MAKING DIFFICULT ASTHMA LESS DIFFICULT: EVALUATING, TREATING AND THE APPLICATION OF PRECISION MEDICINE

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Disclosures

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Approach to Difficult asthma: Defining Severe asthma

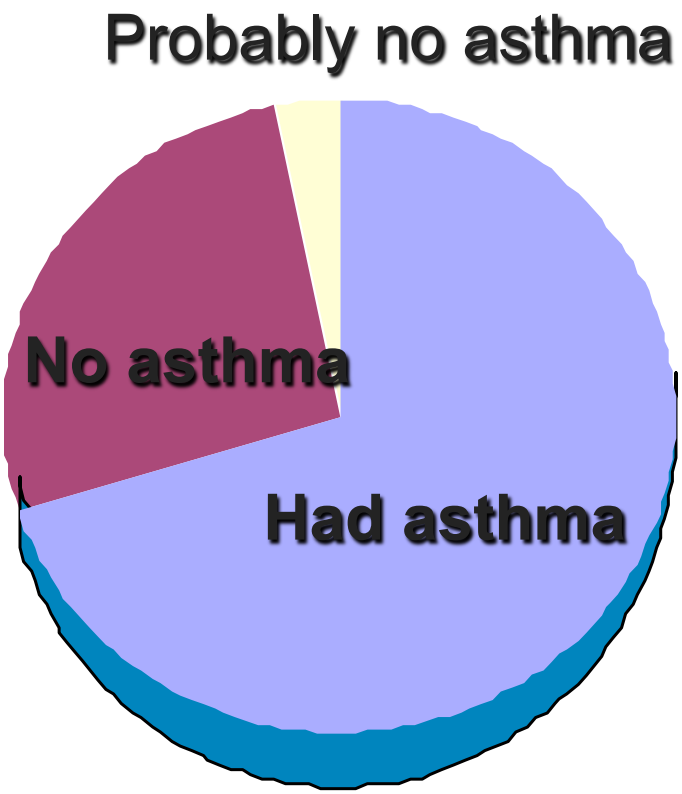
- Step 1: Confirm an asthma diagnosis and identify difficult to treat asthma
- Step 2: Differentiate Severe Asthma from milder asthma
- Step 3: Determine whether Severe Asthma is controlled or uncontrolled

ATS-ERS International Guidelines on Severe Asthma
Eur Resp J 2014

#1 Confirm an asthma diagnosis and identify difficult to treat asthma

- Critical to defining and identifying severe asthma
- Requires other (primary) diagnoses to be excluded, including vocal cord dysfunction
- Requires appropriate treatment of co-morbidities including poor adherence, addressable environmental exposures, etc
- Should include evaluation and treatment by asthma specialist for 3 or more months

#1. Make sure the patient has asthma

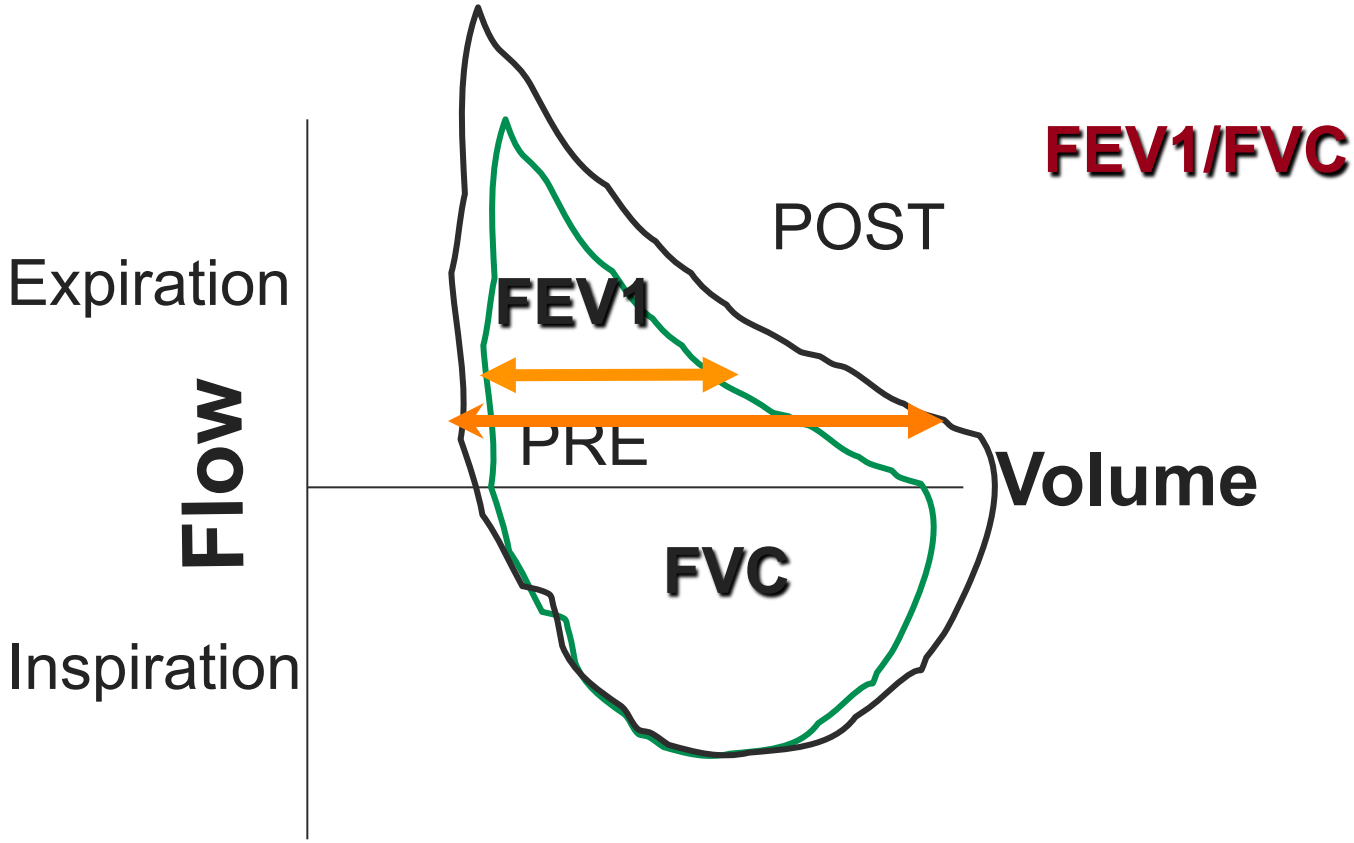


Did not have asthma!

Vitari, C Presented ATS 2009

- 150 pts referred to difficult asthma clinic at UPMC
  - Extensive evaluation
- Similar to results from Canada in milder asthma (random dialing approach evaluating ~500 "asthmatics" *Aaron et al, CMJ 2008*

CRUCIAL testing: pre and post bronchodilator spirometry



Asthma requires 12% improvement in FEV1 (and at least 200 ml)

“Time to think of masqueraders”

- Normal spirometry
  - Symptoms out of proportion to FEV1
  - Lack of bronchodilator response
- Abnormal spirometry
  - Atypical pattern to symptoms
  - Poor response to medications

Primary masquerader: Vocal cord dysfunction

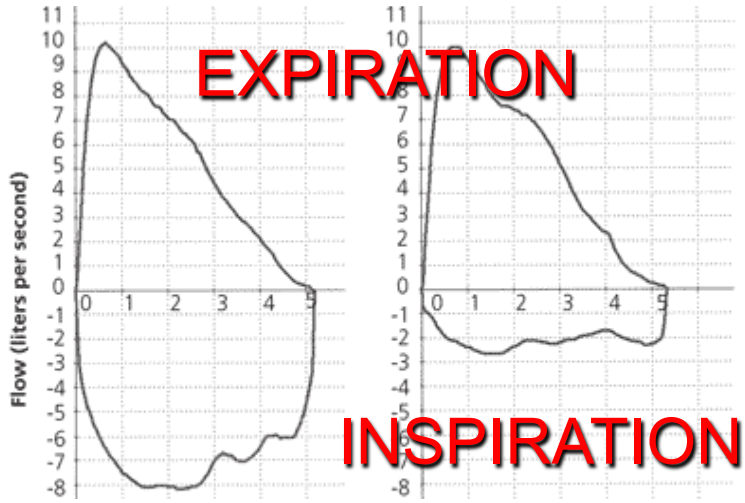
- Episodic usually dry cough
- Episodic chest tightness which often is right below neck
- Difficulty “getting breath in”
  - more common than getting air out
  - Often associated with strong aromas/exercise

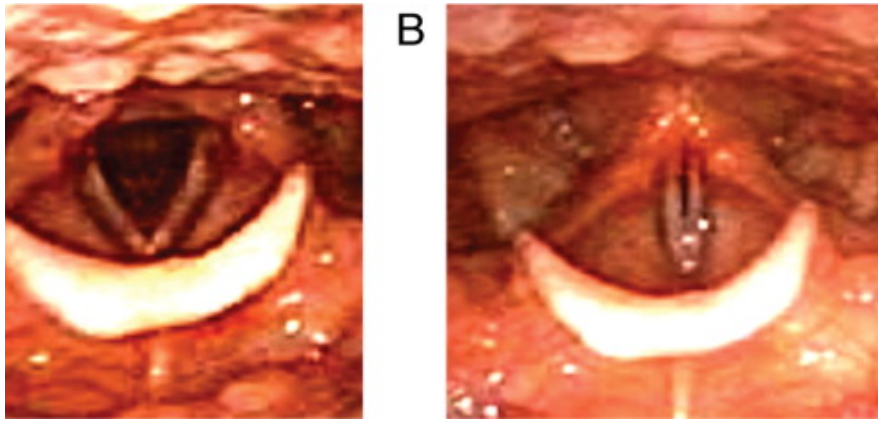
VCD imitating difficult asthma

- RED FLAGS!!

  - Presents with long hx of “asthma exacerbations”
    - often with history of ED visits/hospitalizations
    - high doses of every asthma medication, including systemic CSs but poor response to Rx and resultant side effects
  - Episodic cough and SOB, especially around irritants (“allergies” to roses, perfumes, etc)
  - Can’t get “enough air”
  - Symptoms persist despite normal lung function testing

VCD diagnosis





- Paradoxical inspiratory closure of VCs
  - Induced or spontaneous
- Diagnosed by history, flow-volume loops and definitively by laryngoscopy
- May have concurrent asthma

Abnormal spirometry

- Obstructive pattern (low FEV1 and FEV1/FVC)
  - COPD
  - ABPA
  - Constrictive bronchiolitis
  - Churg-Strauss (usually between flares)
- Restrictive pattern (low FEV1, not FEV1/FVC)
  - Obesity
- Mixed pattern (low FEV1 and FVC, FEV1/FVC still low)
  - Hypersensitivity pneumonitis
  - Churg-Strauss
  - Asthmatic Granulomatosis/Autoimmune airway disease

Dx helped by more advanced lung testing and often Hi Res CT

#2 Differentiate severe asthma from milder asthma

- *Severe asthma* REQUIRES treatment with high dose inhaled corticosteroids (ICS) (≥1000 mcg FP or equivalent) plus a second controller (and/or systemic CS) to prevent it from becoming “uncontrolled” or remains “uncontrolled“ despite this therapy

Potentially Treatment Responsive

- Presence of “reversible” associated factors
  - Smoking
    - ~25% of asthmatics smoke (general population), with associated high HCU Thomson, Eur Resp J 2004
    - likely to have “different” type of disease (less steroid responsive) Lazarus, Am J Resp Crit Care Med 2007
  - Persistent allergen exposure
  - Anxiety
  - Compliance/adherence

Patient not using medications appropriately/correctly

- Severe asthma long labeled as disease of poor compliance
  - In many cases, it is! But, reasons for poor compliance highly variable and common
  - Reasons for compliance issues vary!
    - Don't like taking inhaled meds
    - Can be VERY Expensive!!!
    - Don't want to be dependent on medication: sign of weakness/ admitting poor health especially in younger adults
    - Forgot: How good are you at remembering to take *pill* twice/ day?
      - BTW, cancer chemotherapy compliance rates about same
    - Meds *DON'T WORK*
- Taking inhaled medications, but not using devices correctly
  - So many to choose from!

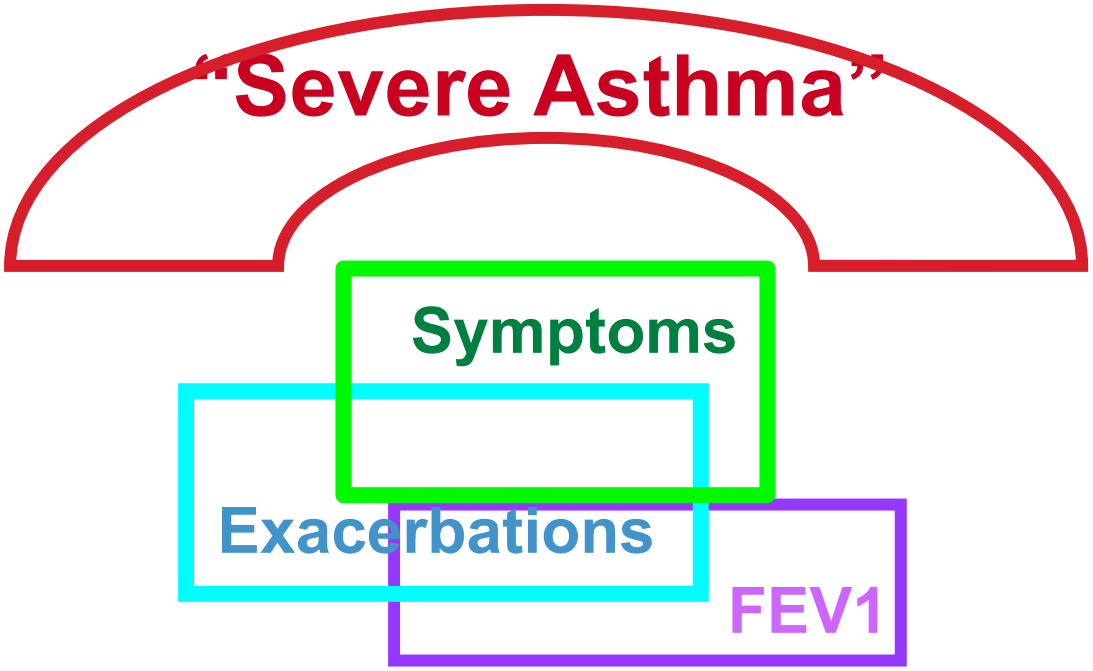
Persistent co-morbidities worsen asthma

- Asthma may not be severe, but complexity of presentation makes it *appear* severe
  - Obesity profoundly worsens SOB but may NOT be due to obstructive physiology and BHR
    - Asthma more likely to be misdiagnosed in obese men, especially with recent urgent HCU Parkhale Chest 2010
    - When IS asthma, may be less responsive to usual meds Peters-Golden Eur Resp J 2006
  - Chronic sinusitis: worsens cough, sputum--difficult to Rx!
  - GERD: Clearly associated with asthma, little evidence for cause-effect Mastronarde NEJM 2009

#3 Determine whether Severe Asthma is controlled or uncontrolled

- *Poor symptom control*: ACQ consistently >1.5 or ACT <20 (or "not well controlled" by NAEPP or GINA guidelines) over 3 months of evaluation
- *Frequent severe exacerbations*: 2 or more bursts of systemic CSs (>3 days each) in previous year
- *Serious exacerbations*: at least one hospitalization, Intensive Care Unit stay or mechanical ventilation in the previous year
- *Airflow limitation*: FEV1<80% predicted (in presence of reduced FEV1/FVC) following med withhold
- Any ONE of these qualifies as uncontrolled

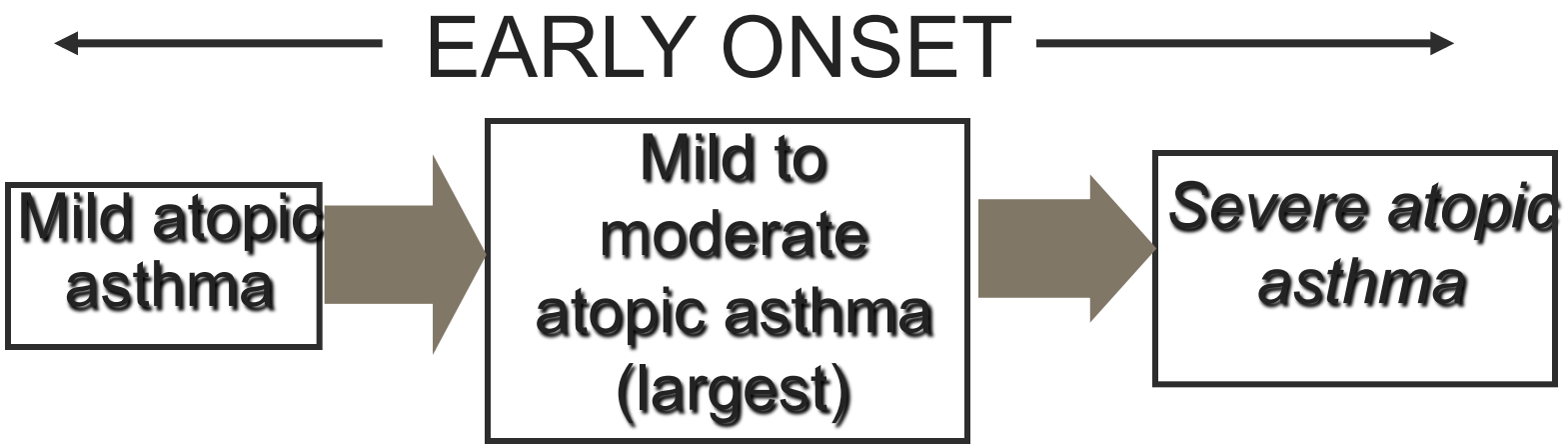
2016: Severe Asthma *umbrella* definition



The 3 “A”s: Arthritis, anemia and asthma

- How are they all alike?
  - They all are *nonspecific and general* characteristics of disease, describing joint swelling, low RBC numbers or reversible airway obstruction
  - They shed almost no light on what caused these characteristics to develop
    - *No self respecting rheumatologist would ever diagnose a patient with “arthritis”*

Clinical Phenotyping in the Severe Asthma Research Program (SARP): Importance of age at onset and FEV1



Moore AJRCCM 2010

The Transition to Inflammatory/ Molecular Phenotypes

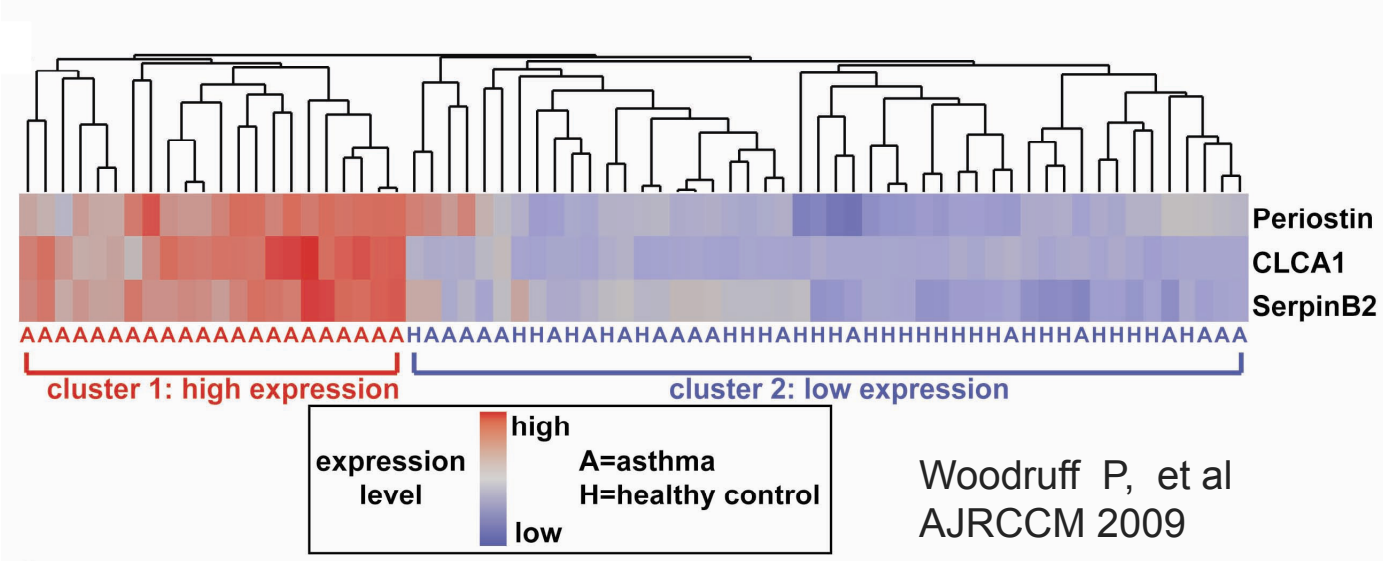
Phenotypes

Overlapping clinical physiologic hereditary characteristics

Inflammatory/Molecular phenotypes

Incorporation of associated pathobiologic MECHANISMS, ideally at molecular level, to molecularly define a clinically recognizable phenotype

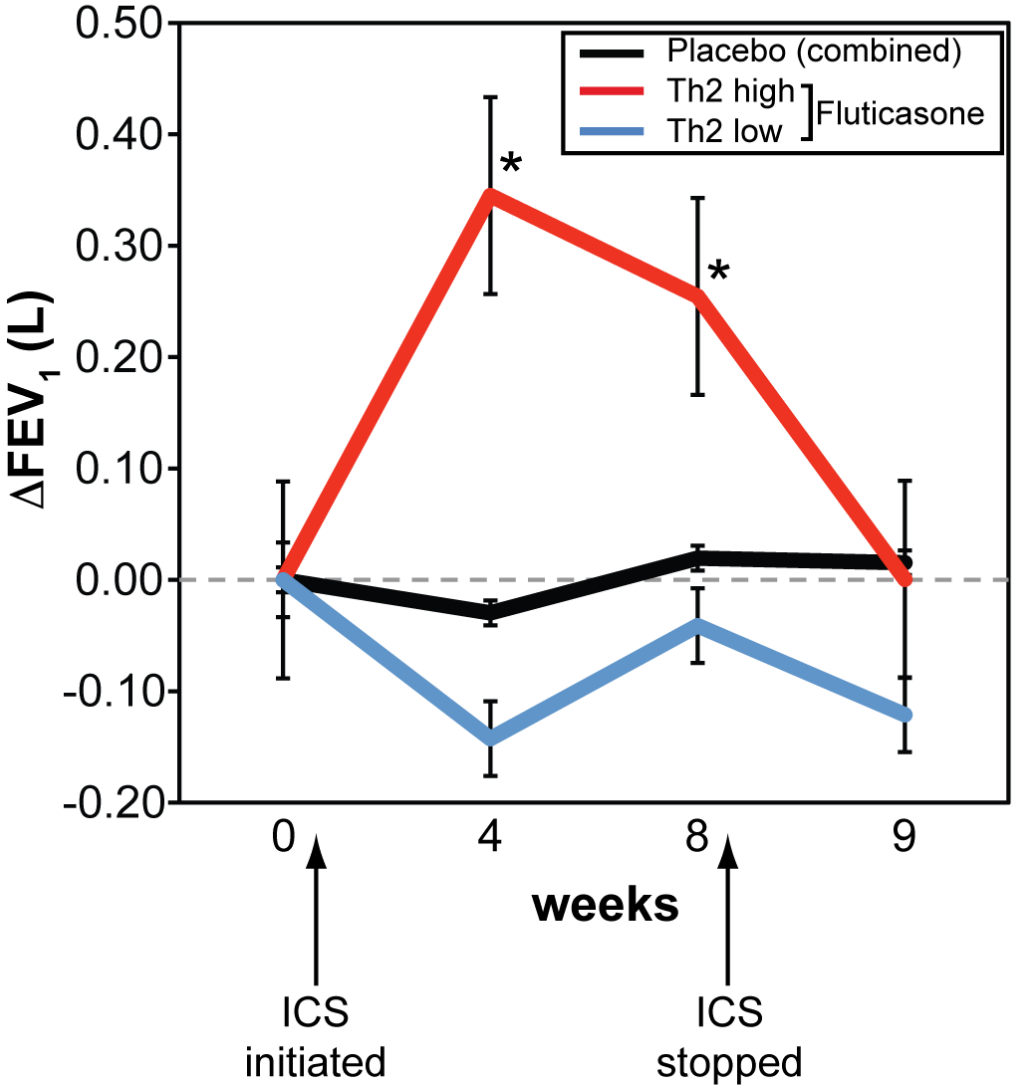
Molecular Phenotypes: Biomarkers identify Th2(like)-Hi



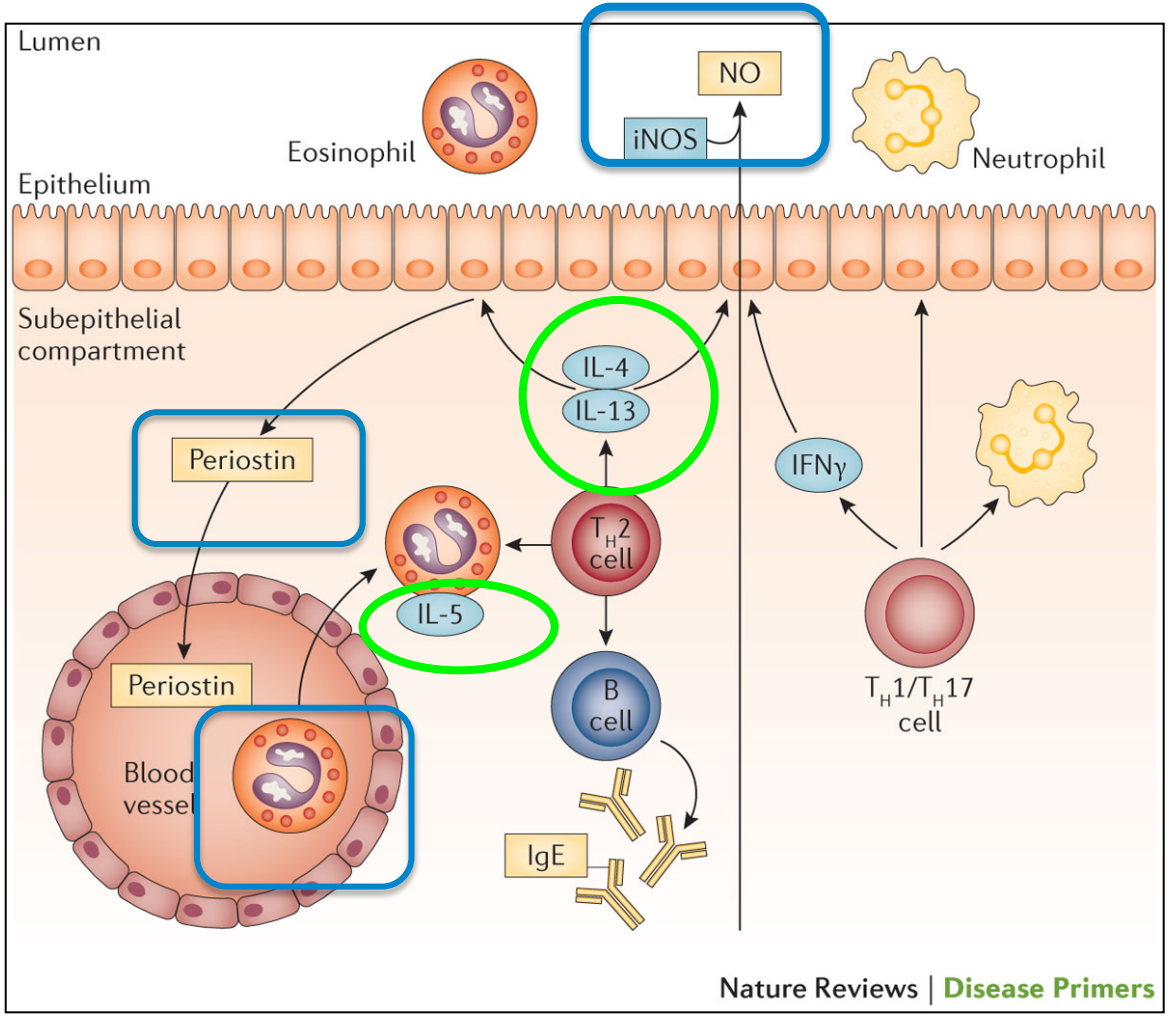
3 signature genes expressed *in vitro* in epithelial cells in response to IL-13 applied to *ex vivo* epithelial cells----"cluster' of <u>mild</u> asthmatics with:

- More atopy, eosinophils, SBM thickening and bronchial hyperresponsiveness and increased Type 2 cytokines in tissue

“Th2/Type-2 Hi”: predicts clinically meaningful responses to ICS Rx

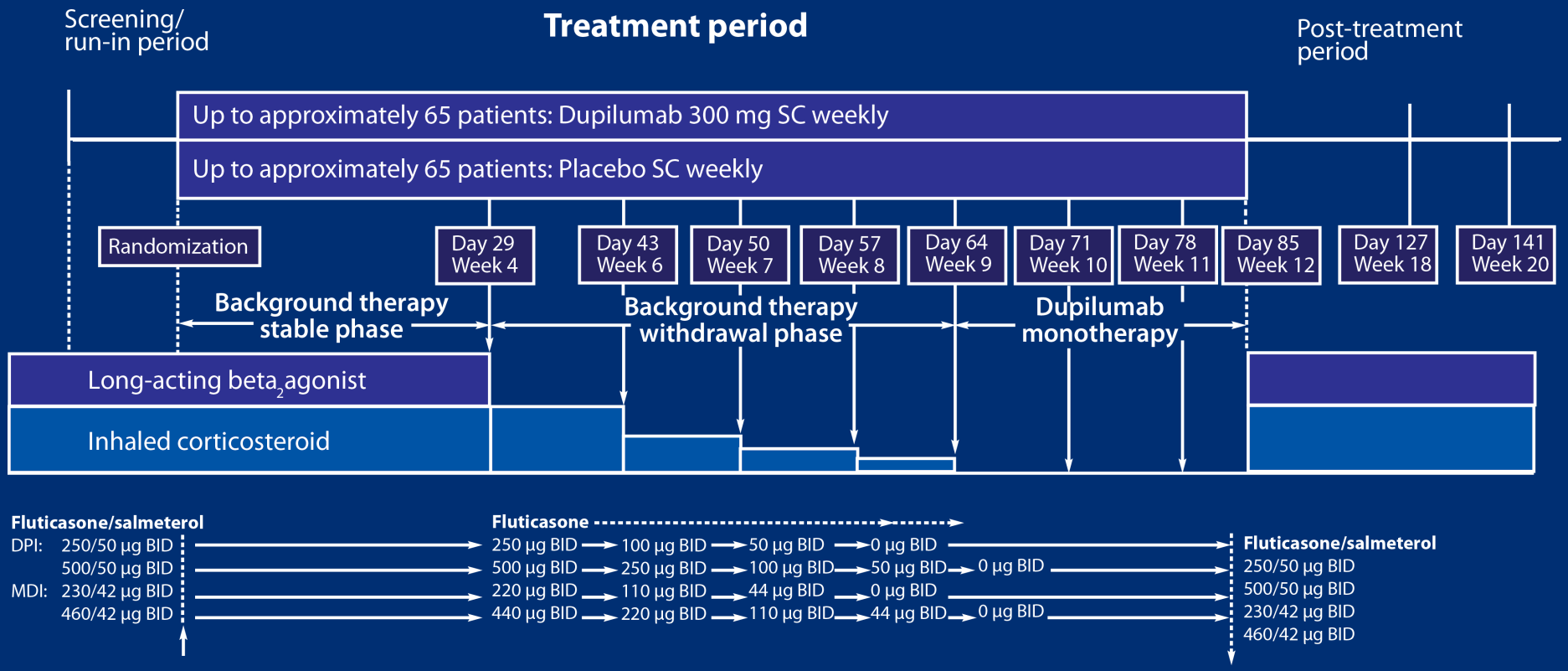


”Type-2” inflammation: The search for biomarkers



Holgate, S. T. Wenzel, Set al. (2015) Asthma Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.25

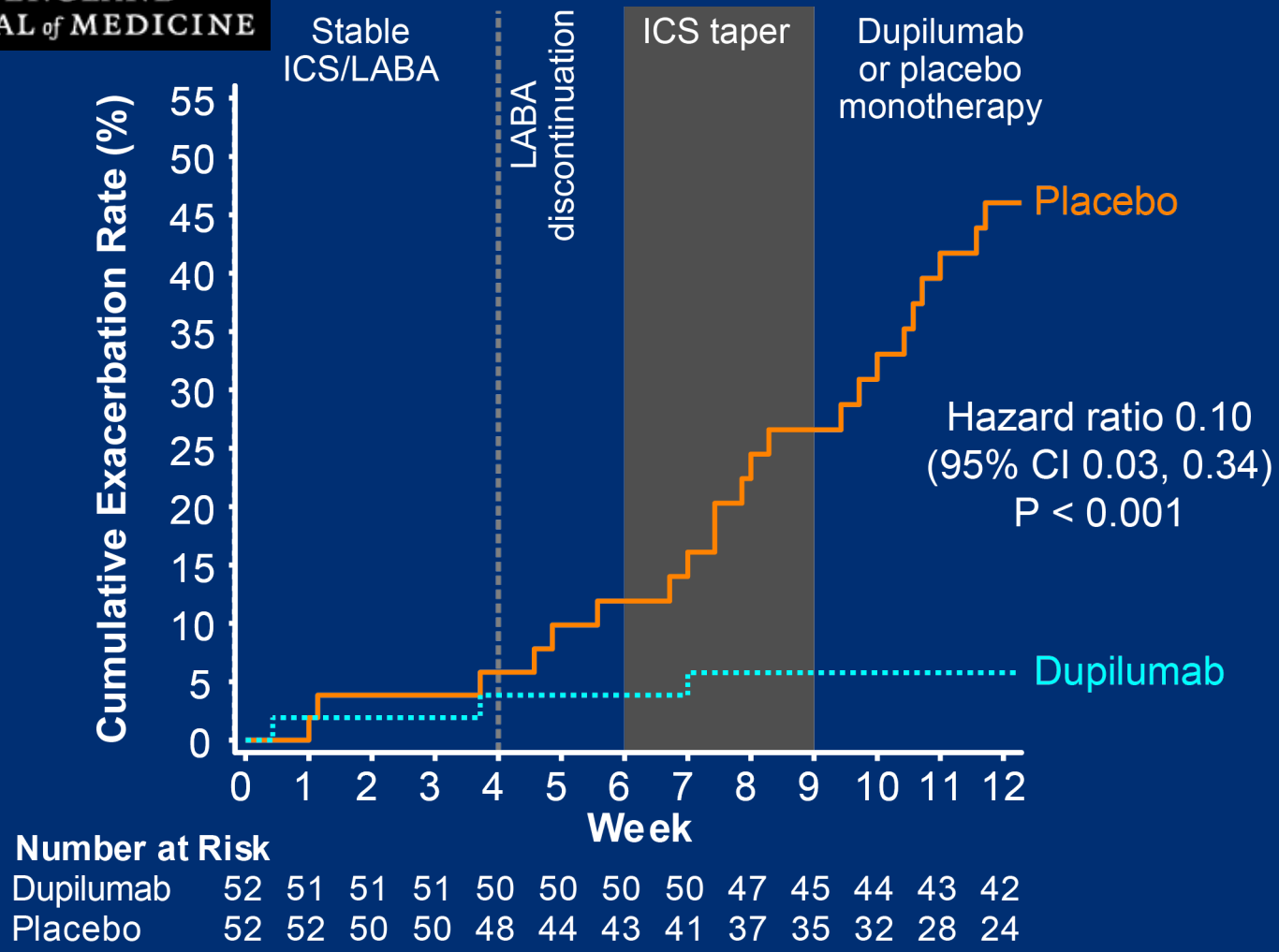
Phase 2a targeting Type-2 Hi/Eos-Hi: Antibody to IL-4Rα



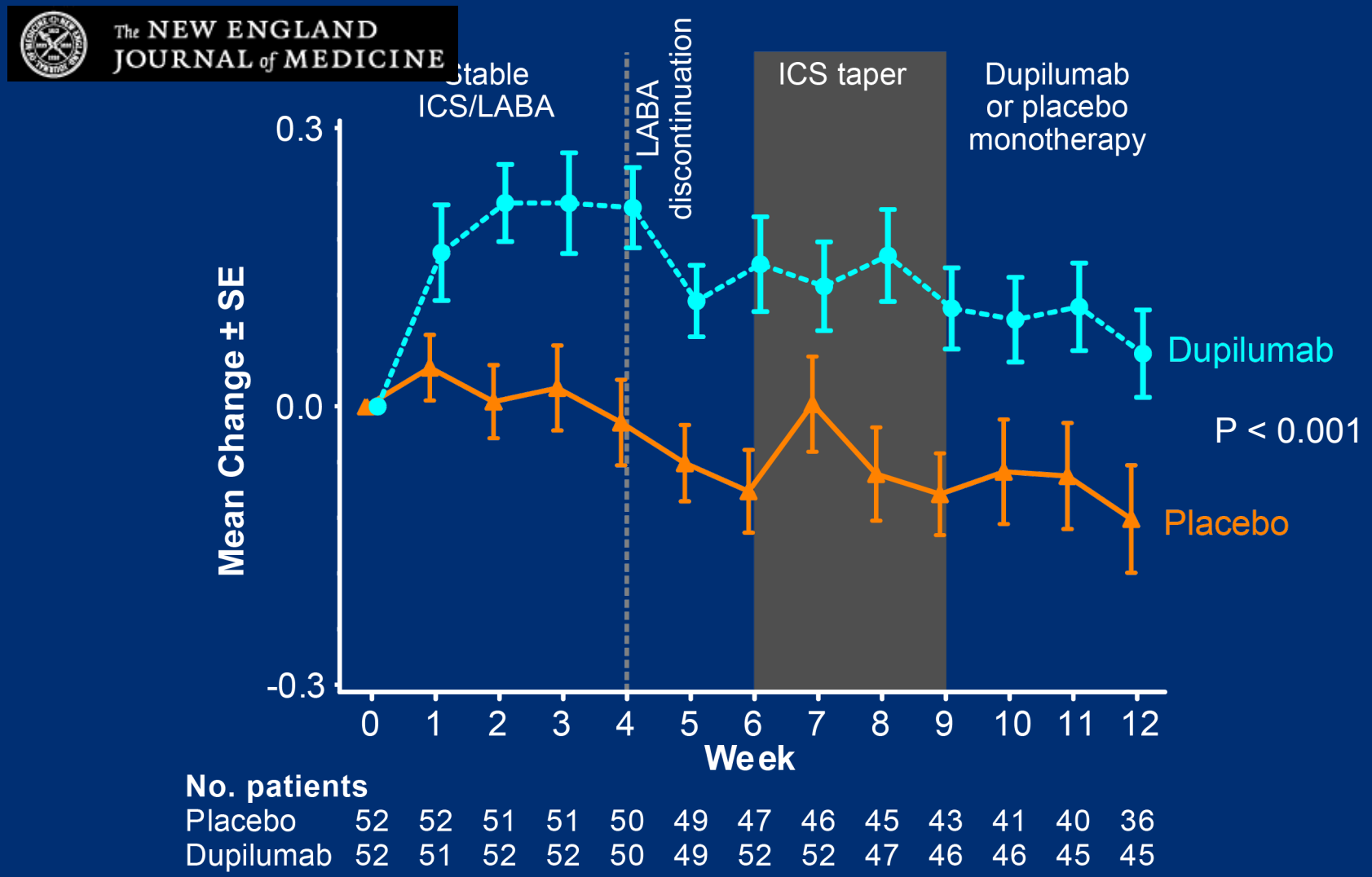
BID = twice daily doing; DPI = dry powder inhalation; MDI = metered dose inhalation; SC = subcutaneous

Wenzel, N Engl J Med June 2013

Inhibition of IL-4Rα: Profound reduction in loss of asthma control

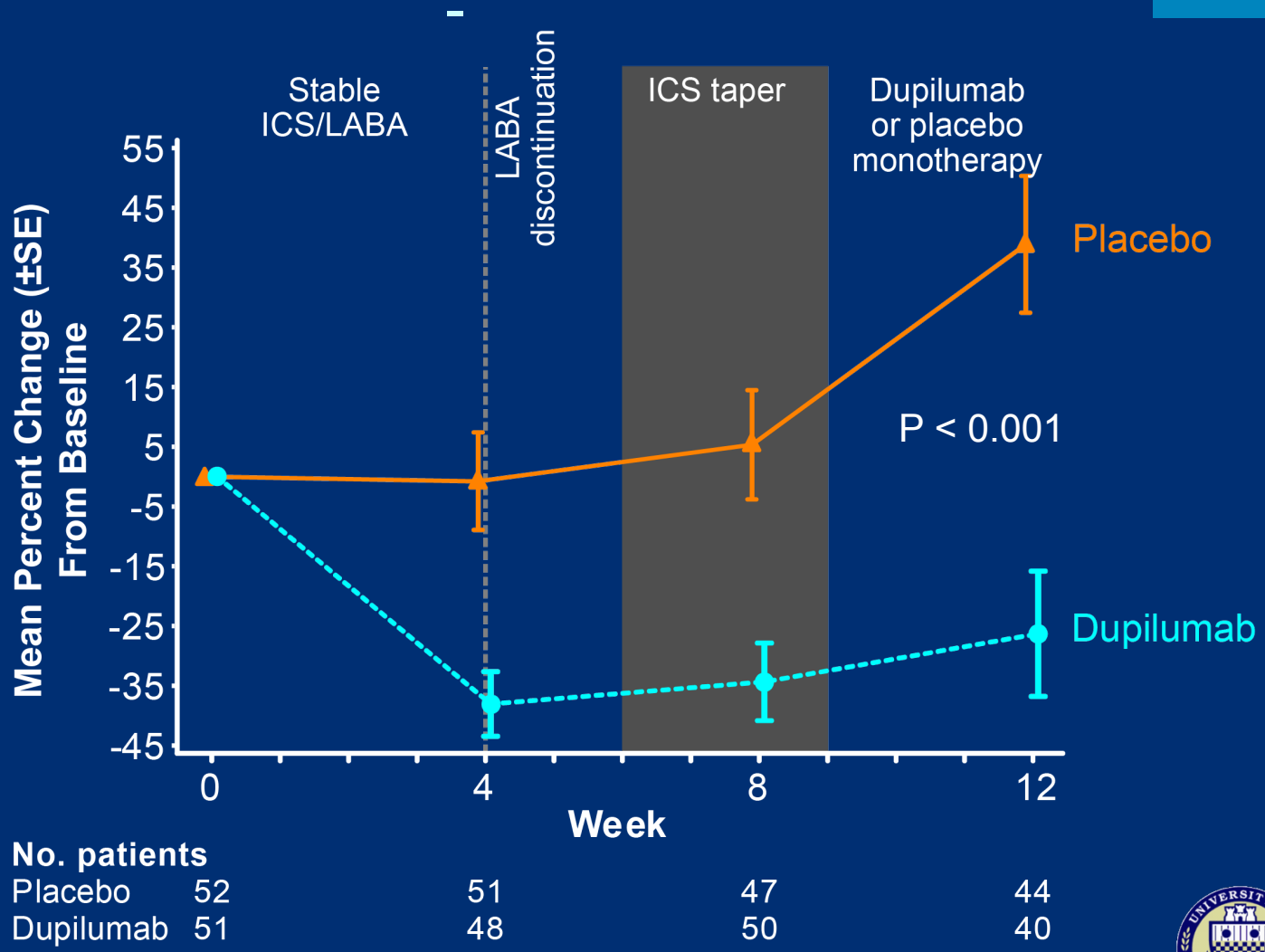


Improvement in lung function, on top of combination Rx

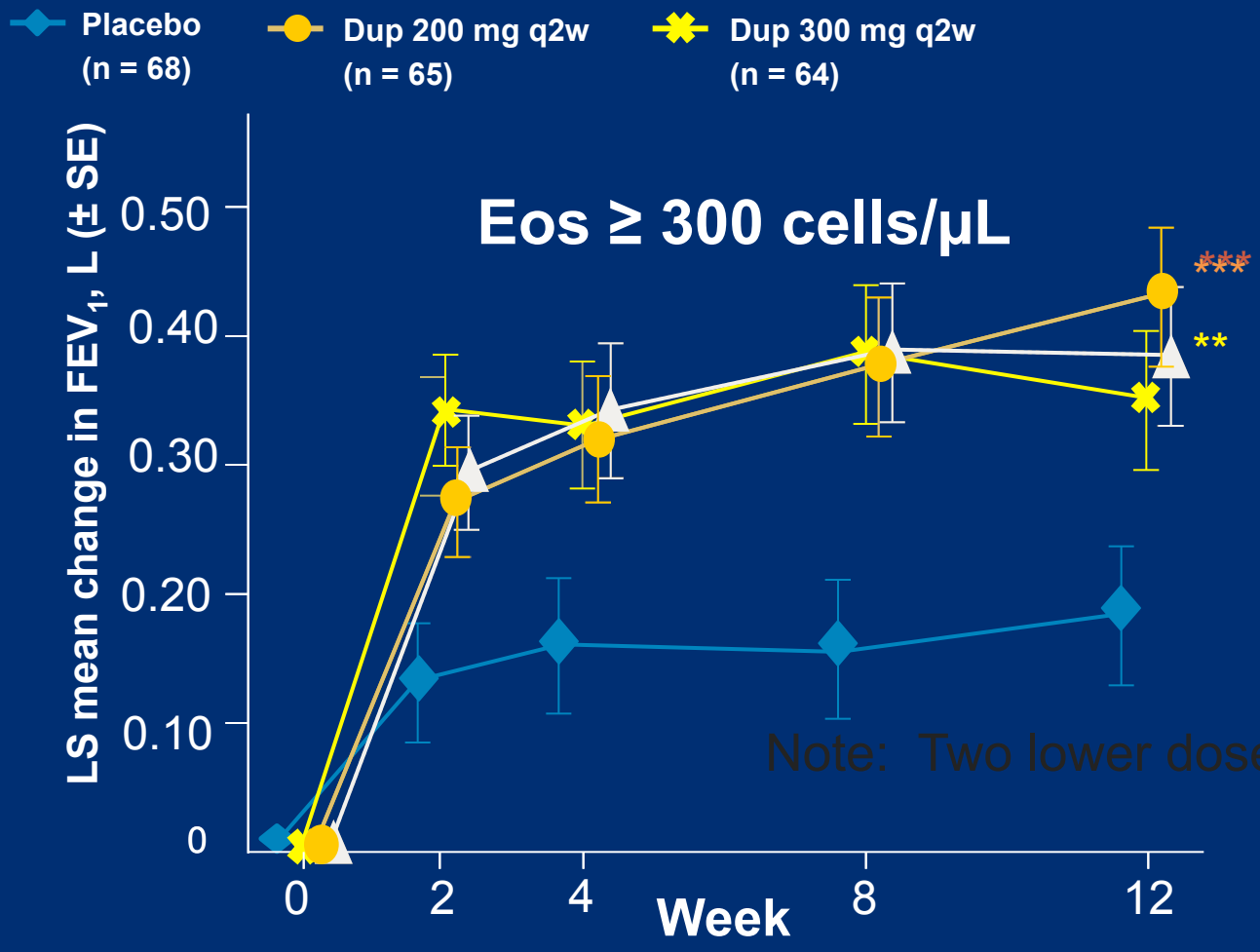


Proof of mechanism: FeNO declined with IL-4Rα blockade

Correlation of FeNO with FEV_1 at Week 12:
r = -0.408
P = 0.009



Phase 2b Primary endpoint: Change in FEV1 in patients with ≥300 eos/µL

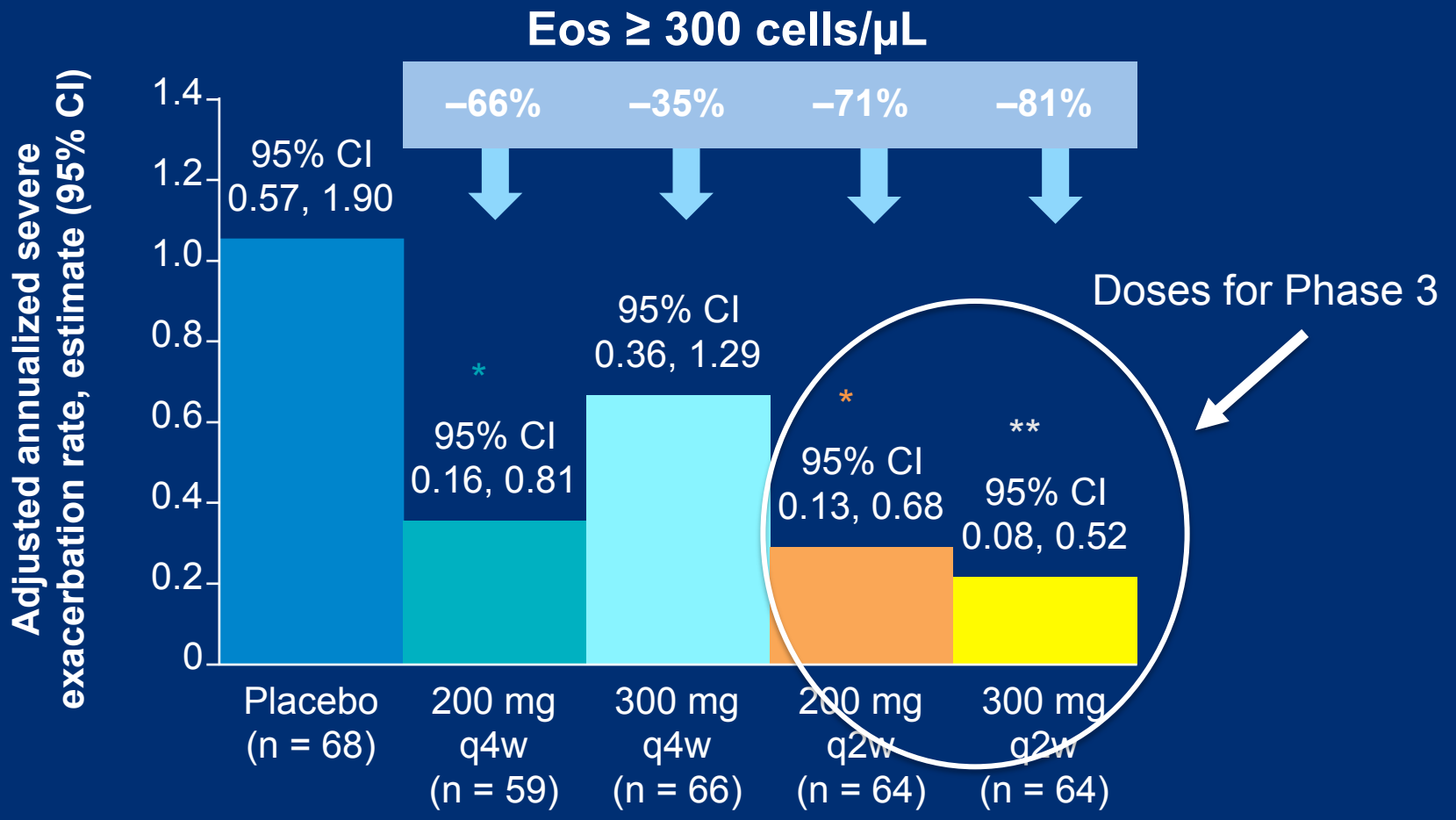


Note: Two lower doses removed

Wenzel, Presented ERS 2015, In Press

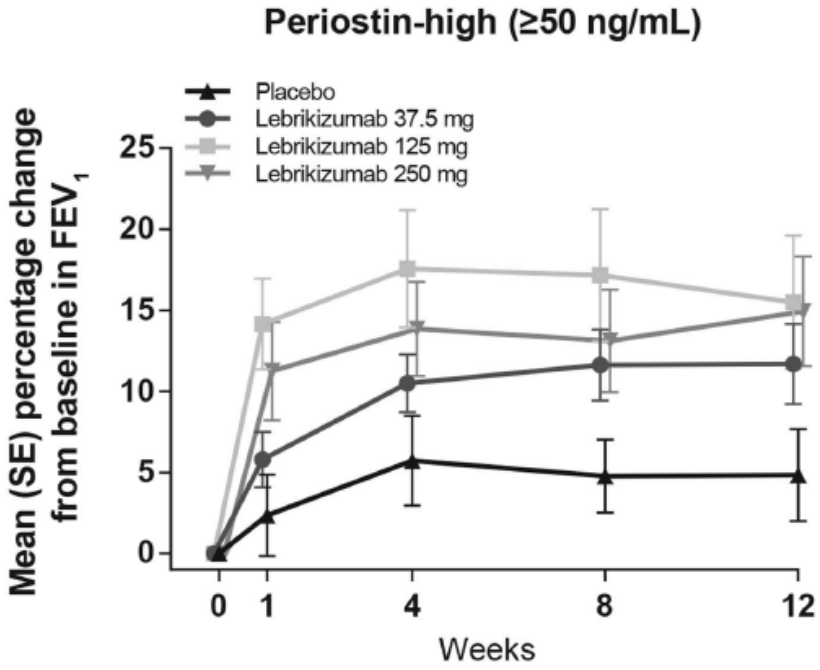
Submitted

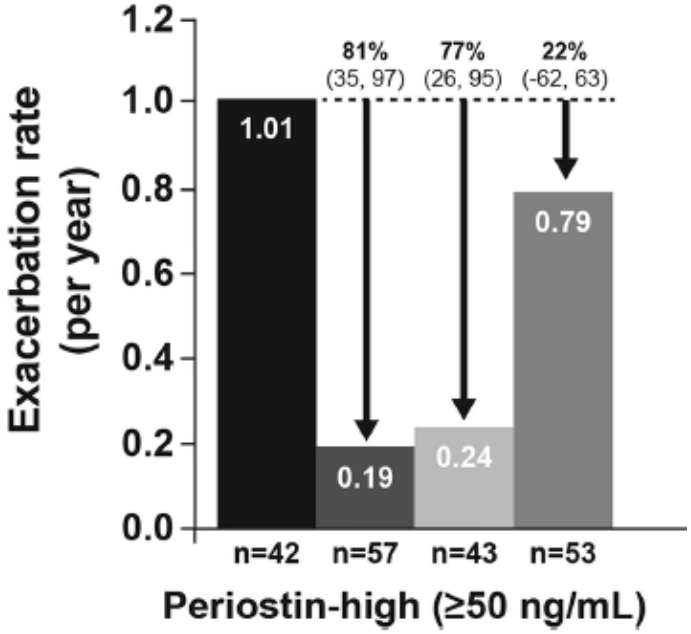
Phase 2b: ~75% reductions in steroid requiring asthma exacerbations



Results with anti-IL-13 Rx support DUAL importance of IL-4 and -13

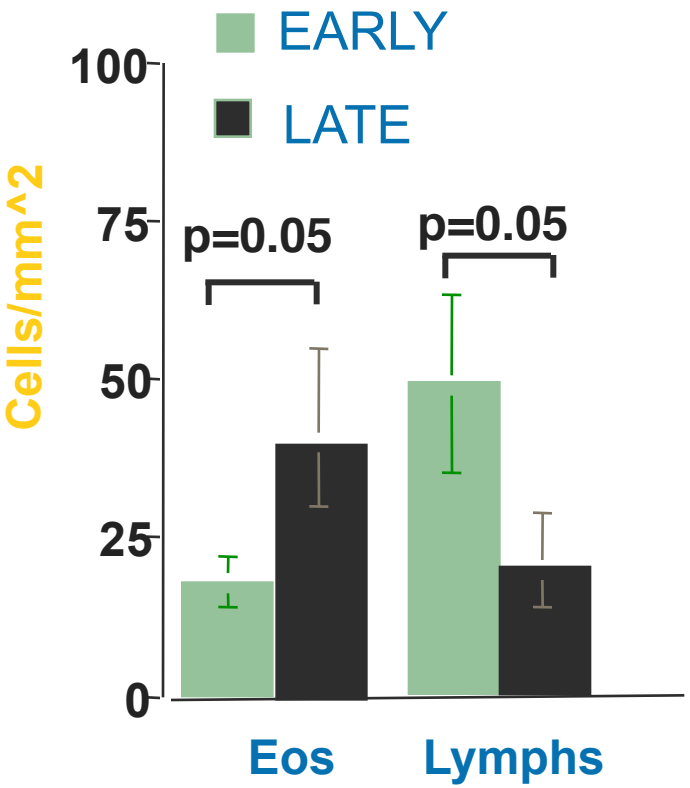
Hanania Thorax 2015

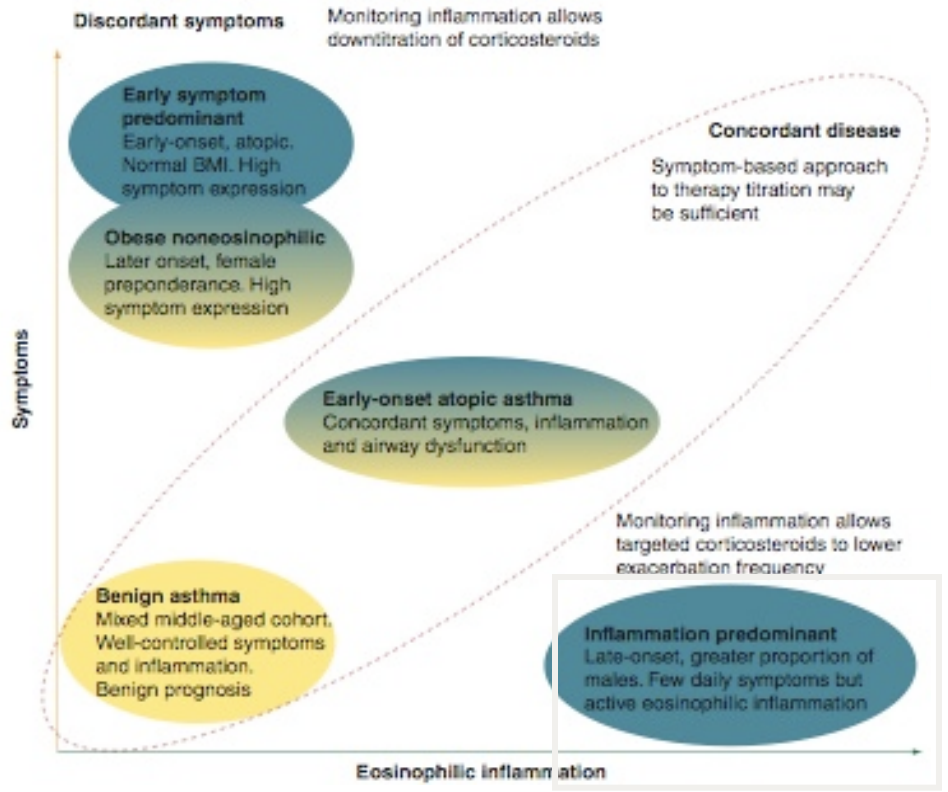




No dose response and little/no impact on symptoms/quality of life.
Phase 3 results “disappointing”

A non-traditional Type 2 phenotype: Highly eosinophilic adult onset SA



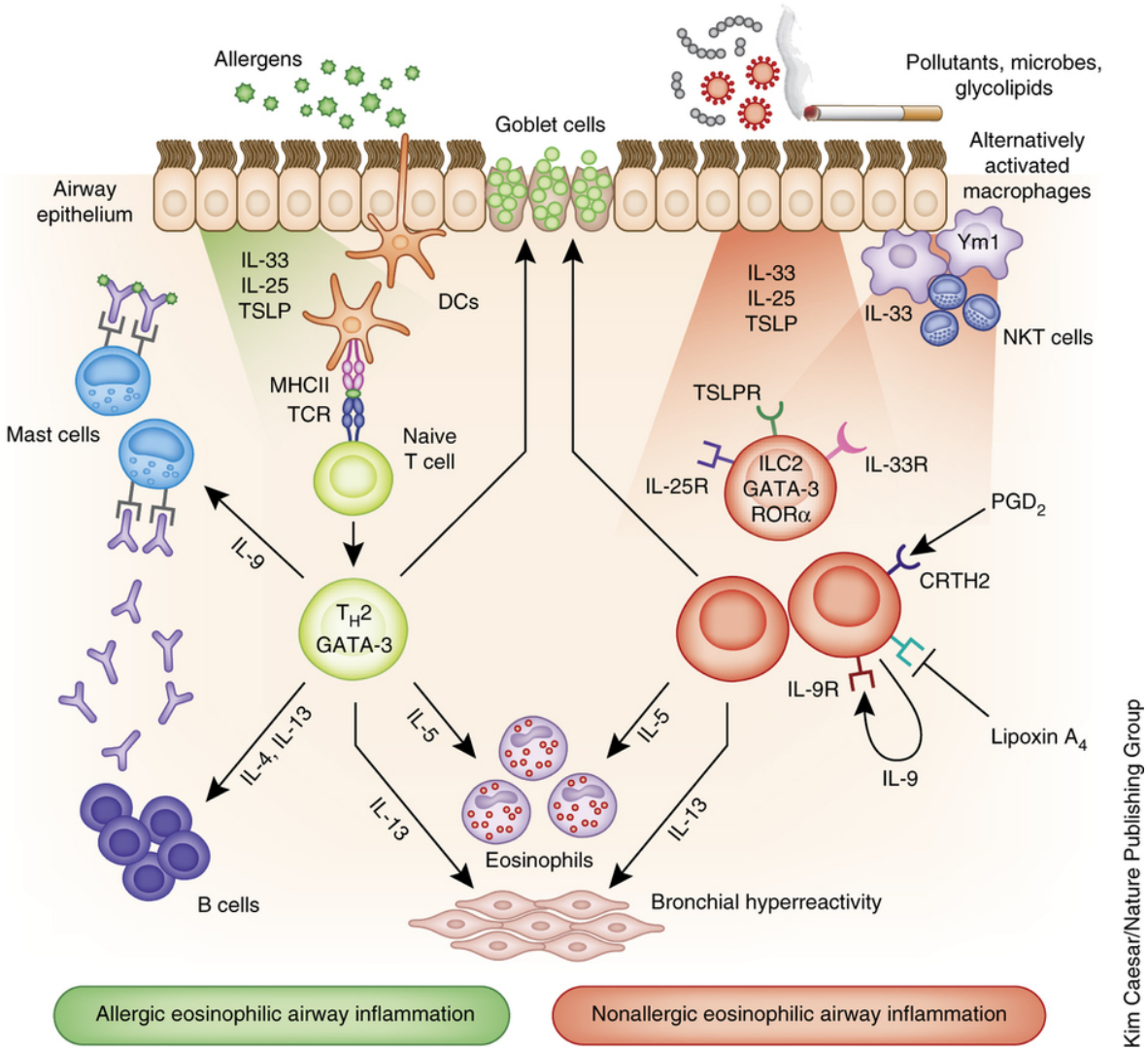


LESS atopy, nasal polyps, aspirin sensitivity

Miranda JACI 2004

Haldar AJRCCM 2008

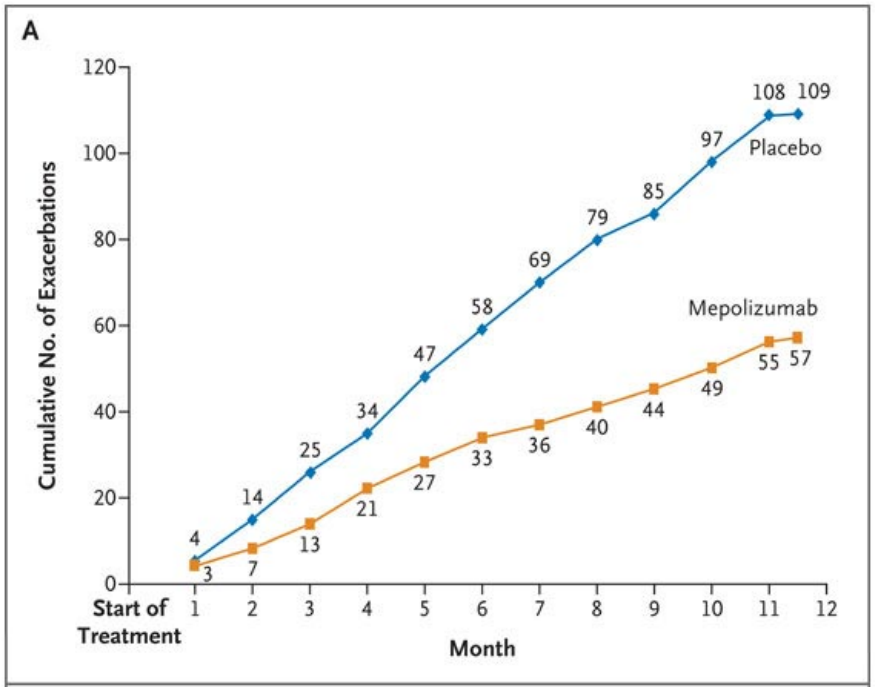
“Less allergic/Hi Eosinophils”: Role for ILC2 cells in adult onset asthma?



Kim Caesar/Nature Publishing Group

Anti-IL-5 confirms IL-5 as *molecular* feature of eosinophilic asthma

Haldar P et al. N Engl J Med 2009;360:973-984

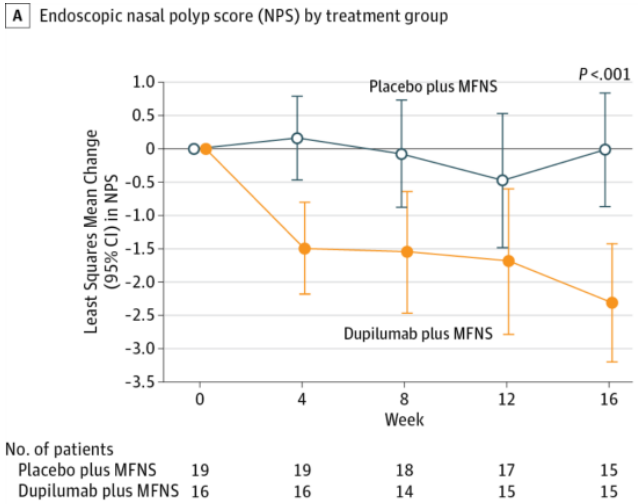


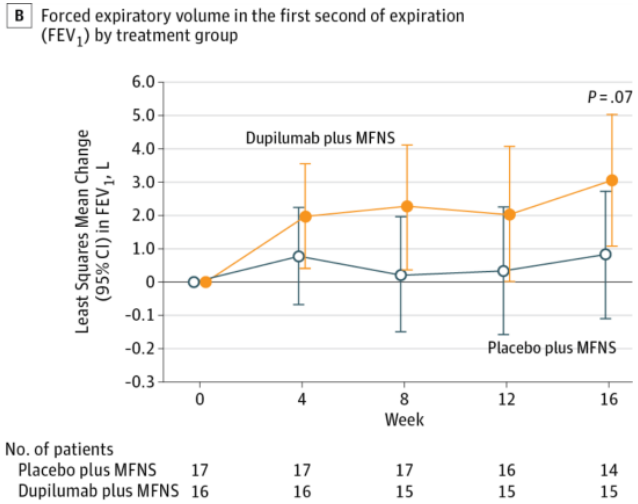
- IL-5 = potent eosinophilc cytokine
- No effect in “all asthma”
- Targeted Anti-IL-5 approach in “eosinophilic asthma” led to 40% reduction in asthma exacerbations
  - Many of these patients with late onset nasal polyp associated disease
- Both mepolizumab and resilizumab now approved in US

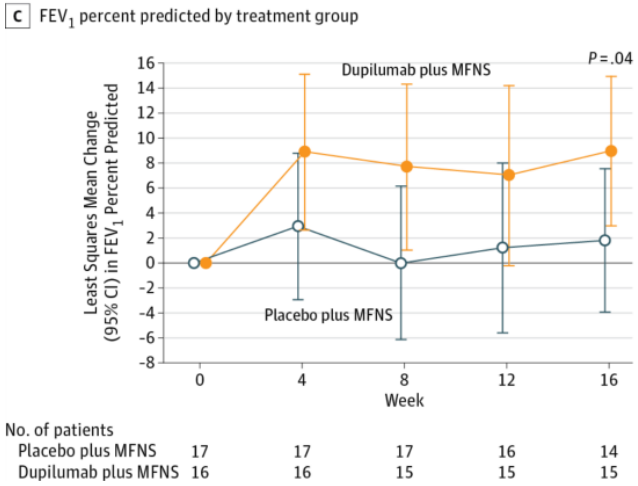
The NEW ENGLAND JOURNAL of MEDICINE

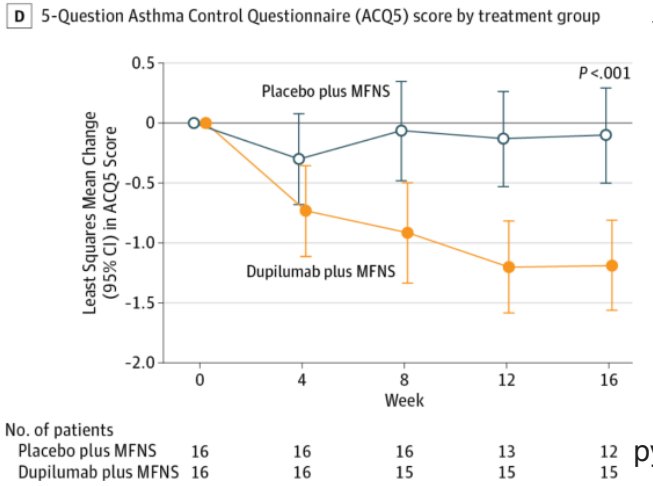
But Anti-IL-4R approach also improves both nasal polyps and asthma

: **Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients With Chronic Sinusitis and Nasal Polyposis: A Randomized Clinical Trial Bachert C et al JAMA 2016**





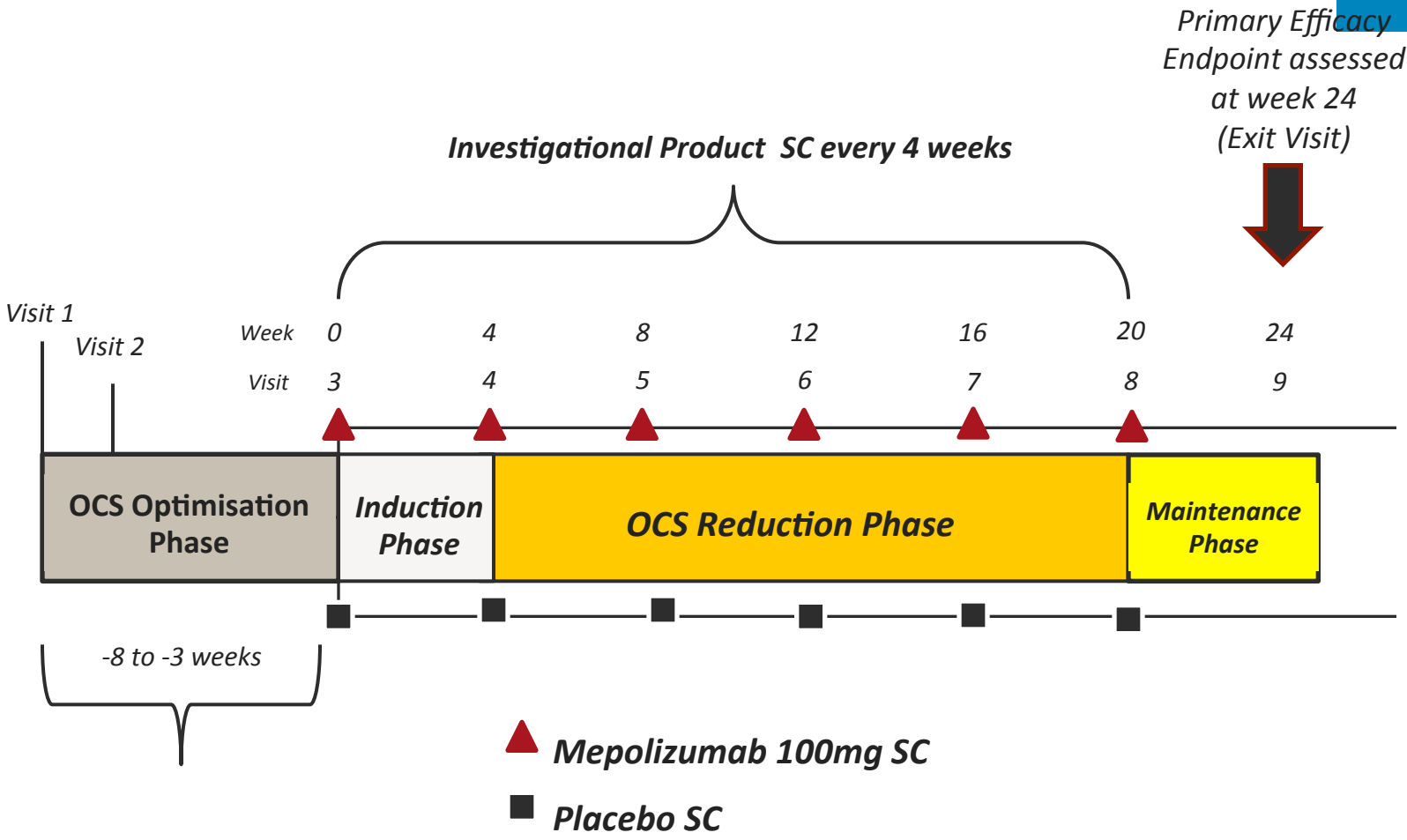




Despite lack of allergic component, supports association with Th2 immunity

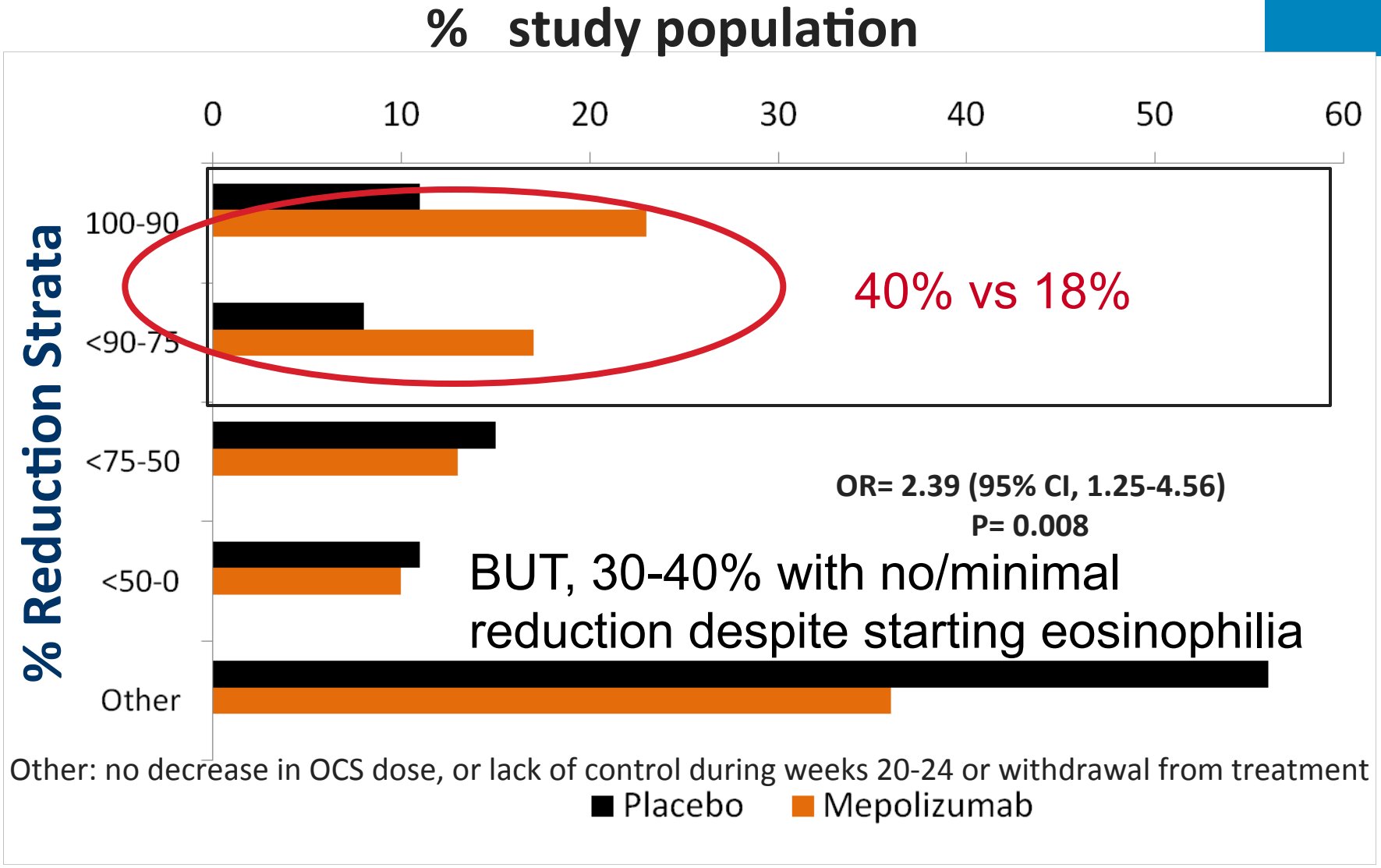
Which will be better approach remains to be studied

Eosinophilic corticosteroid dependent asthma: Role for IL-5?



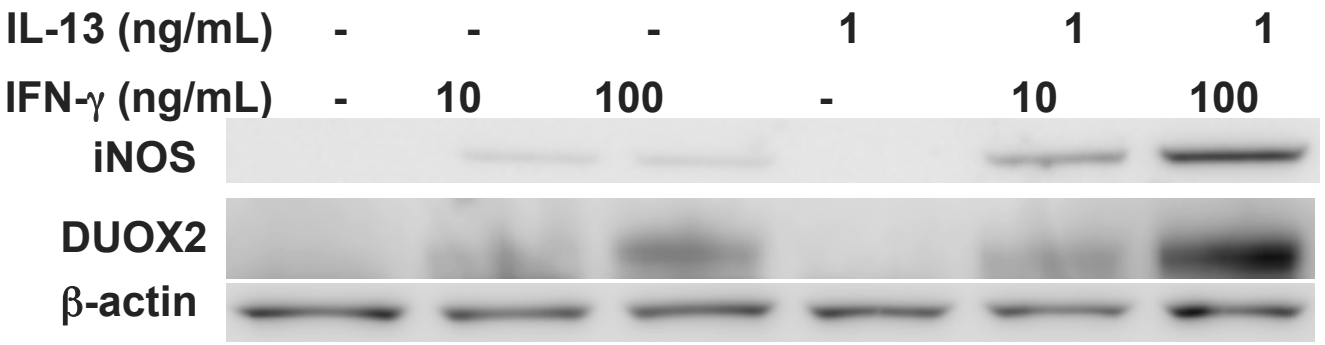
Bel E, et al, N Engl J Med Sept 2014

40% of patients able to decrease OCS by ≥75%



Biomarkers: Type-2 immunity, FeNO and complex asthma

- FeNO associated with Th2/Type 2 responses but seen in mild to severe disease
- FeNO strong predictor of chronic oral CS use in Severe asthma *Wysocki JACI 2014*
- In primary human epithelial cells, Type-2 cytokines induced iNOS and Type-2 blockade *in vivo* decreased FeNO
  - But also induced by IFNγ, and synergistically increased in combo
  - IFNγ higher in severe asthma *Raundhal, J Clin Invest 2015*
-

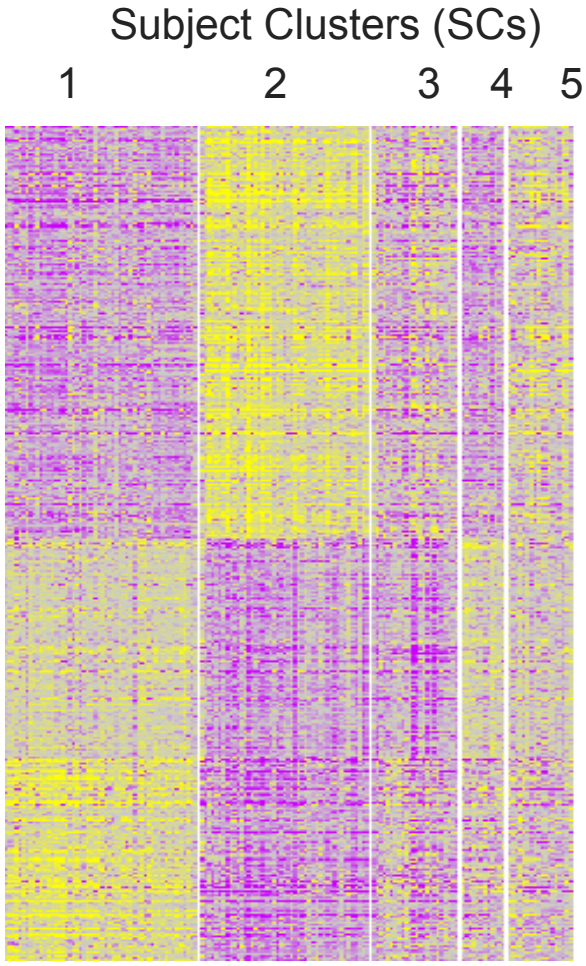


Voraphani Mucosal Immunol 2014

Does FeNO related epithelial gene expression identify useful clinical clusters?

- 155 epithelial brushings from range of asthmatics and healthy controls from SARP *Modena, AJRCCM Dec 2014*
  - Agilent microarrays performed
- 589 genes correlated strongly with FeNO
  - iNOS most stongly correlated rho=0.71
- Clustered genes, identified 5 patient clusters, 3 FeNO Hi and 2 FeNO Lo, with distinct characteristics
- Expanded to 1349 genes differentially expressed across the 5 clusters

K-means clustering identifies 5 molecular participant clusters



Modena AJRCCM 2014

SC1: HC and mild asthma, low inflammation and atopy

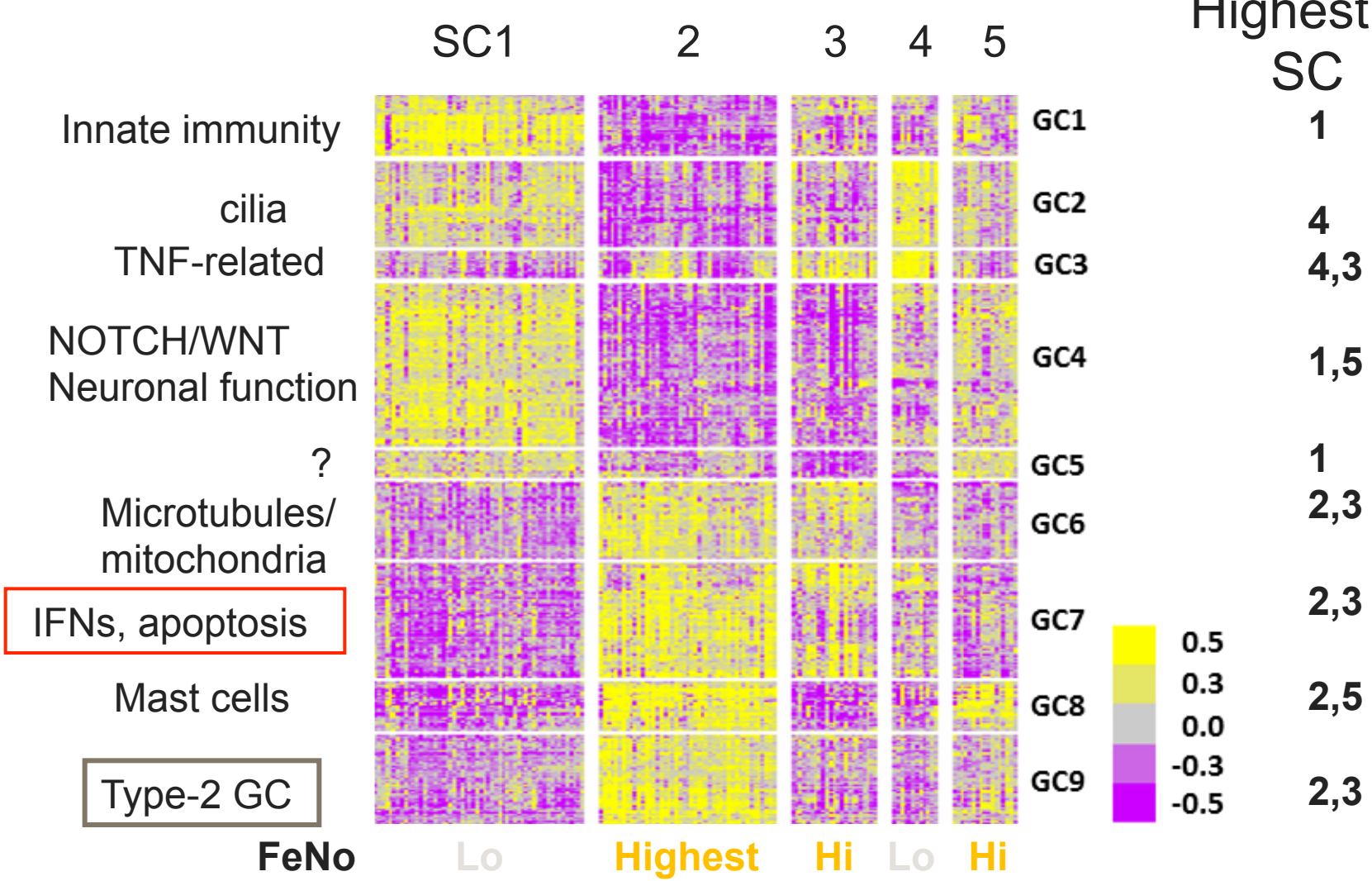
SC2: Early onset, 73% moderate to severe, low lung function, high eos in blood/BAL

SC3: Later onset majority severe, BAL neutrophils, eosinophils and lymphocytes. Nasal polyps (26%) sinus surgery (30%).

SC4: 50% moderate to severe. Earliest age at onset, longest disease duration. 100% atopic (including 4 HCs), high BAL lymphocytes, but low FeNO

SC5: Youngest, early onset, 50% African American, strongest FH/highest IgE

Hierarchical clustering of 1349 additional genes distinguishes 9 gene clusters

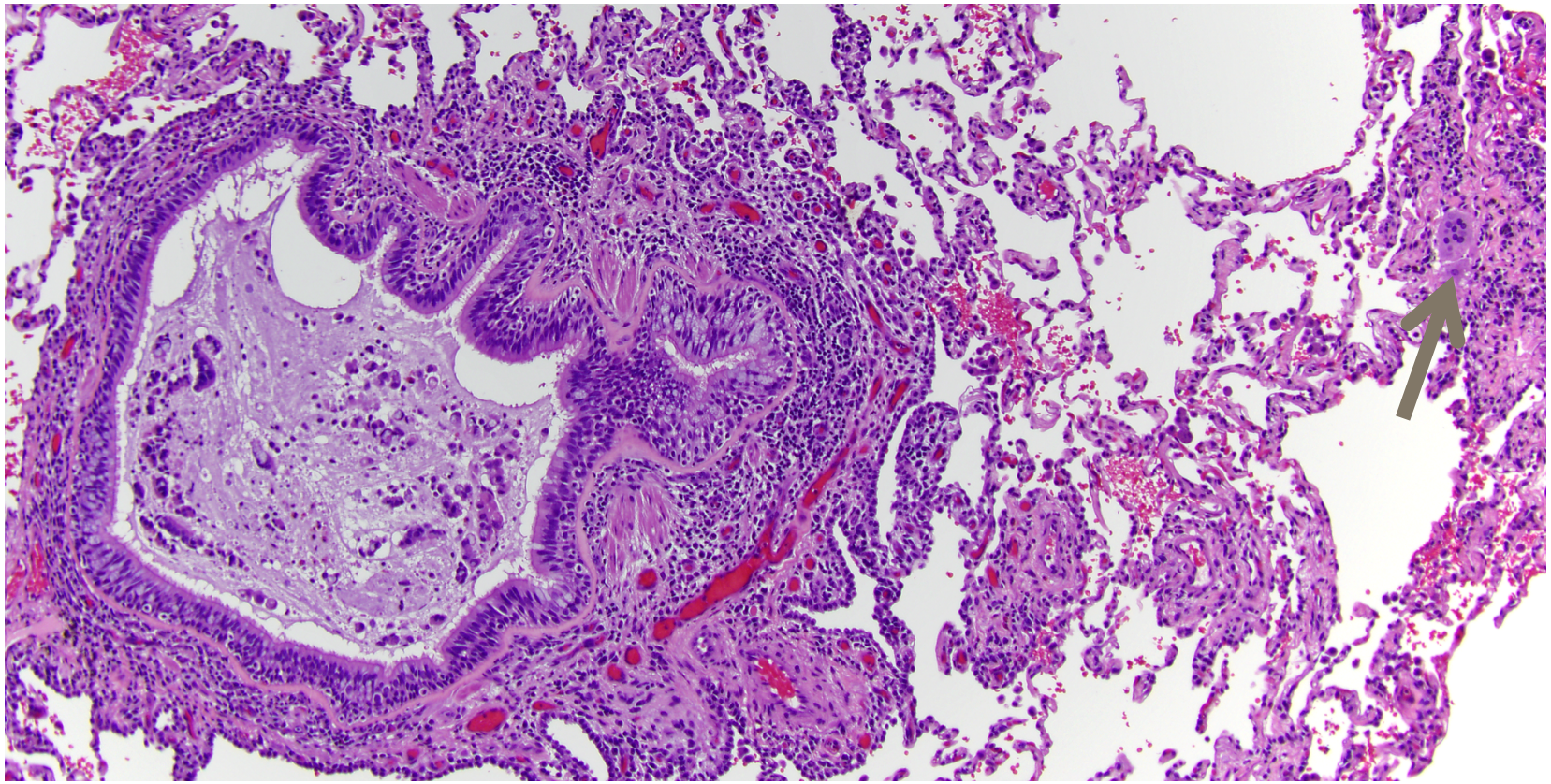


Complex Type-2 reactive airway disease Role for autoimmunity?

- First reported “Asthmatic Granulomatosis” 2012
- 10 “severe asthma” pts (now ~35) who met asthma diagnosis (reversibility or + methacholine)
  - All on systemic corticosteroids (10 mg or above)
- Often adult onset or adult worsening
- Modest obstruction with decrease in FVC and DLCO
- Hi FeNO (and blood eos) despite systemic CSs
- Associated with autoimmune family history in ~70%
- All underwent VATS surgical biopsies

Wenzel Am J Resp Crit Care Med 2012

Small airway inflammation and granulomas: complex immunity



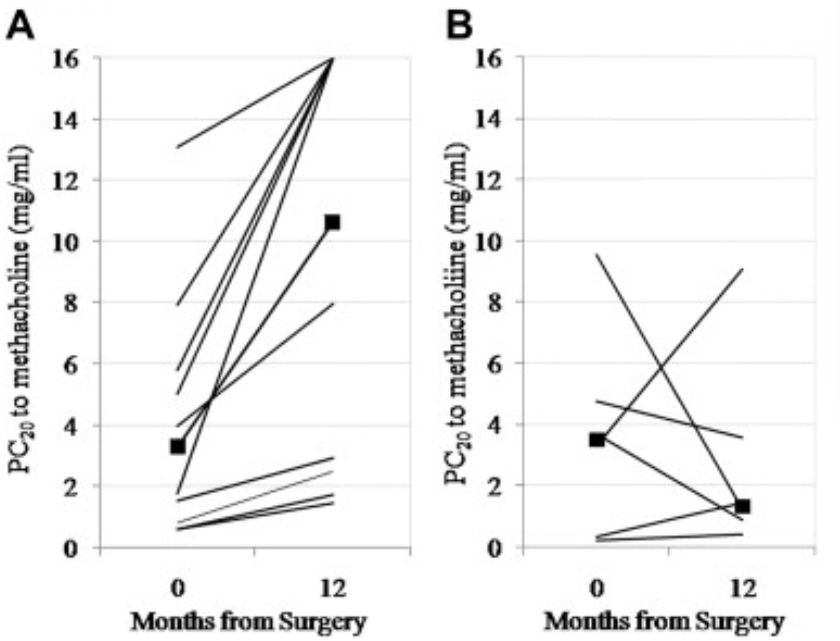
When associated with personal or family history of autoimmunity respond well to azathioprine Doberer ATS 2015

“Type 2-Lo Asthma”

- Much less well defined than Type-2 HI
  - Defined as “apparent” absence of Type 2
    - BUT, defined by our current limited Type-2 biomarkers
  - No definite endotypes, but confounders including obesity, post infectious, smoking, long disease duration likely to play a role
  - ‘omics may provide some clues
- *All* associated with poor CS response

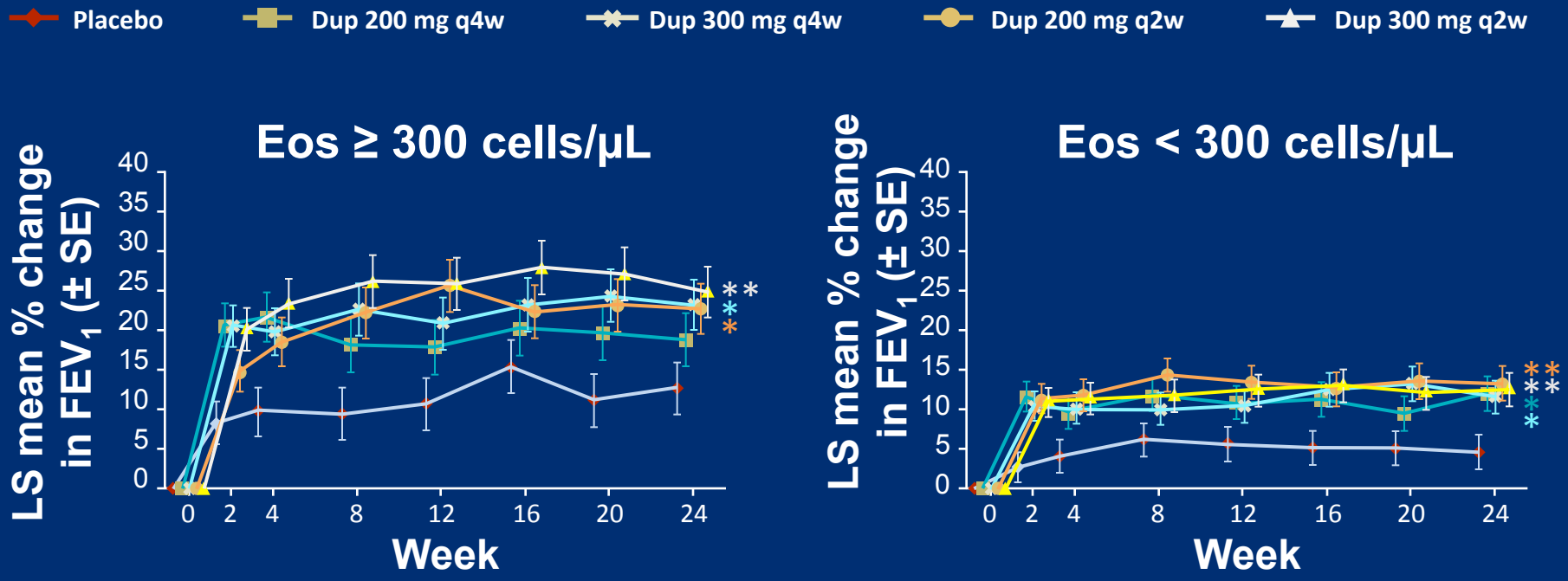
Type 2-Lo late onset obese asthma responds to weight loss

- 23 obese asthmatics evaluated before and 12 mos after bariatric surgery
- Roughly phenotyped patients by median IgE levels (25 vs 305 IU/ml)
  - Late onset asthma=Lower IgE
- Later onset/low IgE obese asthmatics improved PC20 while no effect seen in low IgE/early onset
- Suggest weight loss will be more effective in some phenotypes



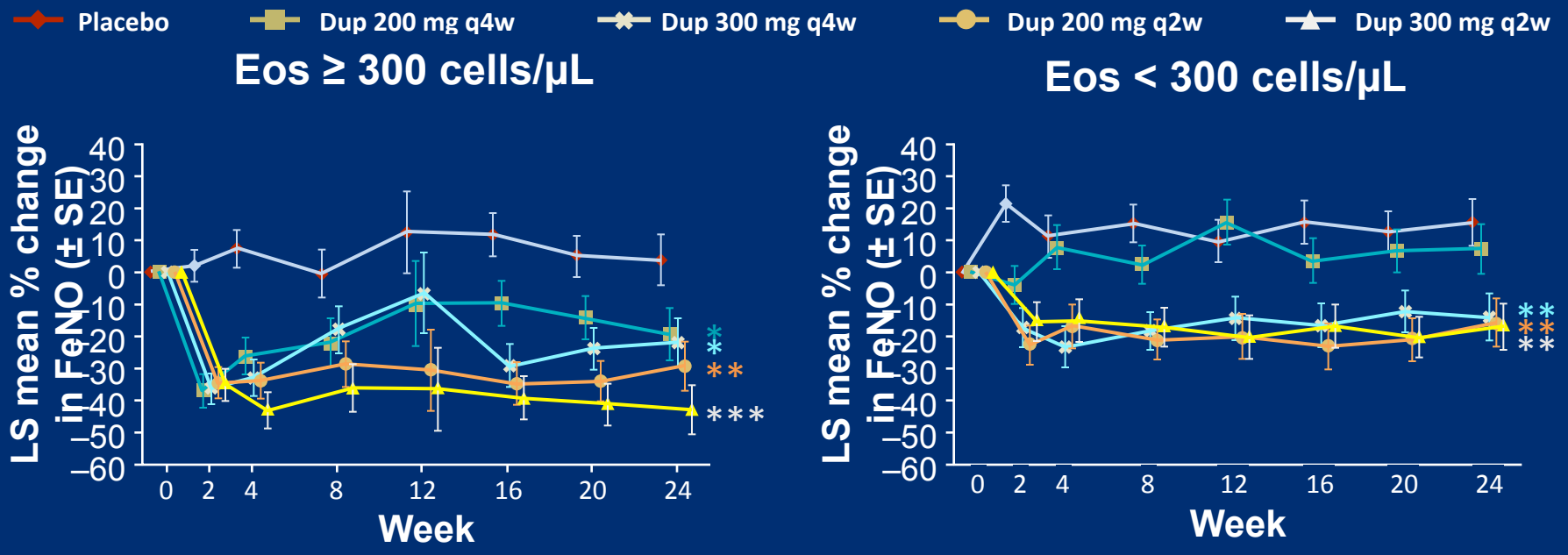
Dixon AE et al J Allergy Clin Immunol 2011

Although changes in FEV1 smaller, IL-4Rα antibody also effective in those with low eos/"low" Type-2



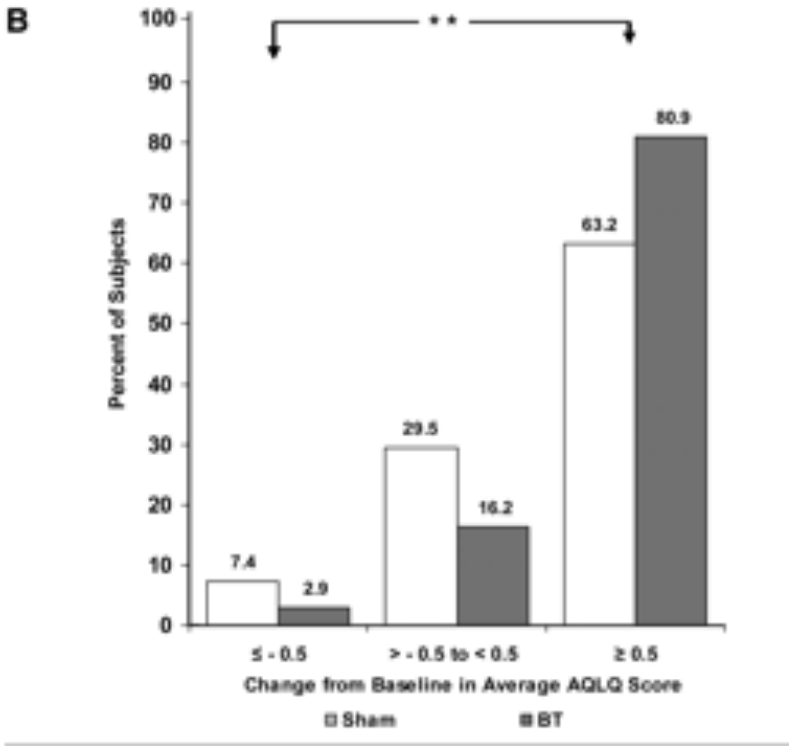
Effective response to IL-4Rα blockade in absence of Type-2 biomarker suggests better biomarkers required!!

Reduction in FeNO, even in low eos patients, on inhaled corticosteroids, supports ongoing Type-2 inflammation



Suggests residual, corticosteroid responsive Type-2 inflammation in large % of patients

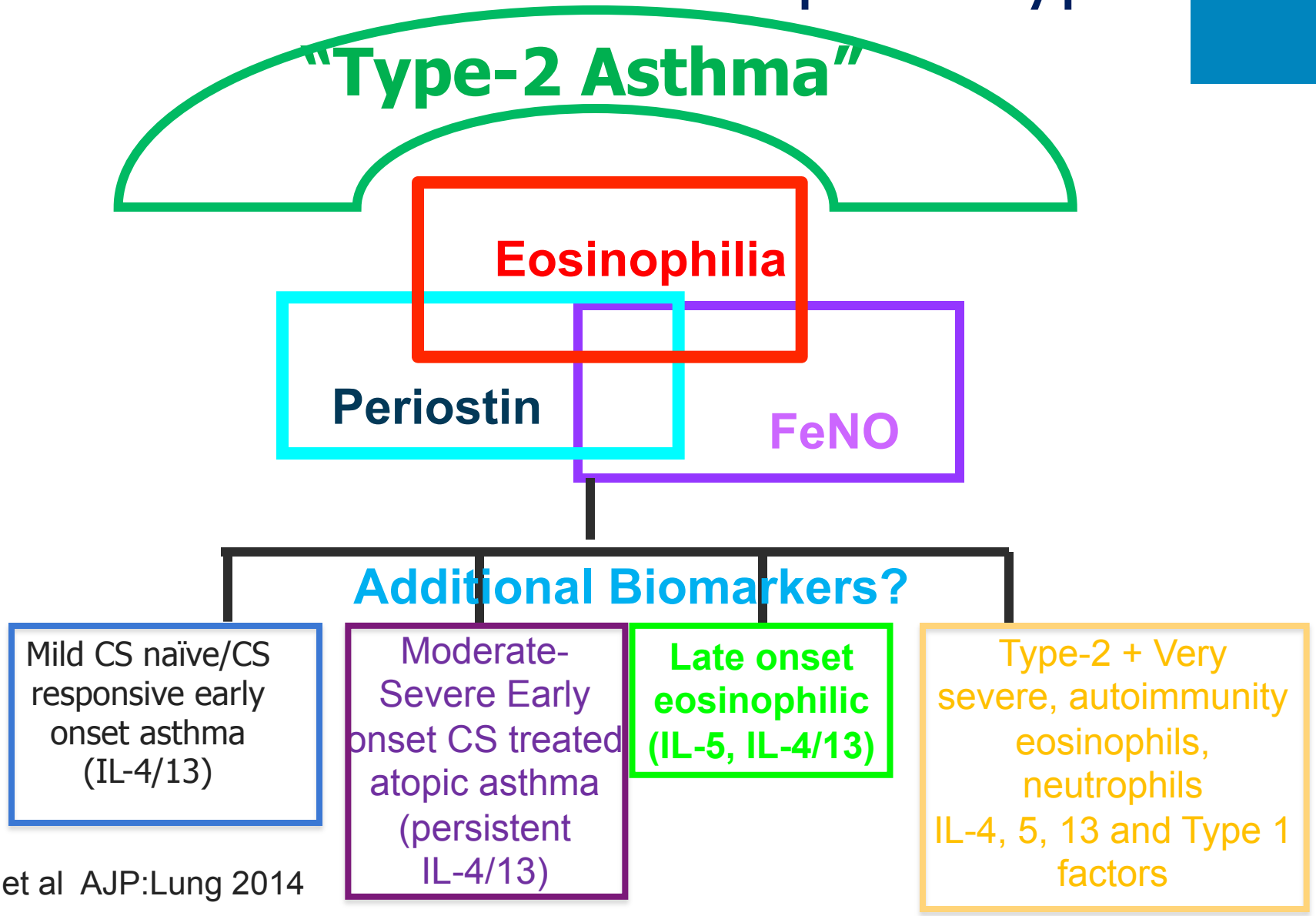
Type 2-Lo:Bronchial Thermoplasty



Castro, M AJRCCM 2010; 181:116-24

- Heat airways to 65^{o}C
- 3 bronchoscopies
- Severe asthmatics excluded on basis of FEV1, sinus disease (rules out many Type 2- HI)
- High # of exacerbations in 1st 3 mos post
- Short term efficacy modest with long term data flawed
- ATS-ERS task force recommends only doing in setting of IRB approved registry or clinical trial

Both Rx responses AND biomarkers are needed to better define phenotypes



Ray A, et al AJP:Lung 2014

Conclusions

- Determine whether the “Difficult Asthma” patient has asthma
- Treat underlying comorbidities and confounders
- Use available biomarkers to identify presence of Type-2 cytokine signature
- Maximize corticosteroids for Type-2 Hi, but consider alternatives, including T2 targeted therapies and diagnostic biopsies, to better understand and treat patients with severe asthma