Therapeutic Interventions in Severe Asthma

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Objectives

- Discuss the definitions of severe and difficult to treat asthma
- Discuss features that can influence severe and difficult to treat asthma
  - Phenotypes
  - Genotypes
  - Biology and Biomarkers
- Discuss strategies to optimize treatment of asthma including the role of personalized medicine

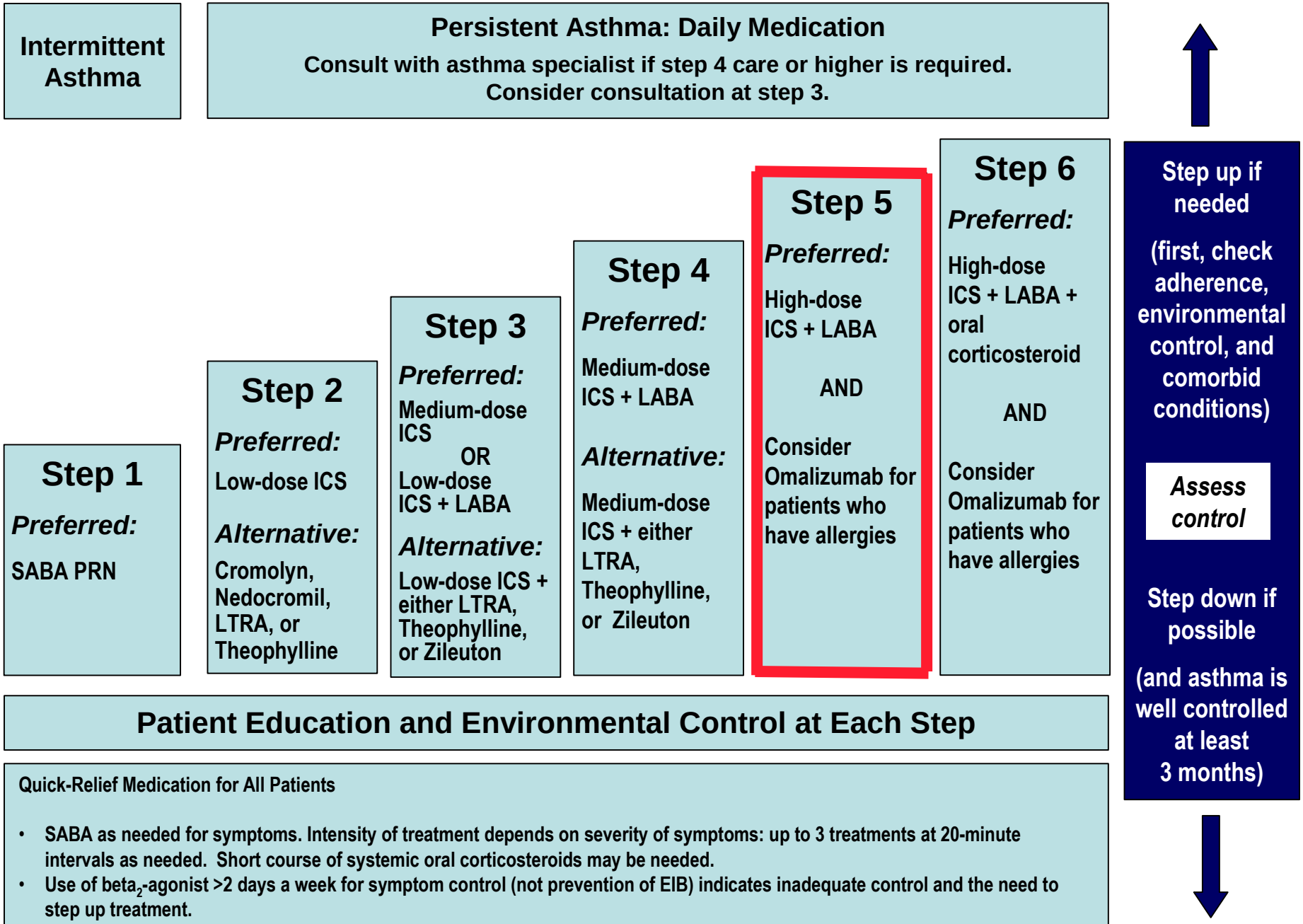
What Is Severe Asthma?

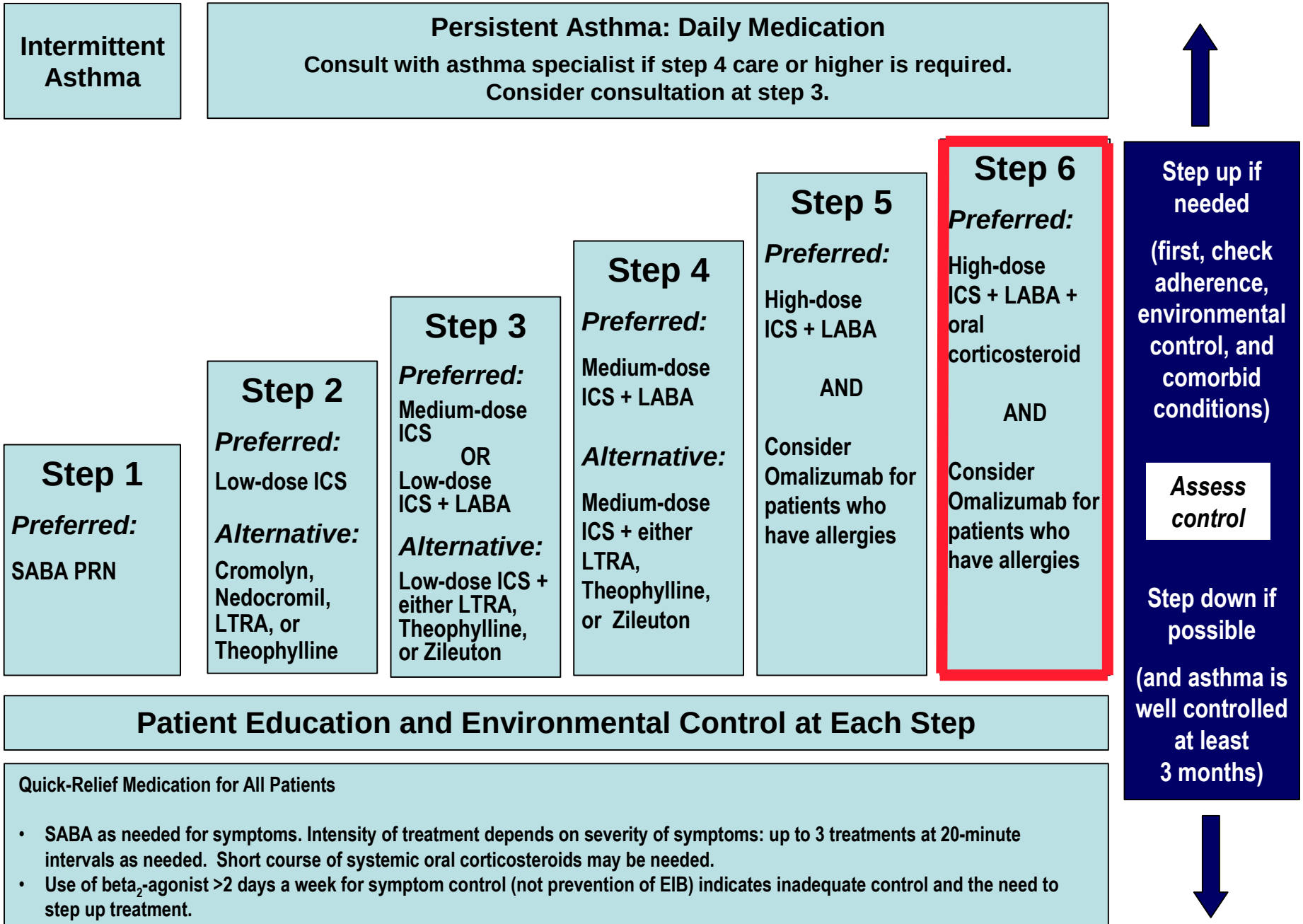
WHO Definition

- **Defined by the level of current clinical control and risks which can result in frequent severe exacerbations and/or adverse reactions to medications and/or chronic morbidity.**

- **3 groups, each carrying different public health messages and challenges.**
  - **Untreated severe asthma**
  - **Difficult to treat asthma**
  - **Treatment resistant severe asthma**
    - **Controlled on high dose medication**
    - **Not controlled on high dose medication**

Bousquet et al, JACI 2010


Intermittent Asthma
Persistent Asthma: Daily Medication
Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.
Step 1
Preferred:
SABA PRN
Step 2
Preferred:
Low-dose ICS
Alternative:
Cromolyn, Nedocromil, LTRA, or Theophylline
Step 3
Preferred:
Medium-dose ICS
OR
Low-dose ICS + LABA
Alternative:
Low-dose ICS + either LTRA, Theophylline, or Zileuton
Step 4
Preferred:
Medium-dose ICS + LABA
Alternative:
Medium-dose ICS + either LTRA, Theophylline, or Zileuton
Step 5
Preferred:
High-dose ICS + LABA
AND
Consider Omalizumab for patients who have allergies
Step 6
Preferred:
High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies
Step up if needed
(first, check adherence, environmental control, and comorbid conditions)
Assess control
Step down if possible
(and asthma is well controlled at least 3 months)
Patient Education and Environmental Control at Each Step
Quick-Relief Medication for All Patients
• SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of systemic oral corticosteroids may be needed.
• Use of beta2-agonist >2 days a week for symptom control (not prevention of EIB) indicates inadequate control and the need to step up treatment.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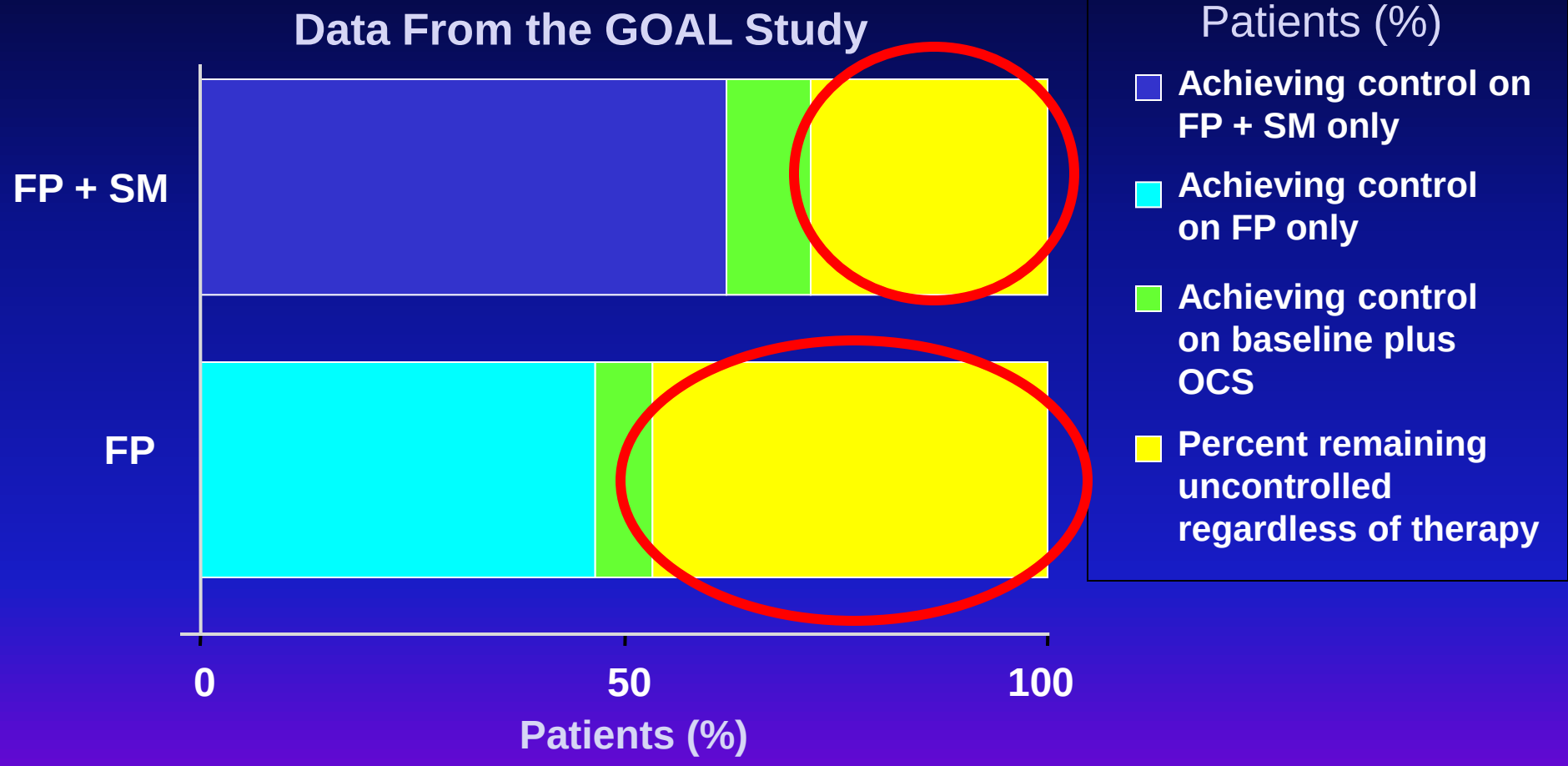
Two Categories Of Treatment-resistant Severe Asthma

- Partially or poorly controlled asthma despite high dose ICS or high dose ICS-LABA combination and frequent or chronic use of systemic CS.
  - Previously been referred to as “refractory asthma” or “severe asthma"
  - In order for a patient to fall into this category, all reasonable efforts to eliminate other, non-asthma diagnoses must have been made.
  - Patients with treatment-resistant severe asthma are considered to be relatively insensitive to either ICS or oral CS

Many Patients* Remain Uncontrolled On Standard ICS and LABA Therapy



LABA=long-acting beta-agonist; FP=Fluticasone Proprionate; SM=Salmeterol; OCS=Oral Corticosteroids.
*All patients received 500-1000 μg/d beclamethasone in previous 6 months.
Bateman ED, et al. *Am J Respir Crit Care Med* .2004;170:836-844.

Reasons for Non-responsiveness: Why Patients Are Difficult To Treat

- Poor compliance/adherence: Nearly 70% of patients fail to refill their ICS in the USA
- Environmental control issues: ETS, allergens, irritants
- Psychosocial and emotional factors
- Co-morbid aggravating conditions
- Pharmacologic response variables
  - Phenotypes (e.g. obesity)
  - Cigarette smoking
  - Genetics
  - Variable pathogenic dominant pathway

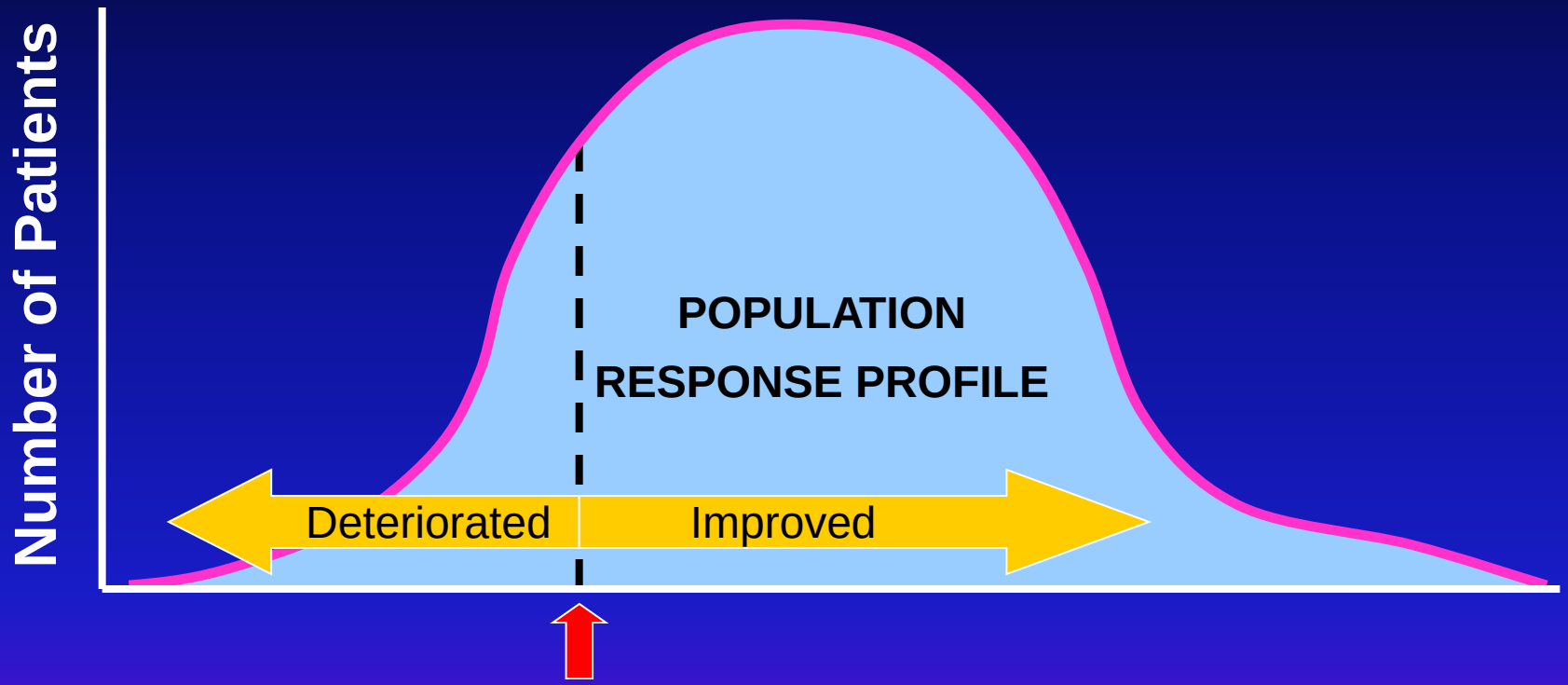
Factors That Impact Asthma Severity And Control

- Asthma severity may be influenced by genetic and environmental factors, underlying disease activity and patient's disease pathobiological processes which differs between patients with differing phenotypes.

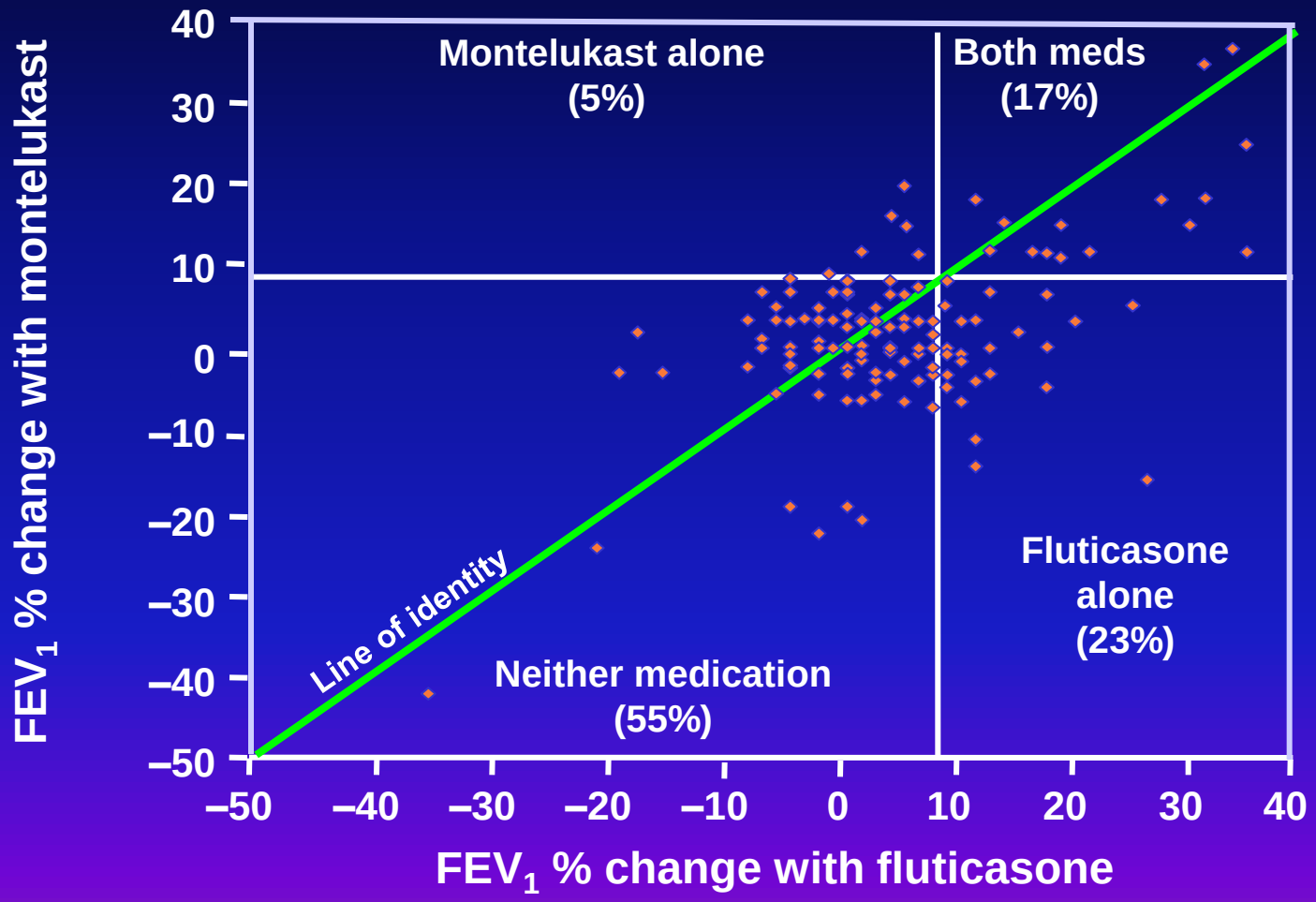
What Are The Potential Approaches For Optimizing Asthma Treatment?

- Adherence
- Environmental control
- Education on medications and the disease
- Matching the correct drug to the patient:
  - Pharmacogenetics
  - Phenotypes/Endotypes
  - Biomarkers
- New and improved medications

Drug Response Profile



Patient Responsiveness to ICS and LTRA Is Highly Variable

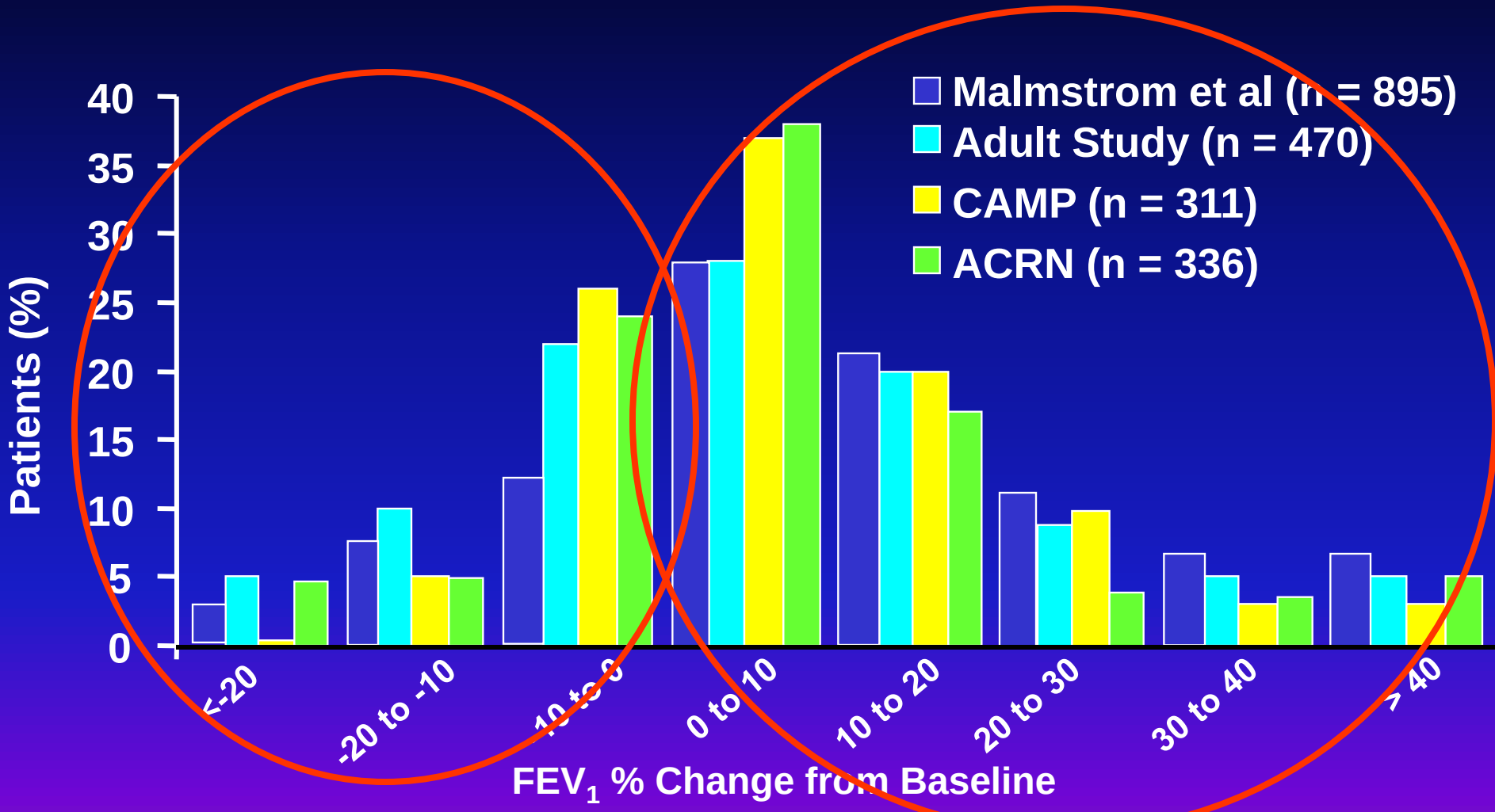


22% Patients respond to montelukast

40% Patients respond to fluticasone

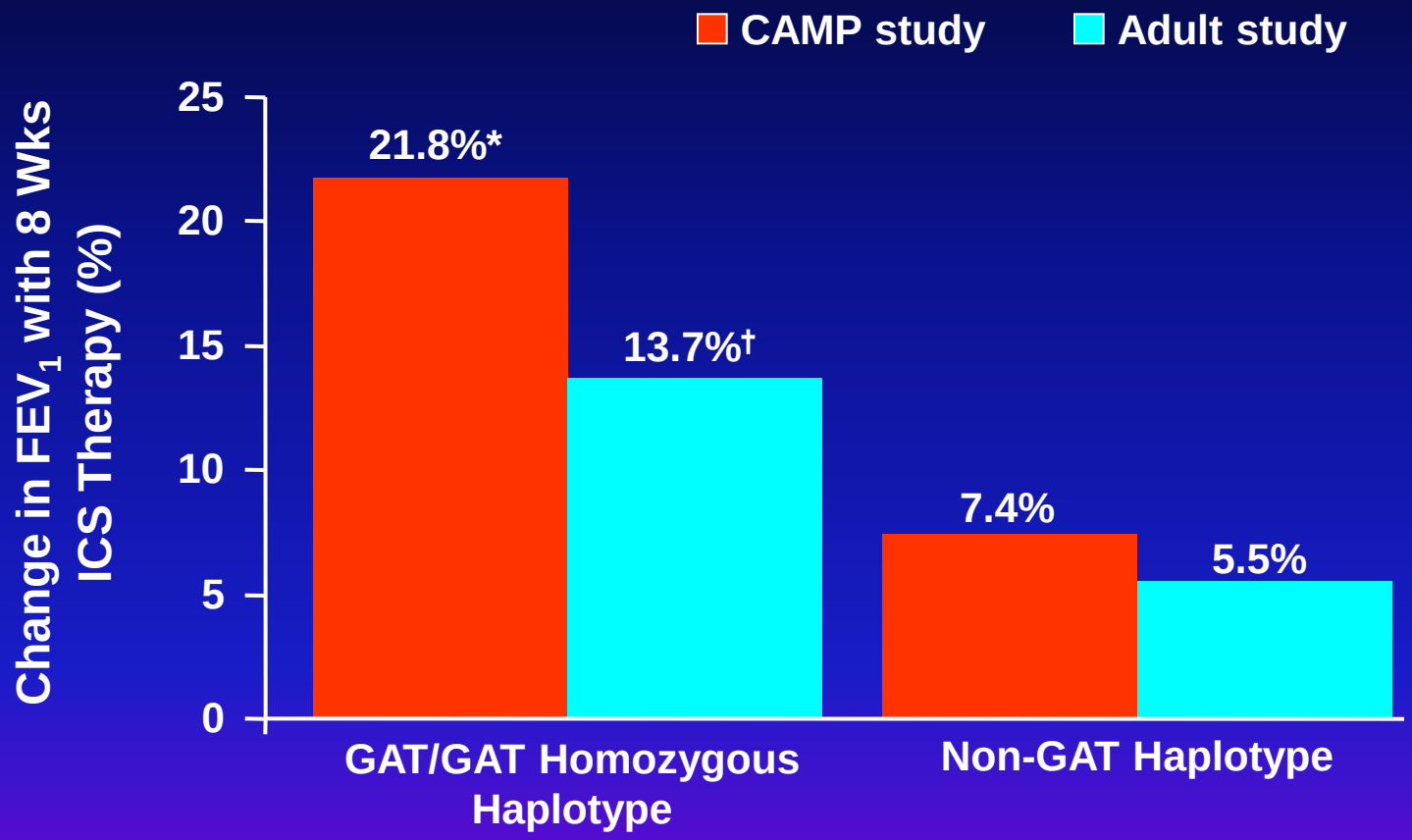
Szefler SJ, et al. *J Allergy Clin Immunol.* 2005;115:233-242.

Analysis of Inhaled Corticosteroid Partial- and Non-Responders



1. Malmstrom K, et al. Ann Intern Med. 1999;130:487-95. 2. Lazarus S, et al. J. Am. Med. Assoc., 2001:285:2583–93.
3. Lemanske RF, et al. J. Am. Med. Assoc., 2001;285:2594–2. 4.Childhood Asthma Management Program Research Group. Control. Clin. Trials, 1999;20:91–120. 5. The Childhood Asthma Management Program Research Group.N. Engl. J. Med. 2000;343:1054–63.

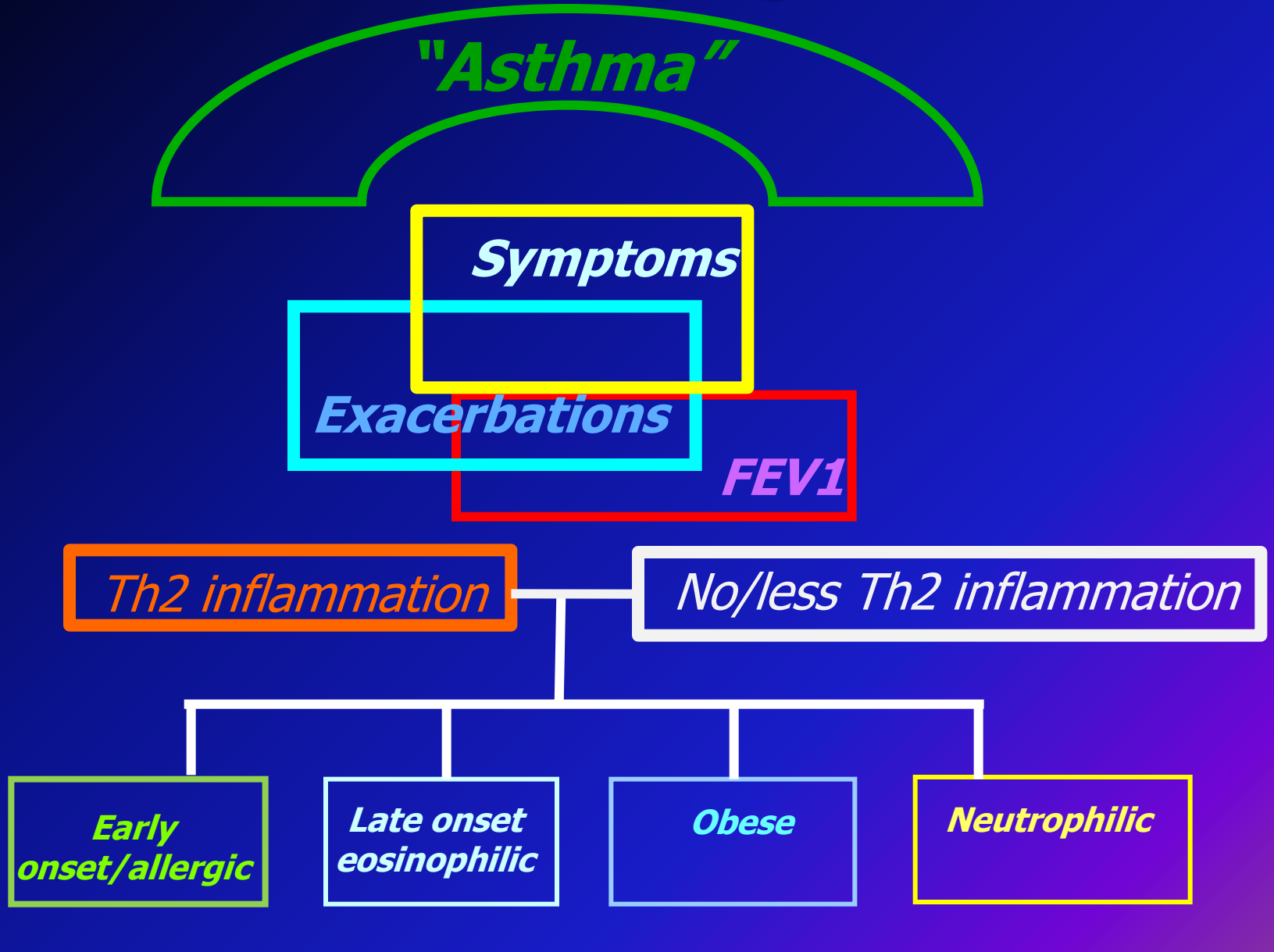
Response To ICS May Be Genetically Determined: Effects Of CRHR1 Genotype



*P<0.02 vs non-GAT.
†P<0.01 vs non-GAT.

Tantisira KG, et al. *Hum Mol Genet.* 2004;13:1353–1359.

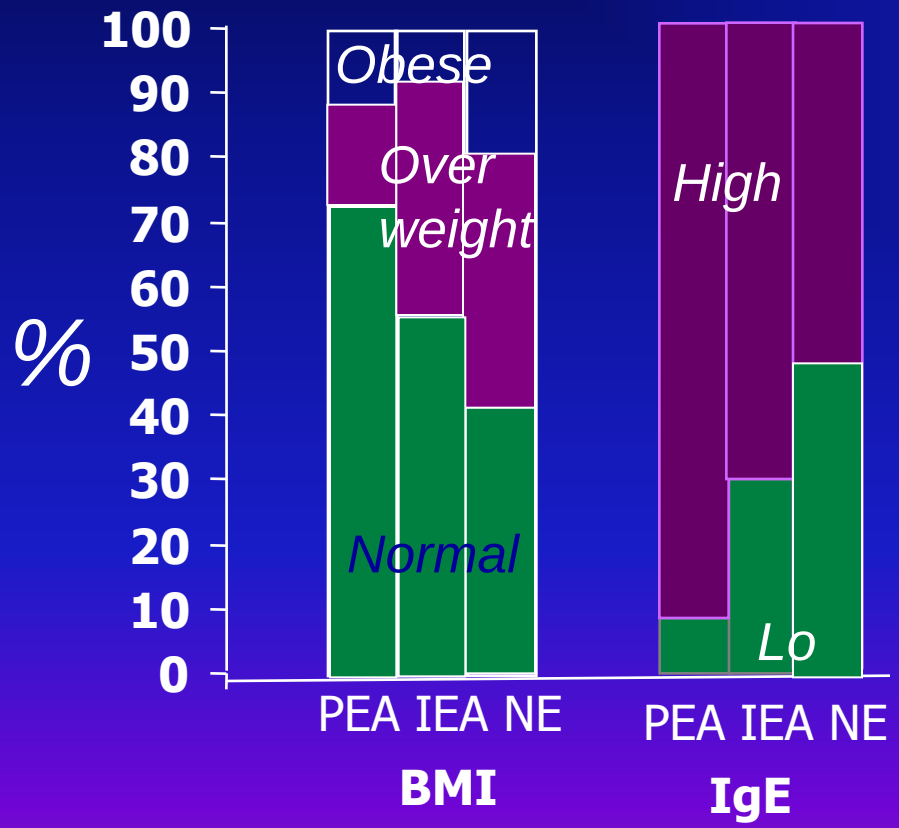
The *Transition* to Phenotyping And Endotyping

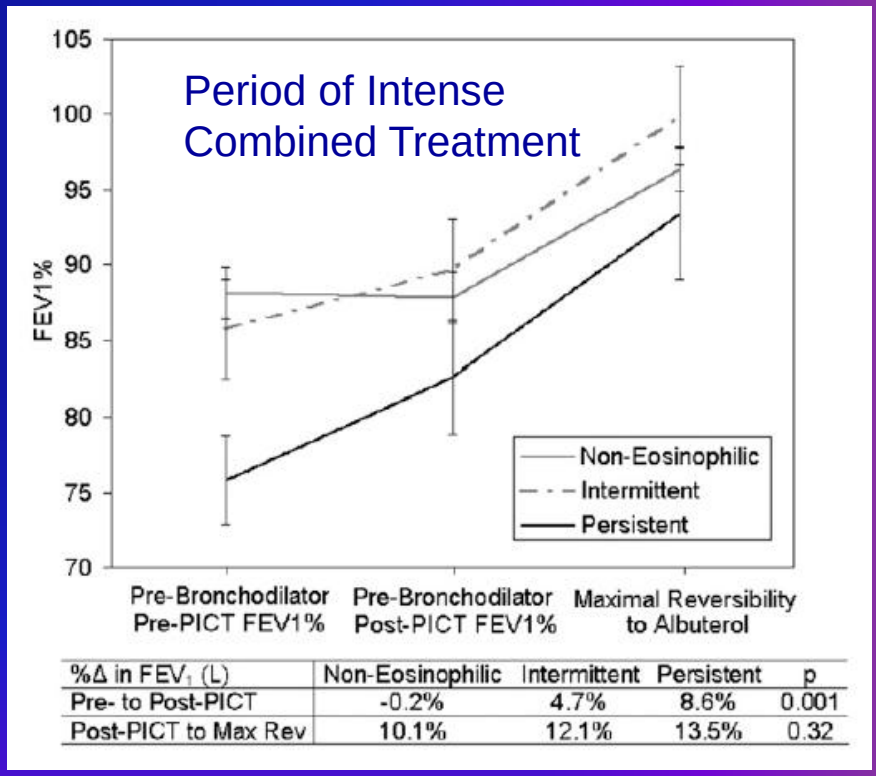


Endotyping: "Th2-Lo Asthma"

- Defined as "apparent" absence of Th2
- Much less well defined that Th2-Hi
- Generally adult onset
- May include obesity-related, post infectious, neutrophilic, smoking related…
- *All* associated with poor CS response

In Untreated Pts, No Eos Associated With Obesity, Low IgE And Poor Steroid Response

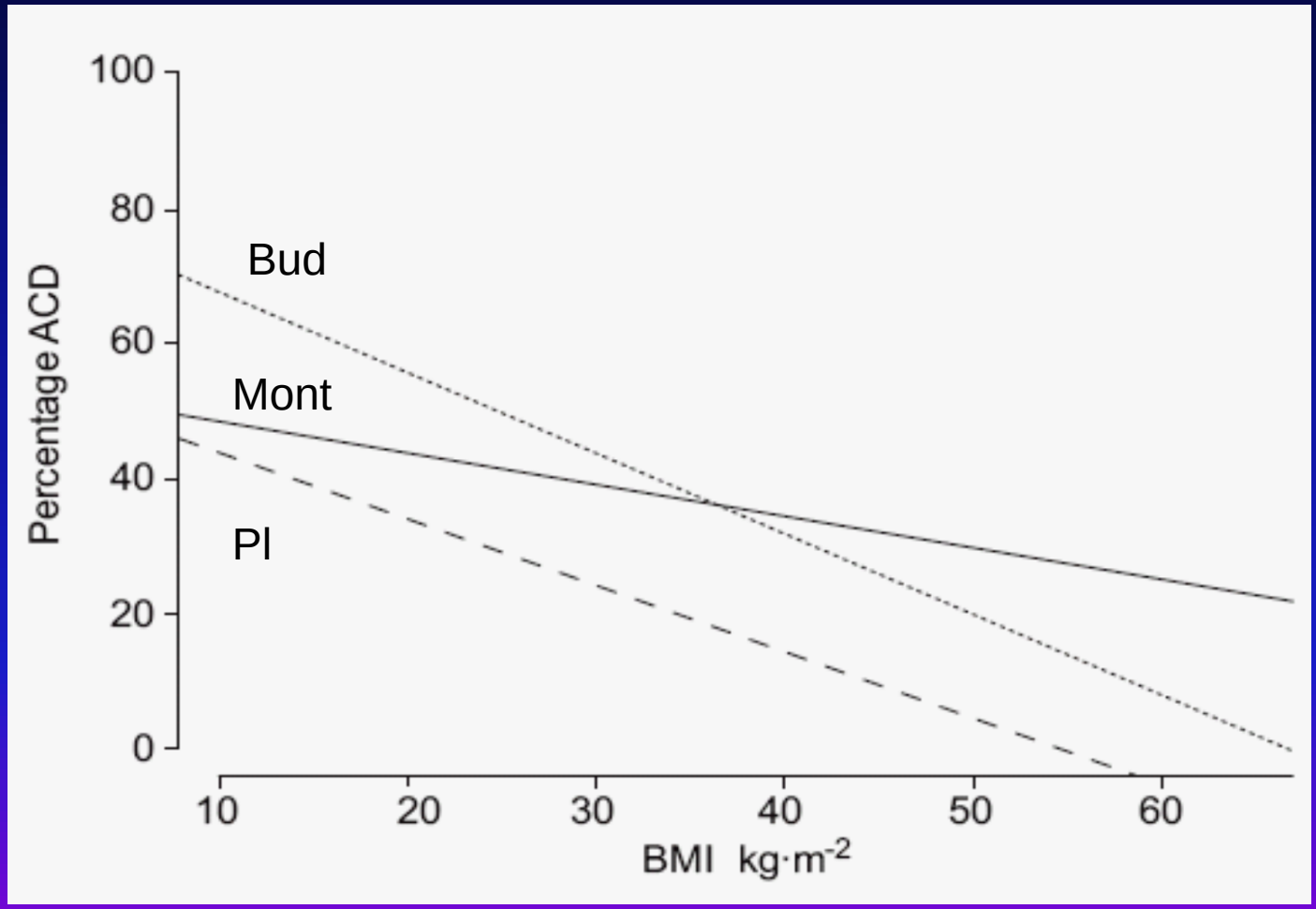




%Δ in FEV_1 (L)	Non-Eosinophilic	Intermittent	Persistent	p
Pre- to Post-PICT	-0.2%	4.7%	8.6%	0.001
Post-PICT to Max Rev	10.1%	12.1%	13.5%	0.32

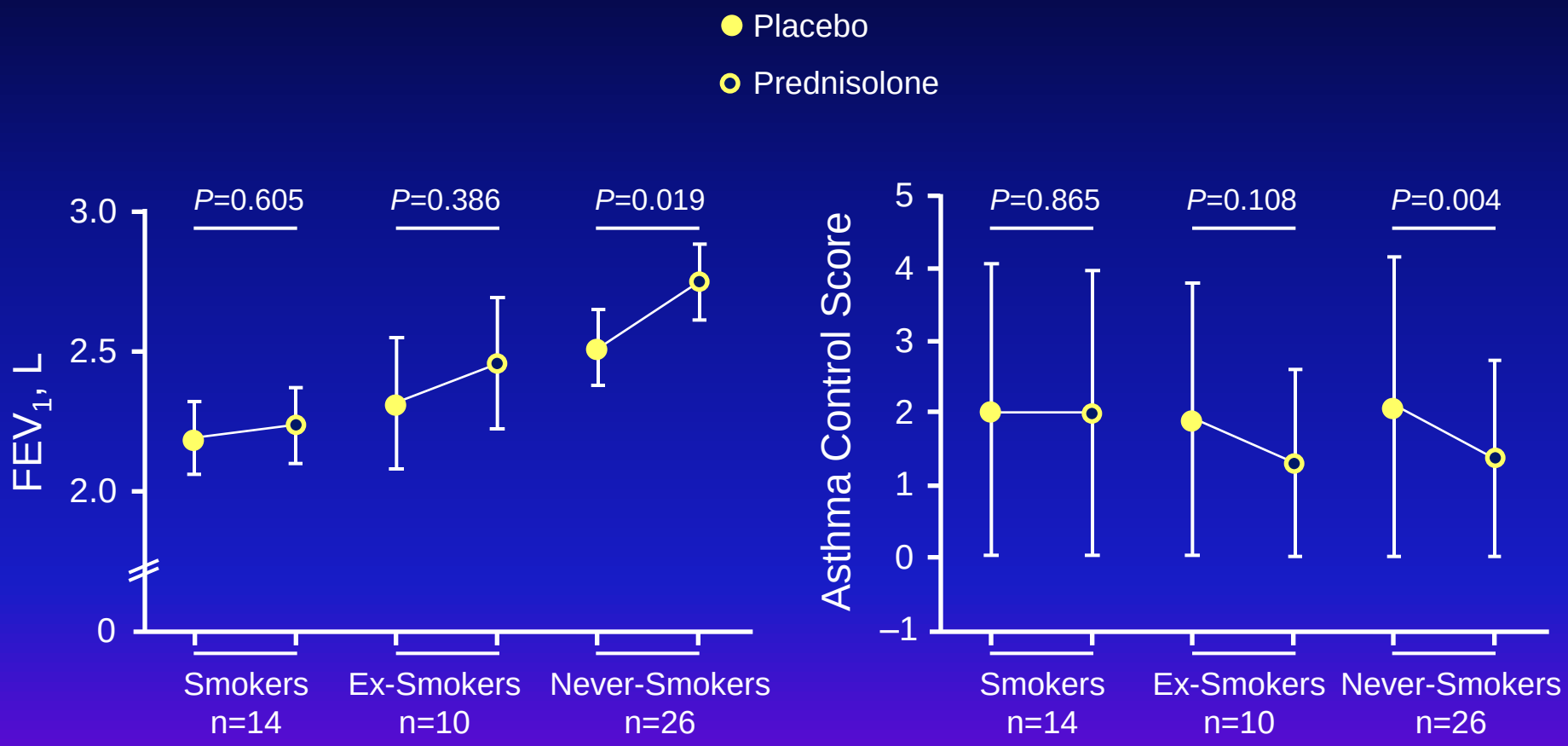
Adapted from McGrath AJRCCM 2012

Influence Of BMI On Asthma Control Days: Comparison Of Montelukast Vs. Budesonide



M. Peters-Golden, ERJ, 2006

Cigarette Smoking and Asthma Variability: Reduced Response to Oral Corticosteroids



Chaudhuri R et al. *Am J Respir Crit Care Med.* 2003;168:1308–1311.

Endotyping: Th2-Hi Asthma

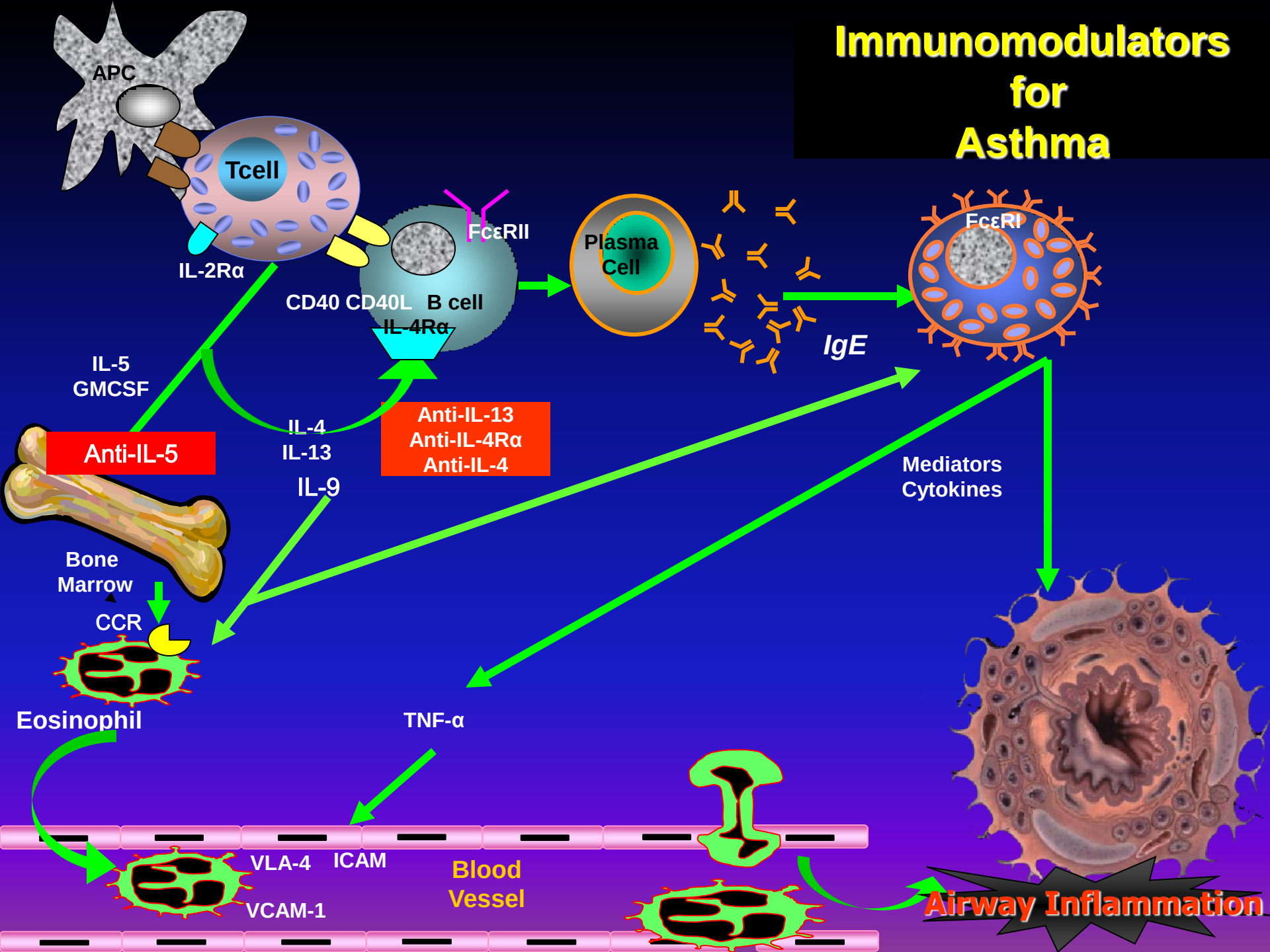
- Atopy/IgE (probably worst indicator)
- Early age at onset
- Blood/Lung eosinophilia
- Exhaled NO (FeNO)
- Mast cells
- Gene profiles/biomarkers (periostin)

Are There Variable Responses To Th2 Immunomodulators As Well?

- Due to the heterogeneity of asthma, it is inevitable that distinct dominant pathogenic mechanisms exist (e.g. eosinophil/IL-5 or IgE dominant inflammation).

- Finding which pathogenic factor(s) are important in individual patients is a challenge in treating severe asthma.

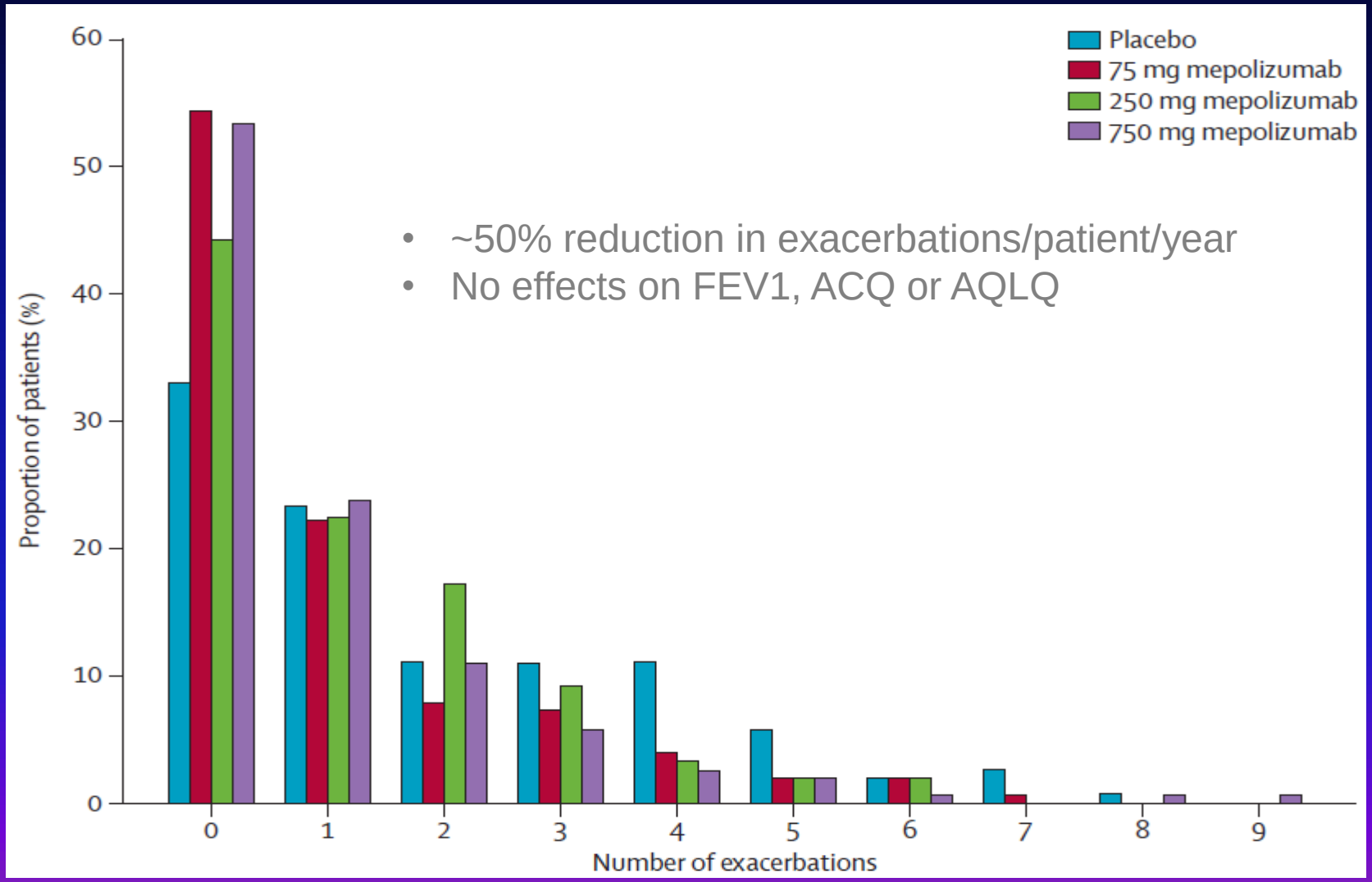
- A broad spectrum immunomodulator approach for all patients is problematic due to potential adverse consequences.


Immunomodulators for Asthma
APC
Tcell
IL-2Rα
CD40 CD40L
B cell
IL-4Rα
FcεRII
Plasma Cell
IgE
FcεRI
IL-5
GMCSF
Anti-IL-5
IL-4
IL-13
IL-9
Anti-IL-13
Anti-IL-4Rα
Anti-IL-4
Mediators
Cytokines
Bone Marrow
CCR
Eosinophil
TNF-α
VLA-4
ICAM
VCAM-1
Blood Vessel
Airway Inflammation

Role of Anti IL-5 in Asthma

- Several older studies confirmed reductions in blood & sputum eos w/o significant changes in AHR, lung function or symptoms
- 2 NEJM studies (March, 2009):
  - Unlike previous studies , high sputum eosinophils , >3% required (<5% of uncontrolled asthma patients)
  - Reduction of eosinophils
  - Had no /modest effect on FEV1, AHR or symptoms
  - Significantly reduced exacerbations
- Recent Lancet paper inclusion criteria (70%):
  - Sputum eos >3%, FeNO>50, blood eos >300, deterioration of asthma after <25% reduction in ICS or OCS
  - ≥2 asthma exacerbations in previous year

Mepolizumab for Severe Eosinophilic Asthma



- ~50% reduction in exacerbations/patient/year
- No effects on FEV1, ACQ or AQLQ

Pavord et al, Lancet 2012

Th2 (IL-4, -5, -9, -13) Cytokine Inhibitors

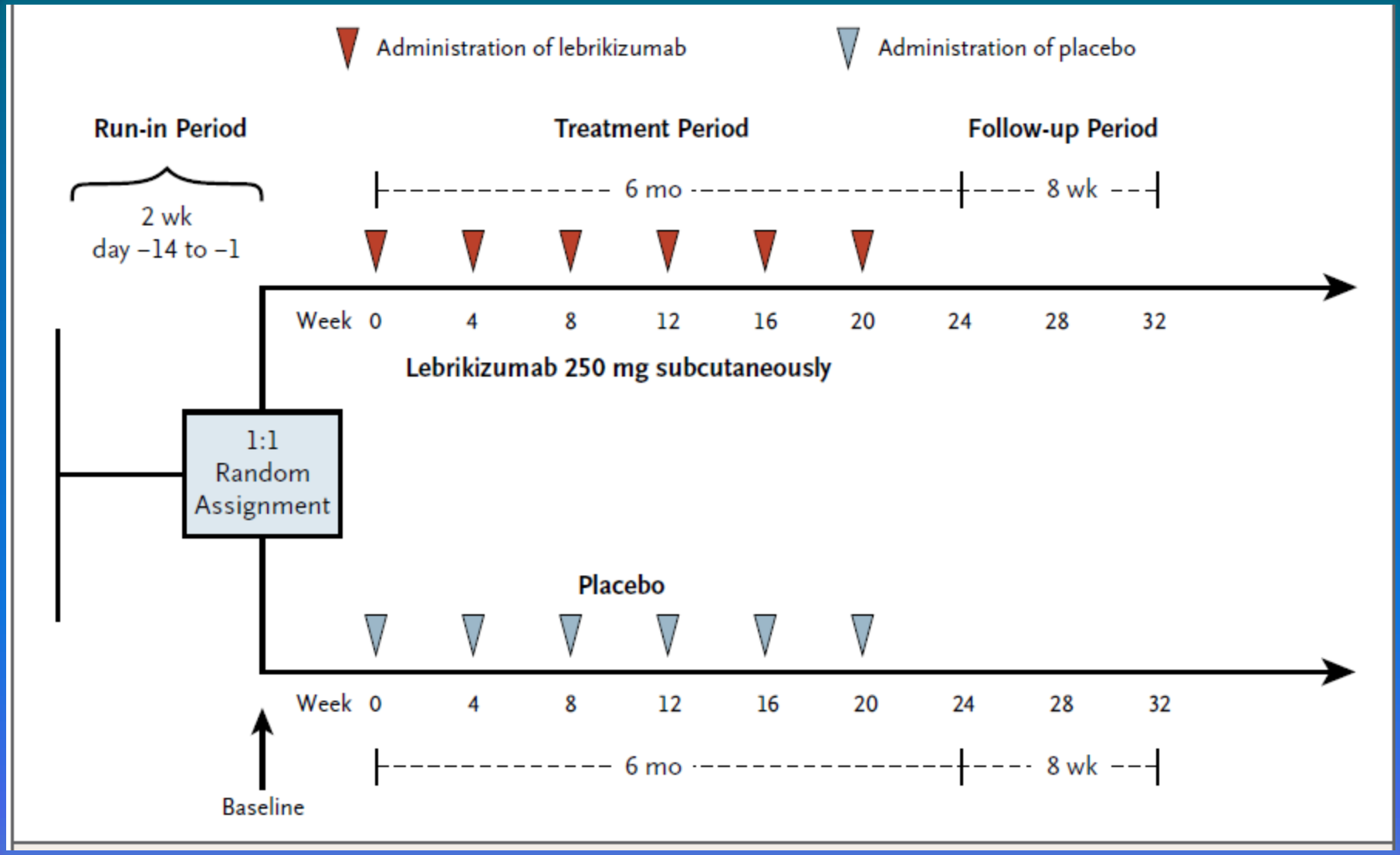
- Anti-IL-4 strategies alone not very successful
  - Strategies aimed at both IL-4 and IL-13 may be better option
- MAb aimed at IL-9 : Failed to meet endpoints..D/C
- Mono-specific IL-13 strategies initially had disappointing results despite IL-13's putative importance in AWH, mucus, AWR, IgE, eotaxin production, etc.
  - Several new studies have shown good results

Airway Epithelial Periostin

- Up-regulated in bronchial epithelial cells of asthmatic subjects
  - Increased by IL-13
- Autocrine effects: activation of TGF-β and up-regulation of type I collagen
- Paracrine effects: TGF-β–mediated incr in type I collagen production in fibroblasts
- Likely contributes to incr airway fibrosis and decr airway distensibility

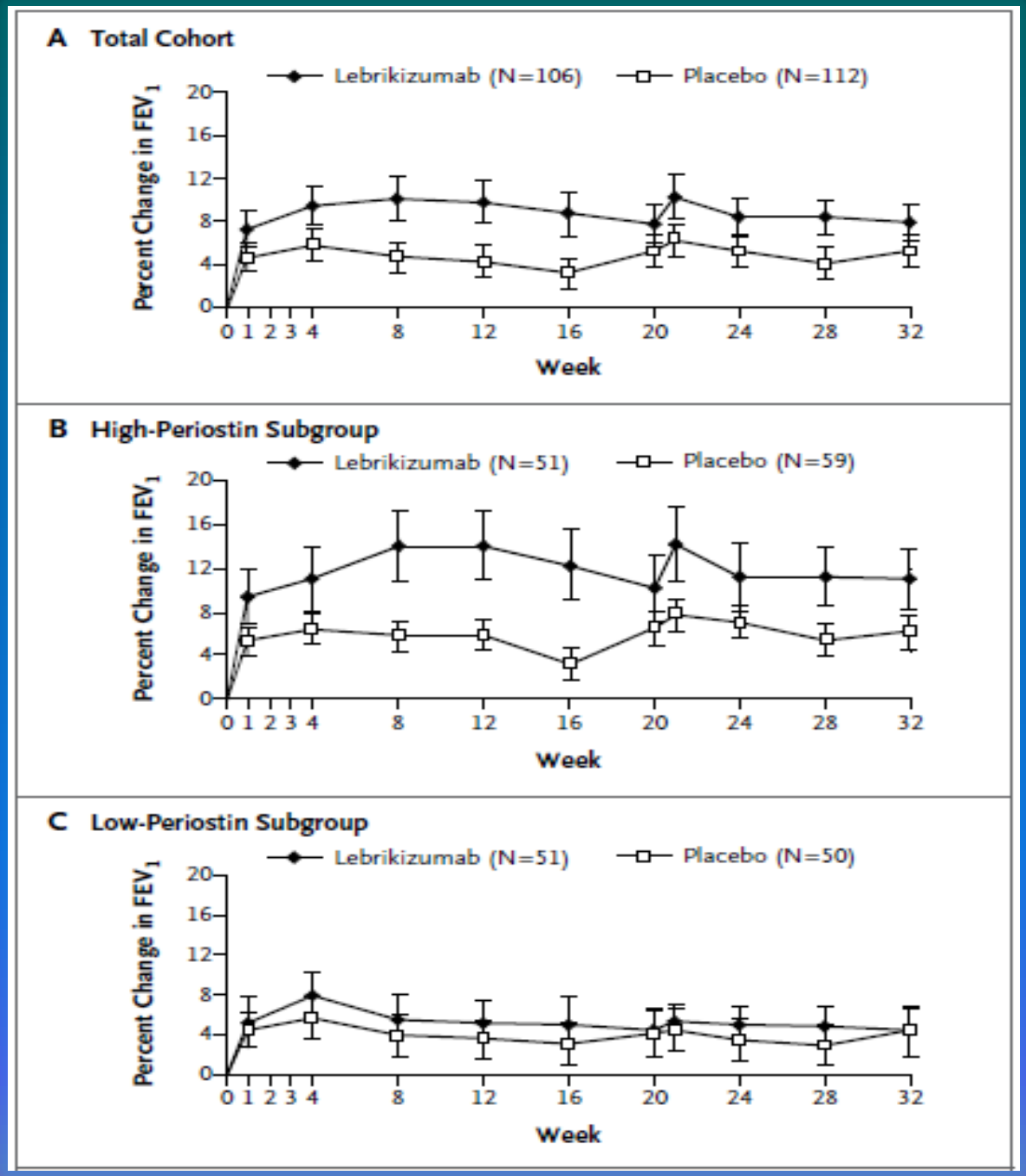
Sidhu et al. PNAS, 2010

Lebrikizumab Treatment in Adults with Asthma: Study Design



J Corren et al, NEJM, 2011

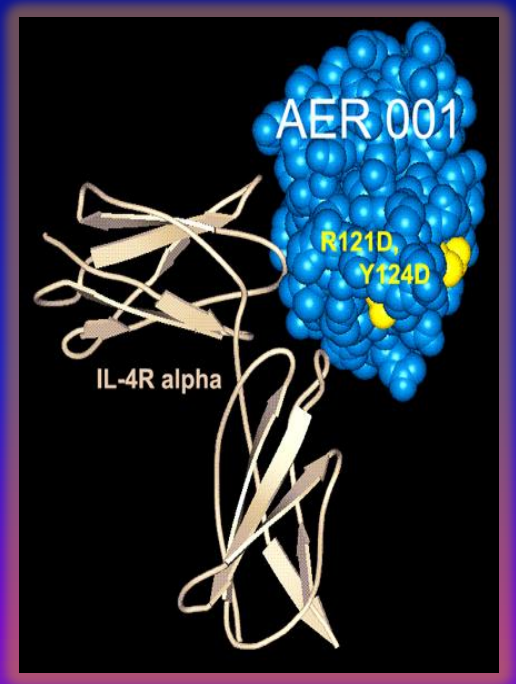
Lebrikizumab Treatment in Adults with Asthma

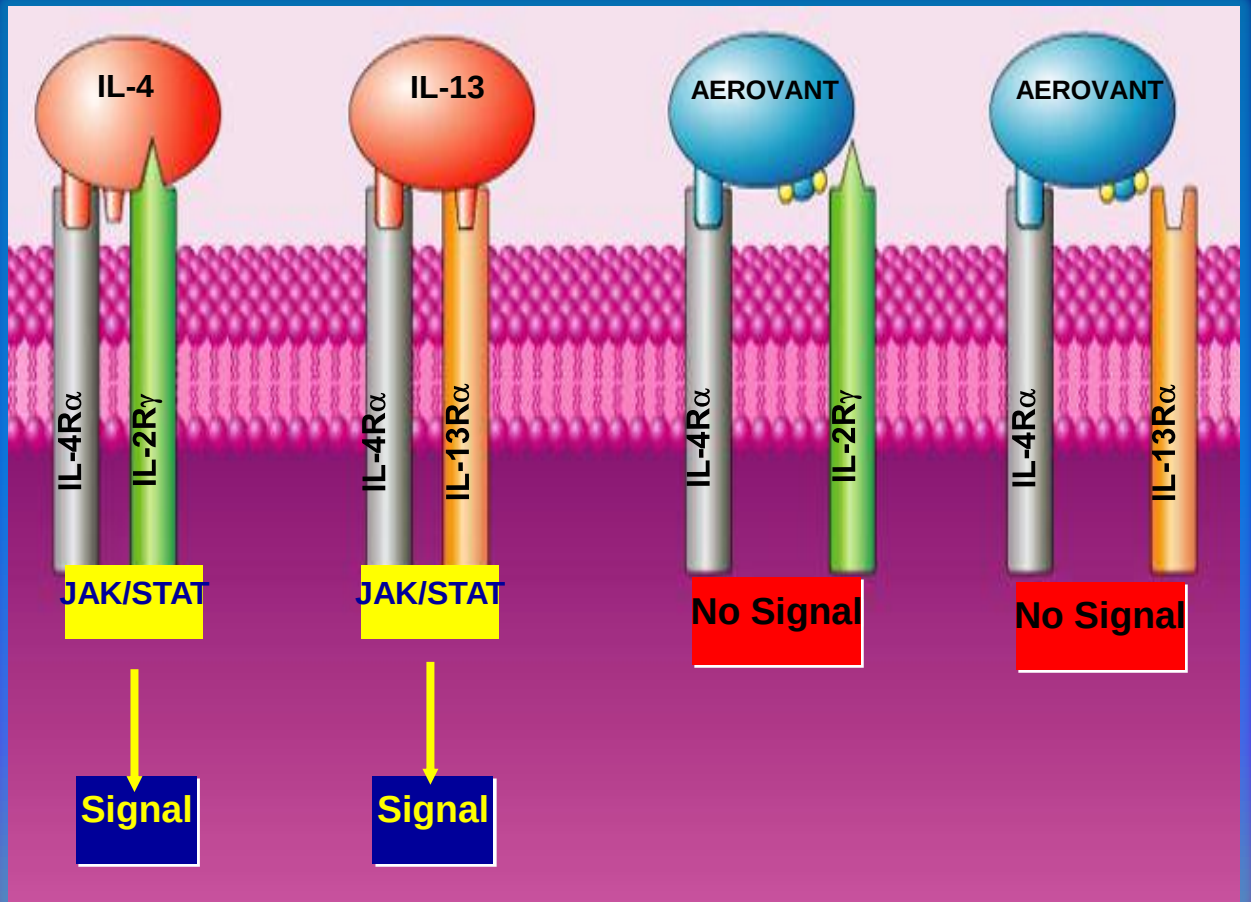


J Corren et al, NEJM, 2011

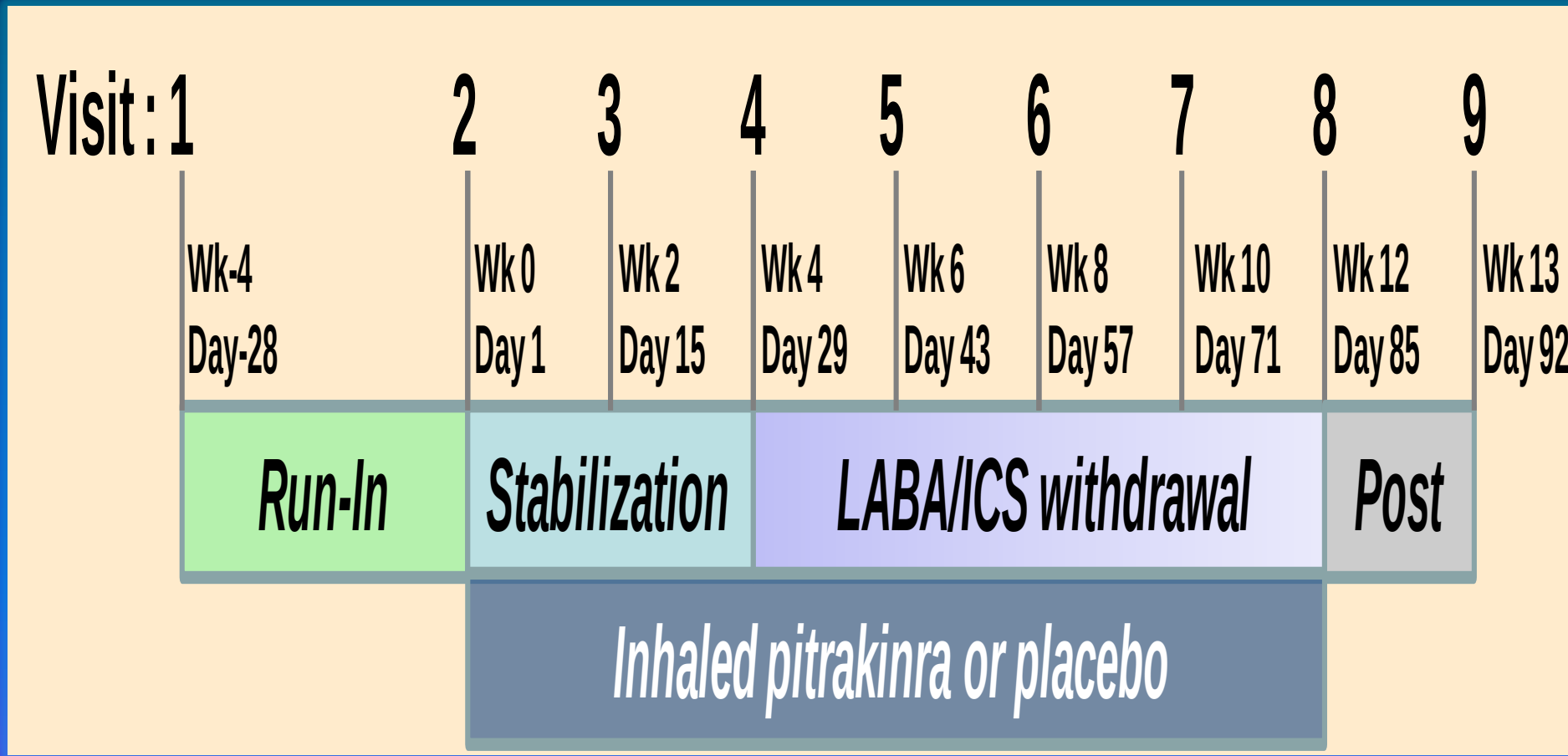
IL-4Rα Receptor Blockers: IL-4 and IL-13 Binding Site

- Pitrakinra (Aerovant): 14 kDa IL-4 mutein vs. IL-4Rα



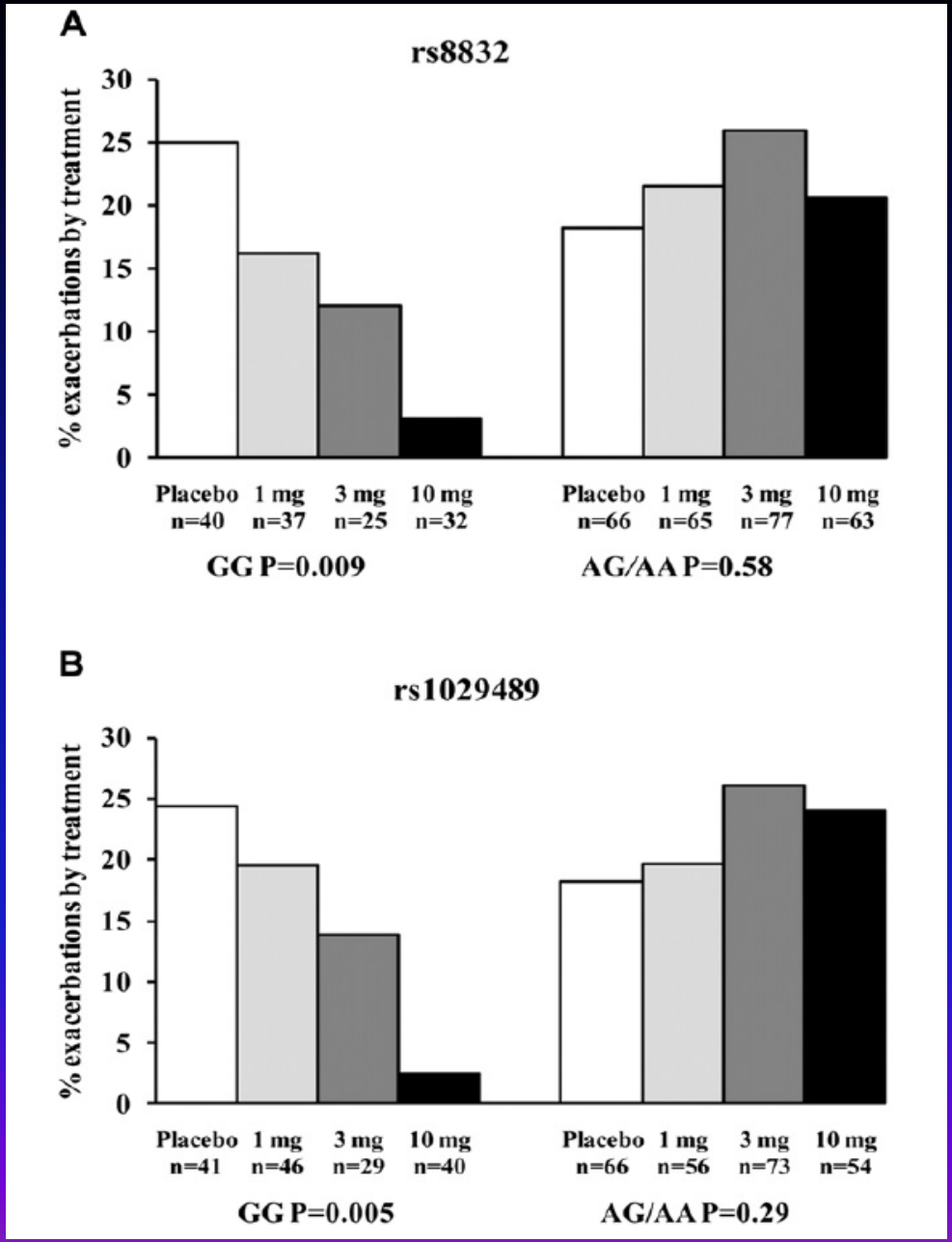


First “Real World” Study With Pitrakinra

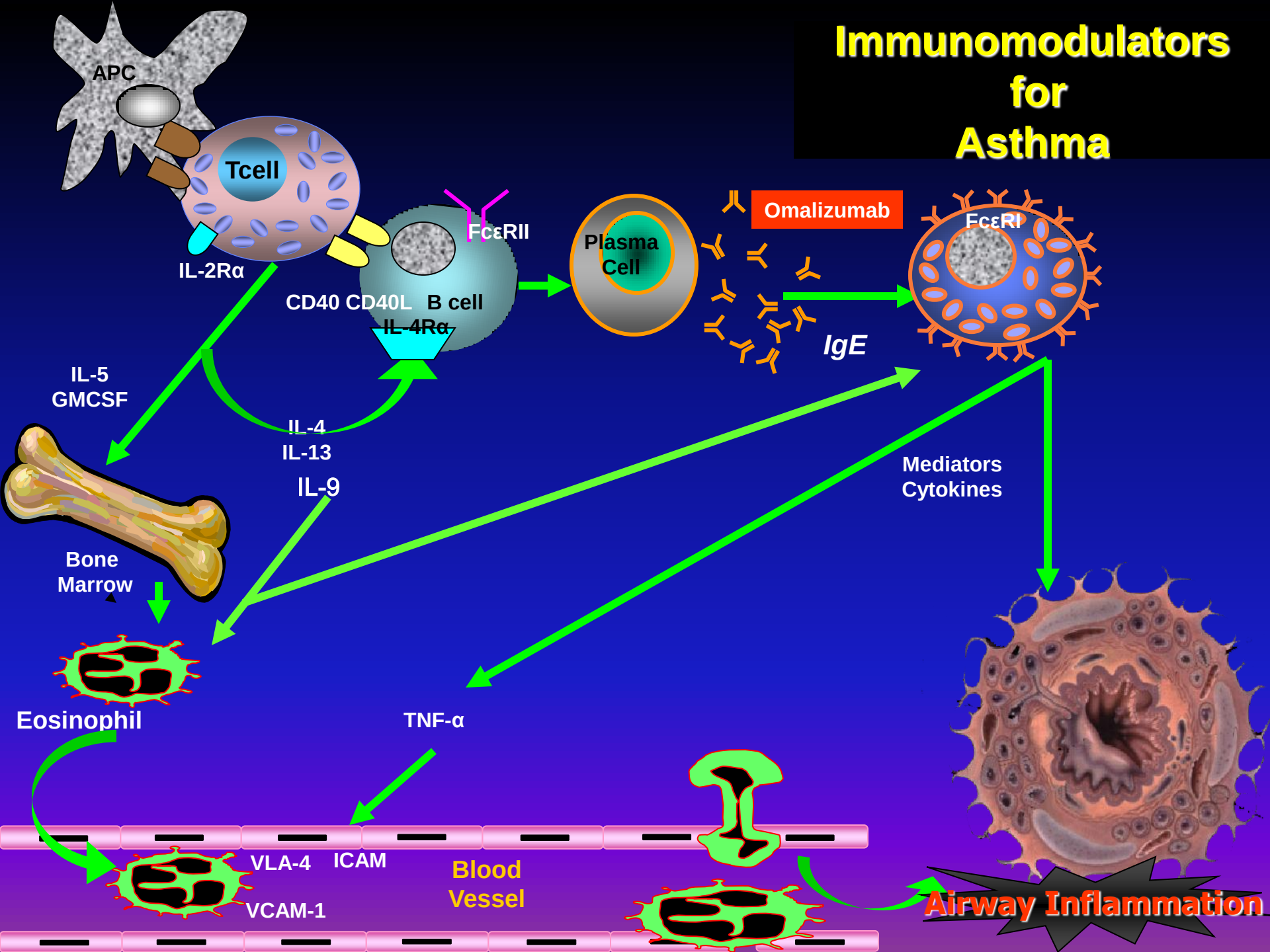


Pitrakinra

- Better effects in patients with:
  - High Blood eos (>350)
  - Certain SNPs at 3' end of IL4RA



Slager et al, JACI, 2012


Immunomodulators for Asthma
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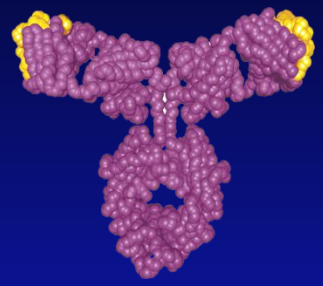
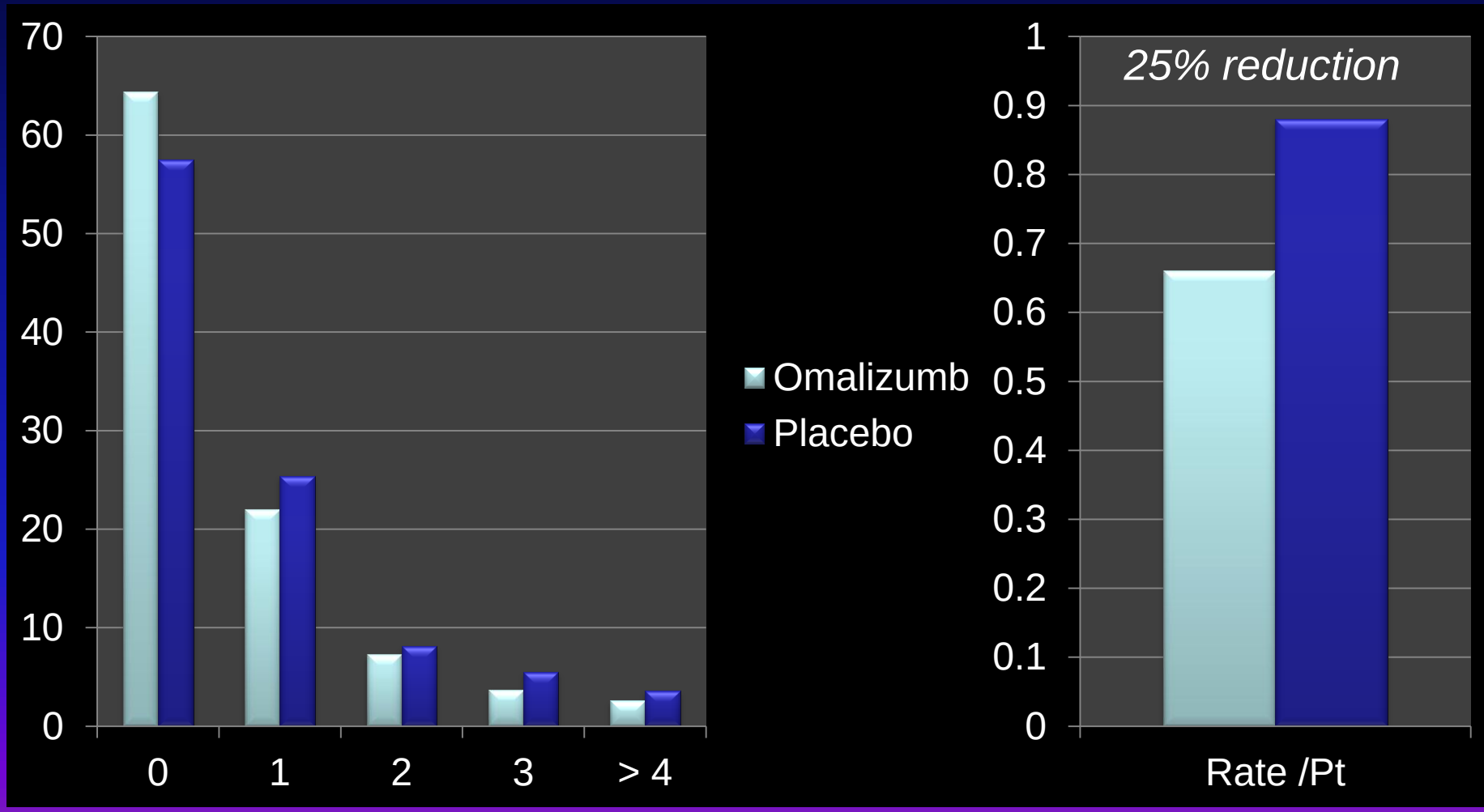
Tcell
IL-2Rα
CD40 CD40L
B cell
IL-4Rα
FcεRII
Plasma Cell
Omalizumab
IgE
FcεRI
IL-5
GMCSF
IL-4
IL-13
IL-9
Bone Marrow
Mediators
Cytokines
Eosinophil
TNF-α
VLA-4
ICAM
VCAM-1
Blood Vessel
Airway Inflammation

Omalizumab Indications



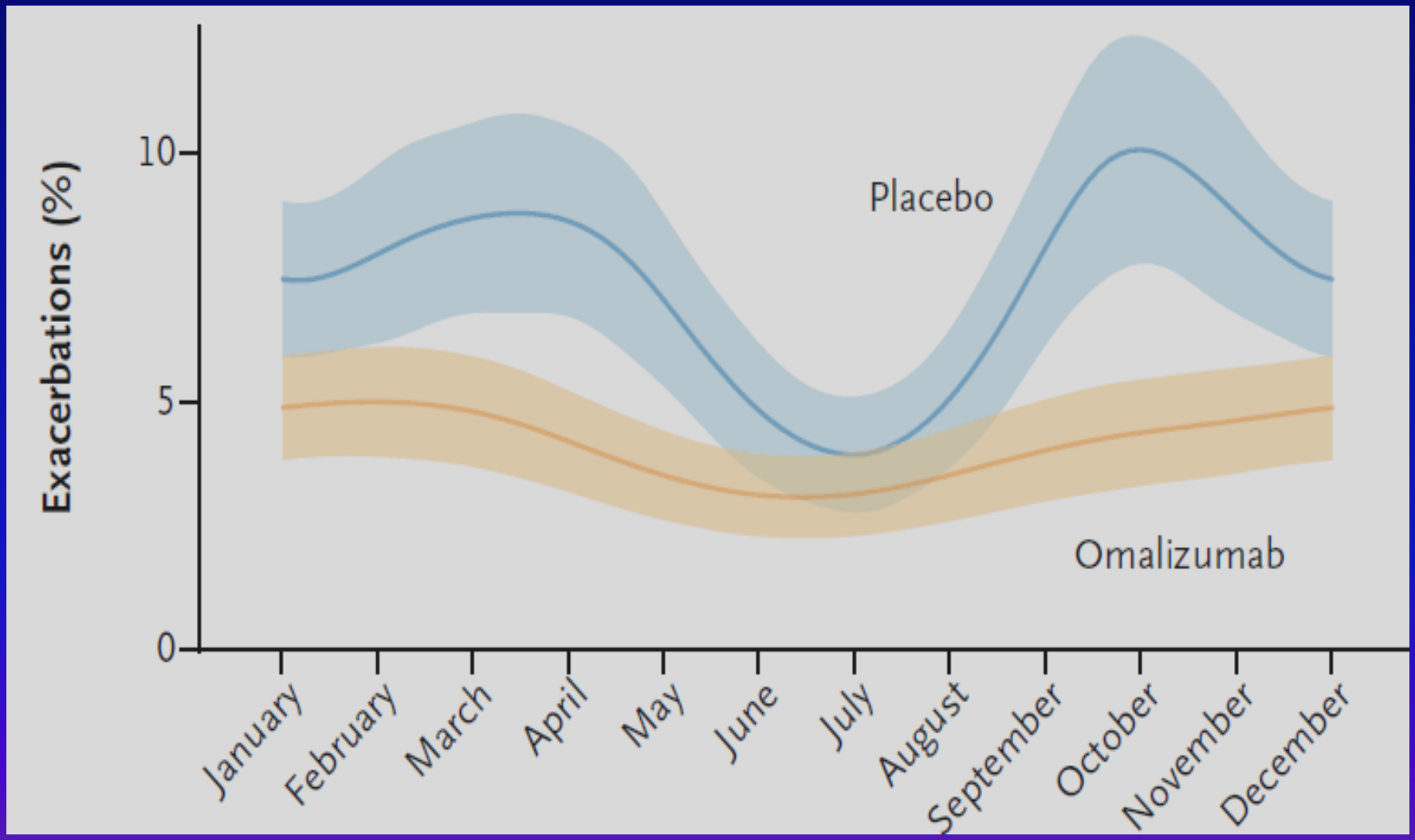
- **Moderate to severe persistent asthma in patients with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS+/-LABA.**

Asthma Exacerbations Over 48 Weeks In EPR3 Step 5/6



Hanania et al, Ann Int Med ,2011

Omalizumab and Seasonal Asthma Exacerbations In 6 to 20 y/o



NEJM, 3/11

Factors Predictive Of Clinical Response

- Reasons for omalizumab being ineffective for some (~40%) patients are unknown.

- Improvements correlate w/ IgE reductions, BUT free IgE levels in nonresponders are similar to those found in responders[1]

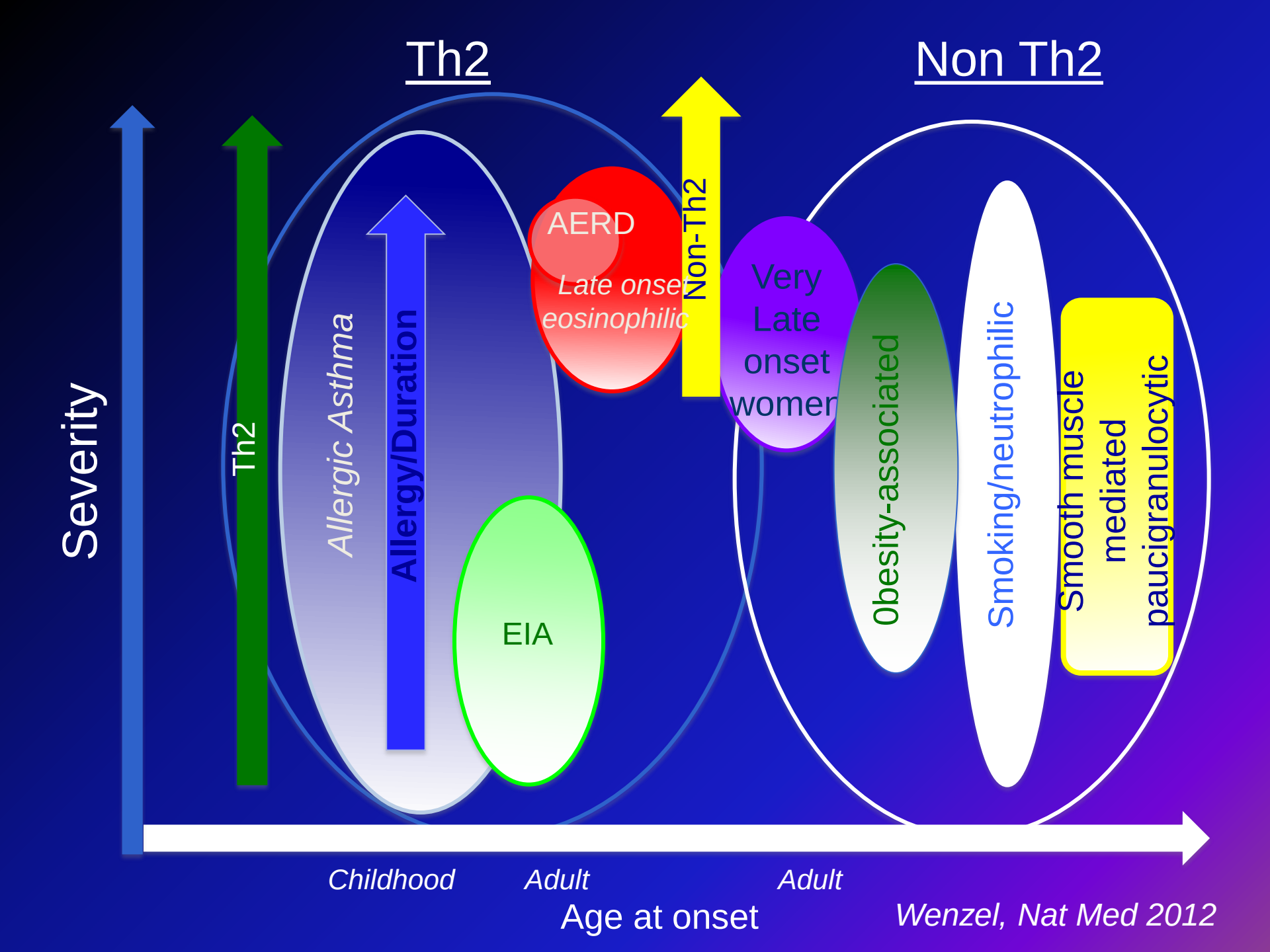
- Possible reasons:[2]
  (1) Relationship between free IgE levels and FcεR1 expression
  (2) Ratio of specific IgE to total IgE
  (3) Intrinsic cellular sensitivity.

- Recent data indicate that response at 16 wks is highly predictive of persistent response at 32 wks[3]

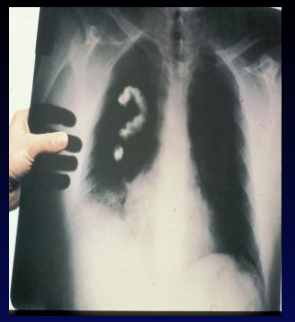
1. Slavin, et al. JACI ,2009; 2. MacGlashan. JACI 2009; 3. Bousquet et al, Allergy,, 2011

Omalizumab and Asthma Summary

- Omalizumab is effective in children and adults in reducing exacerbations and steroid requirements
  - Also positive effects on SABA use, QOL, Sxs and PFTs (minor)
- Omalizumab has anti-inflammatory effects
- If not effective by 4-6 months, probably will not be effective
  - Predictors of who will respond are unclear
- Whether omalizumab can be stopped with sustained clinical efficacy is unclear
  - May depend on duration of treatment


Th2
Non Th2
Severity
Th2
Allergic Asthma
Allergy/Duration
AERD
Late onset eosinophilic
Non-Th2
EIA
Very Late onset women
Obesity-associated
Smoking/neutrophilic
Smooth muscle mediated paucigranulocytic
Childhood
Adult
Adult
Age at onset
Wenzel, Nat Med 2012

Critical Issues for Immunomodulators



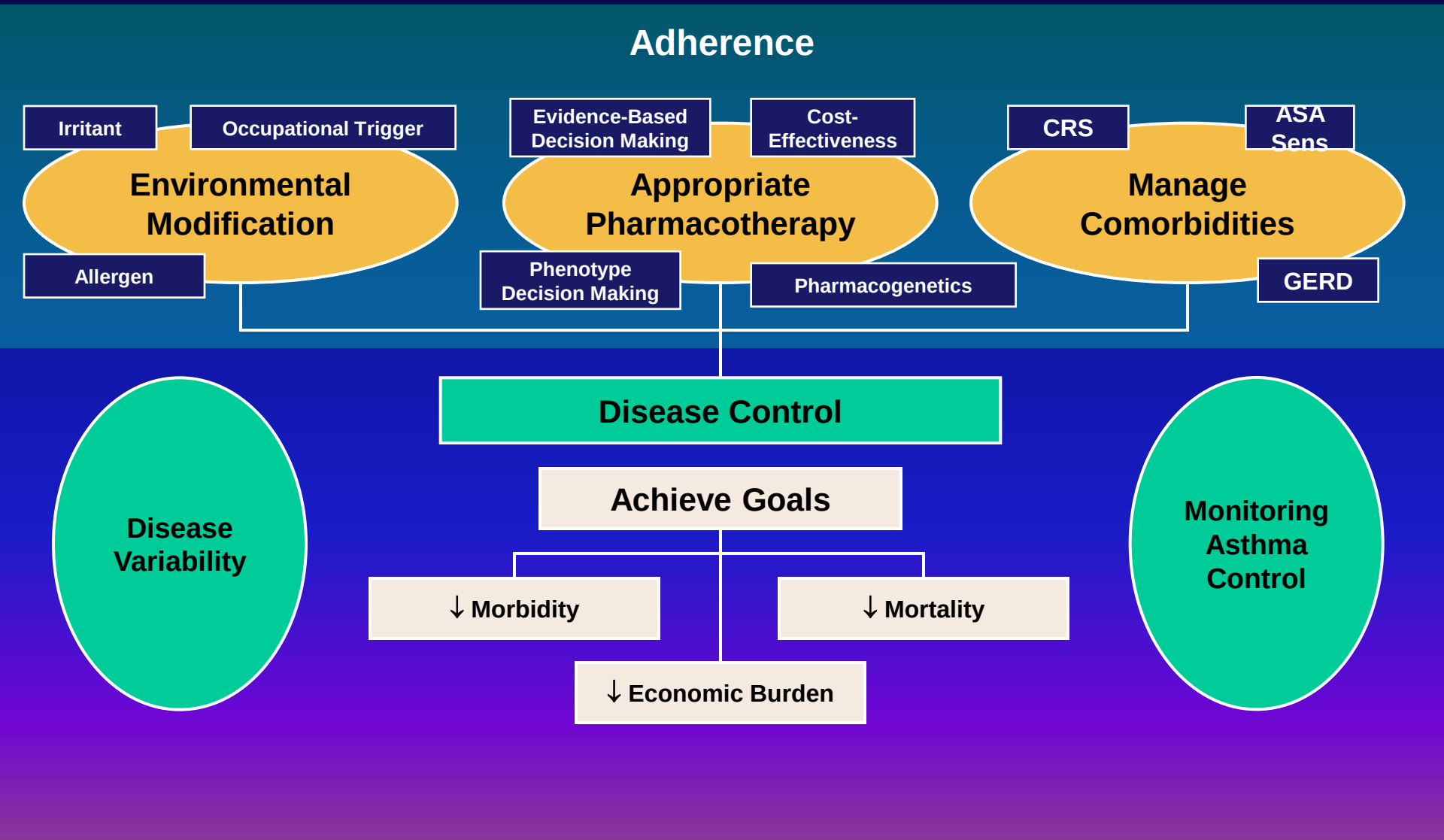
- Many options for the same or similar patient population.

- Which will provide better therapeutic options?
  - Phenotype/Endotype (Biomarker) driven?
  - Decrease sxs & exacerbations & improve QOL
  - True Immunomodulation: prevent/alter disease course
  - Cost effective
  - Have favorable risk/benefit ratio

Too Powerful
Broad-spectrum

Too Weak
Very Specific

Severe Asthma Management Paradigm



Conclusions

- **Severe asthma is a major public health issue that causes significant morbidity and mortality.**
- **What Is Needed To Improve Care Of Patients With Severe Asthma?**
  - Cluster analyses and biomarkers identifying different phenotypes important in defining pharmacologic responses
  - Identification of novel genetic variants that contribute to response heterogeneity
  - Identification of new therapies that have favorable risk/benefit ratios and are immunomodulating:
    - Permanently ***Reprogram*** the immune system to ignore "insignificant" threats without compromising its ability to respond to real threats

Personalized Medicine