But for the therapy-resistant minority, precision medicine offers a new horizon.*