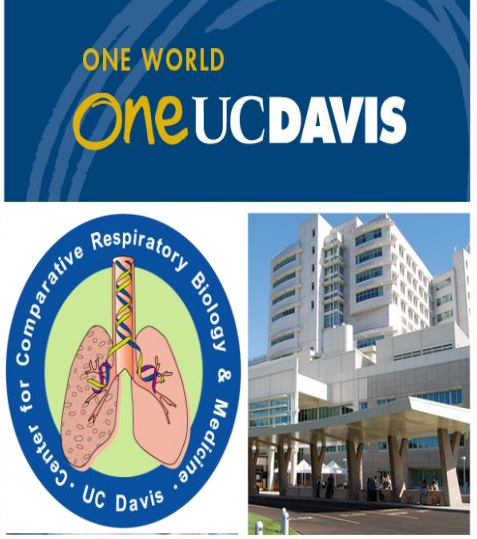


UC DAVIS

PULMONARY, CRITICAL CARE AND SLEEP MEDICINE

roviders' Best Practices Update: sthma

ndian Health Service Conference
acramento, CA
ay 11th, 2016

icholas Kenyon, MD

rofessor and Chief
ivision of Pulmonary, Critical Care, Sleep Medicine
o-Director, UC Davis Asthma Network
niversity of California, Davis

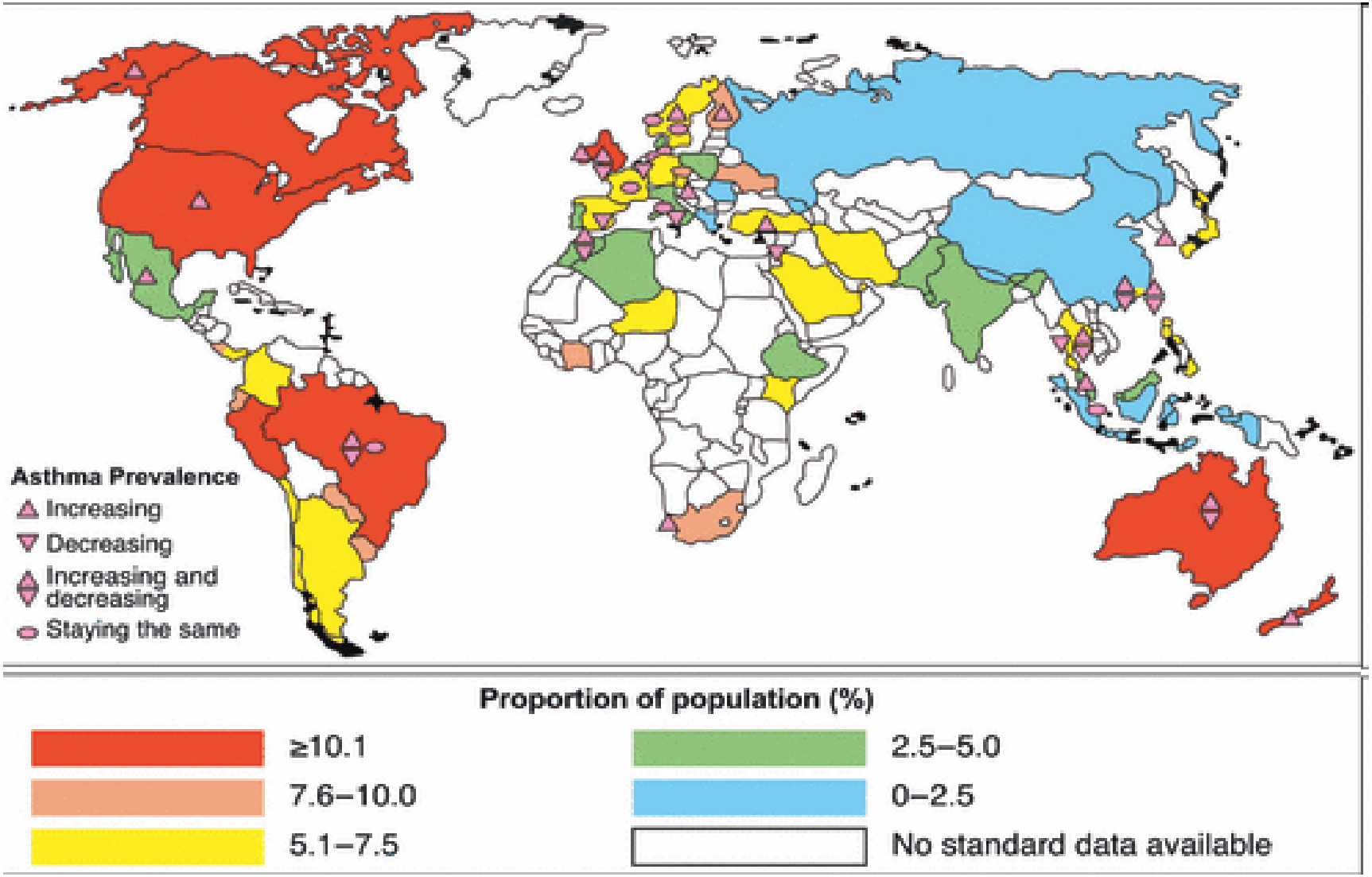
Disclosures

- **Research Support**: NIH-- NHLBI, NIAID, NIBIB, NIEHS, NCATS; CA ARB; INTEL; Hartwell Foundation

Summary: Management of Asthma

- Epidemiology Trends for Asthma
- Definitions and Diagnostic Concerns
- Updates with the Management Guidelines
  - Similarities and Differences
- Novel Therapies for Asthma
- UC Davis Asthma Management Programs

Asthma in the Developed World, 1990-2008



Anandan et al. Allergy 2010

California Department of Public Health, 2010

Summary of Asthma Measures by Race/Ethnicity

Measures (All Ages Unless Otherwise Specified)	Black	AI/AN	White	Hispanic	A/PI
Lifetime Asthma Prevalence (p. 31)	20.8%	21.2%	14.9%	10.0%	12.1%*
Current Asthma Prevalence (p. 31)	13.0%	15.6%	9.0%	5.9%	6.5%*
Percent with Well-Controlled Asthma (adults with current asthma, p. 52)	45.8%	52.0%†	54.7%	48.5%	58.1%*†
Asthma ED Visit Rate (per 10,000, p. 114)	157.5	26.9	38.6	43.2	17.9
Medi-Cal Asthma ED Visit Rate (per 10,000, p. 147)	317.0	227.7	164.9	115.1	60.8
Asthma Hospitalization Rate (per 10,000, p. 128)	29.0	4.7	7.6	8.7	6.1
Percent with Repeat Asthma Hospitalizations (p. 140)	18.8%	4.3%	11.3%	8.9%	10.5%
Medi-Cal Asthma Hospitalization Rate (per 10,000, p. 151)	63.0	31.1	25.3	19.5	17.4
Asthma Death Rate (per million, p. 161)	32.7	6.8	11.5	9.0	15.2*

* Asian only (does not include Pacific Islanders)

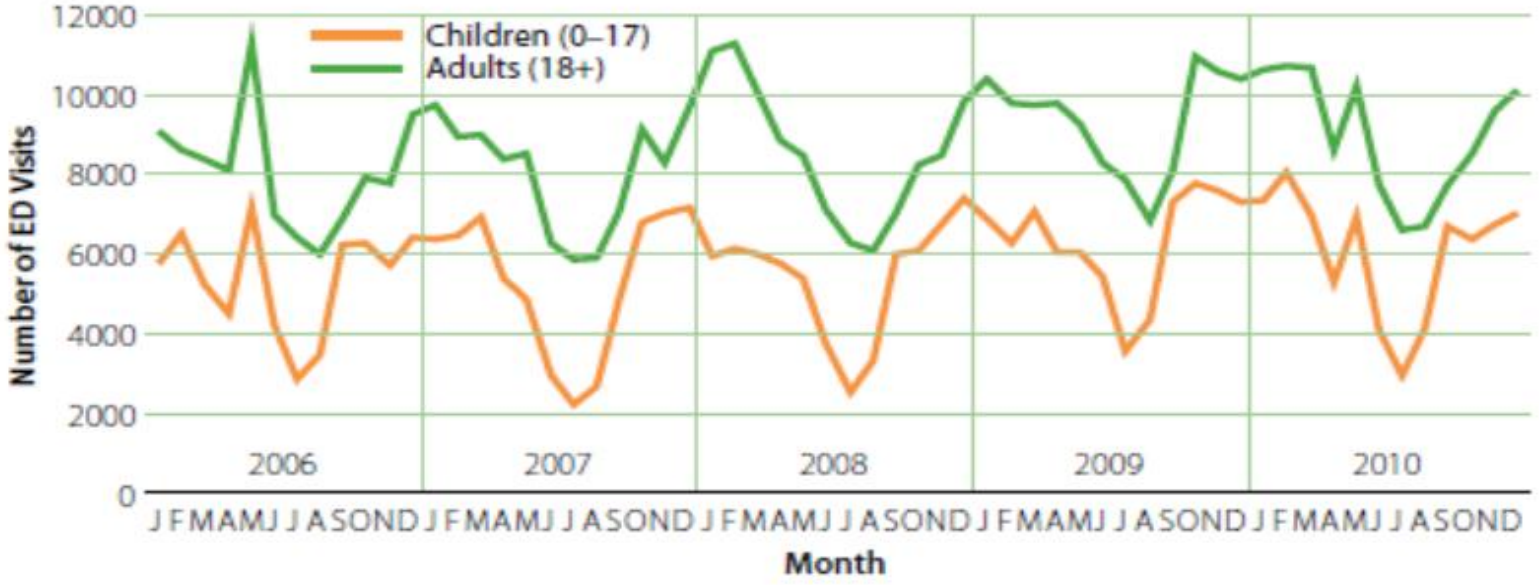
† Unstable estimate – please note the wide confidence interval (see Technical Notes for details).

Factors Associated with ED Visits in California

California Department of Public Health, 2010

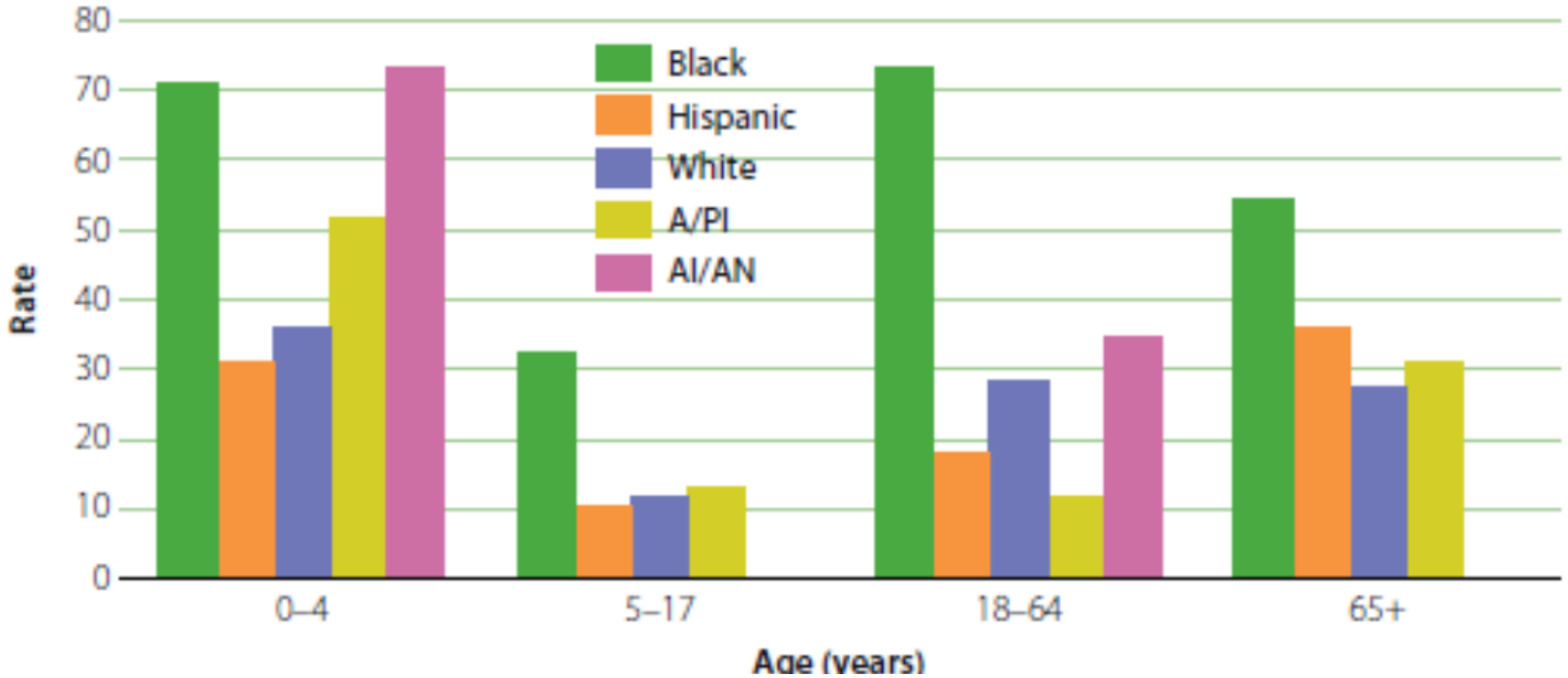
Asthma ED Visits by Month and Age, California 2006–2010

Asthma ED visits show some consistent trends by season. The number decreases in the summer months for both children and adults.



Hospitalizations for Asthma in California

California Department of Public Health, 2010



Medi-Cal Asthma Hospitalizations per 10,000 Continuously Enrolled Beneficiaries by Age and Race/Ethnicity, 2010

COPD is much larger burden in hospital

- 1.5 million Emergency Department (ED) visits for severe COPD exacerbations in United States
  - 726, 000 hospitalizations annually (48%)
  - 270,000 require mechanical ventilation
  - 120,000 deaths annually CDC, 2000
- 2 million Emergency Department (ED) visits attributed to acute asthma exacerbations annually in United States
  - 500,000 hospitalizations annually (25% of visits)
  - 25,000 intubations annually (5% of hospitalizations)
  - 5,000 deaths annually, majority occur outside hospital

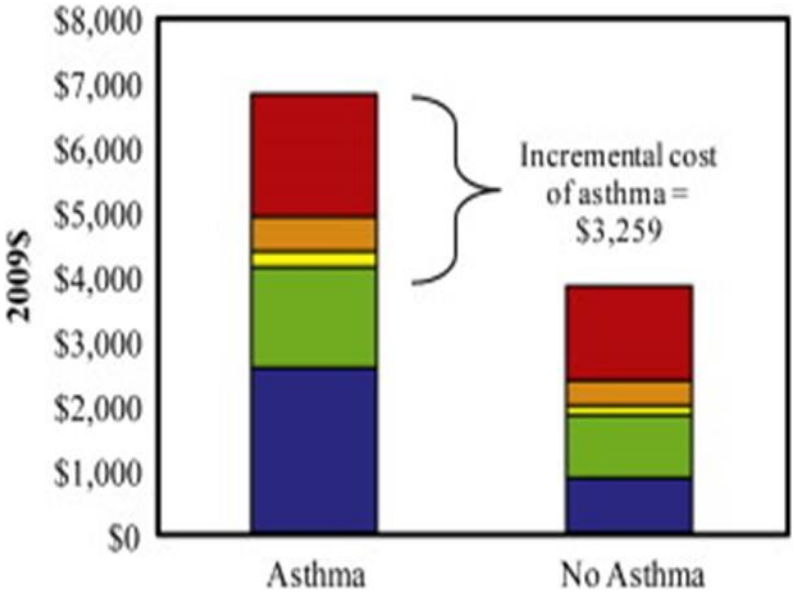
The Soaring Cost of a Simple Breath, NY Times

October 12th, 2013

40 million asthmatics in US; Asthma Costs are $56 billion/yr

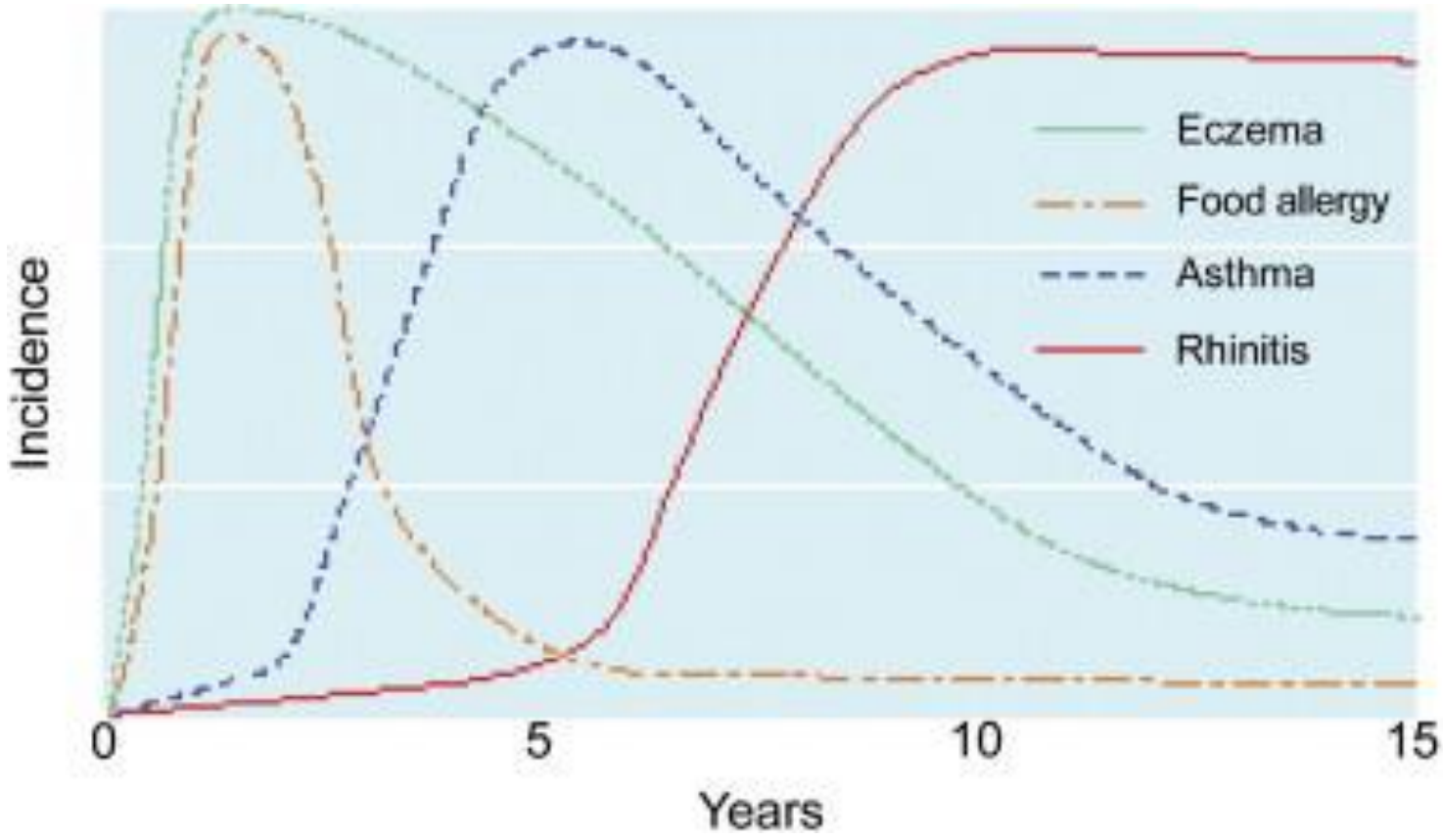
Costs of Asthma in the US and World

Asthma Key Metrics	
US Asthma-diagnosed	61 million
US Asthma-treated	41 million
2007 US total cost	$ 56 billion
2013 US drug market asthma	$ 10 billion
2013 World market asthma	$15 billion
2023 World market asthma	$23 billion



Red: Inpatient costs
Orange: Outpatient costs
Yellow: ED costs
Green: Clinics costs
Blue: Prescriptions

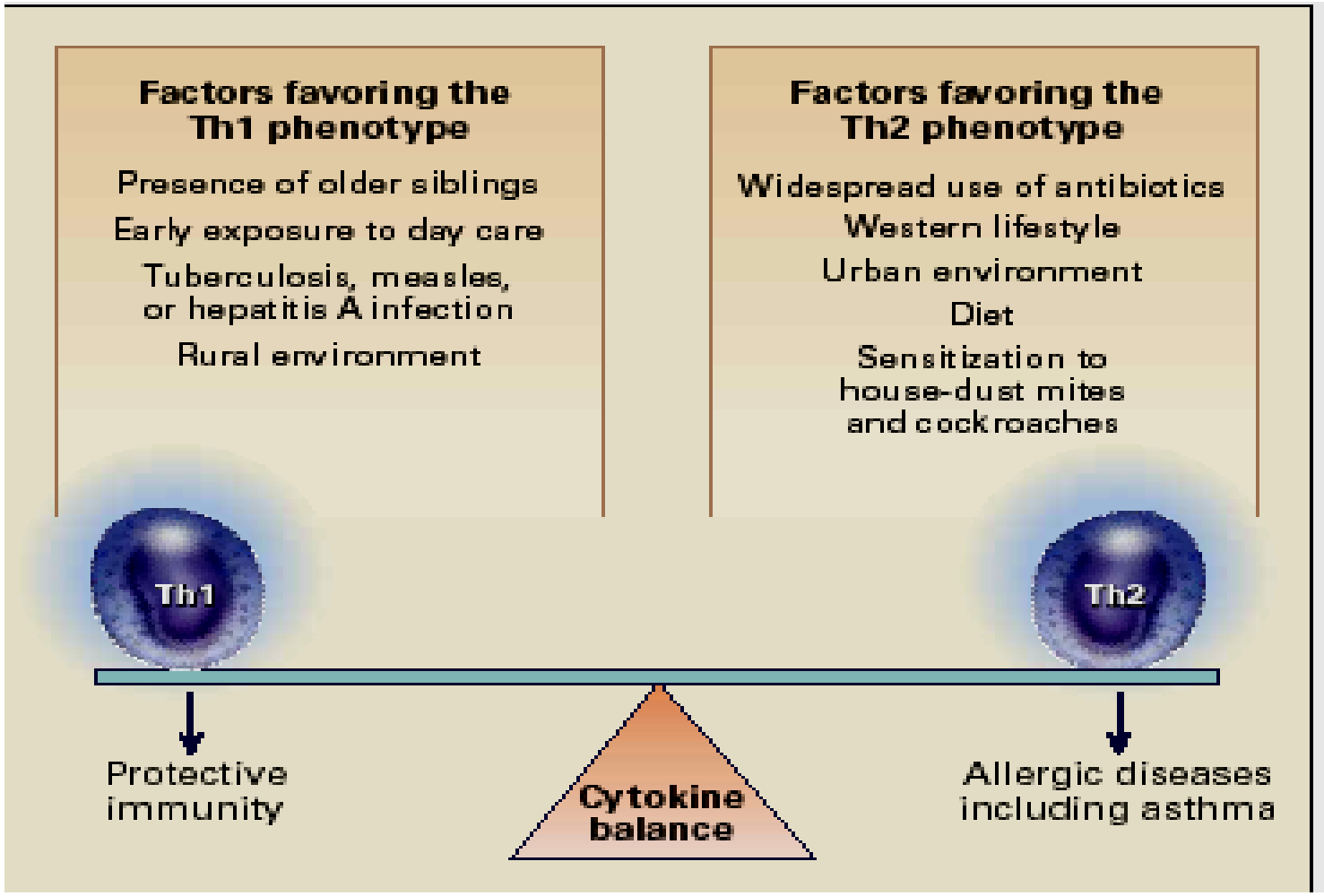
Atopic March—Allergic airway inflammation in early years



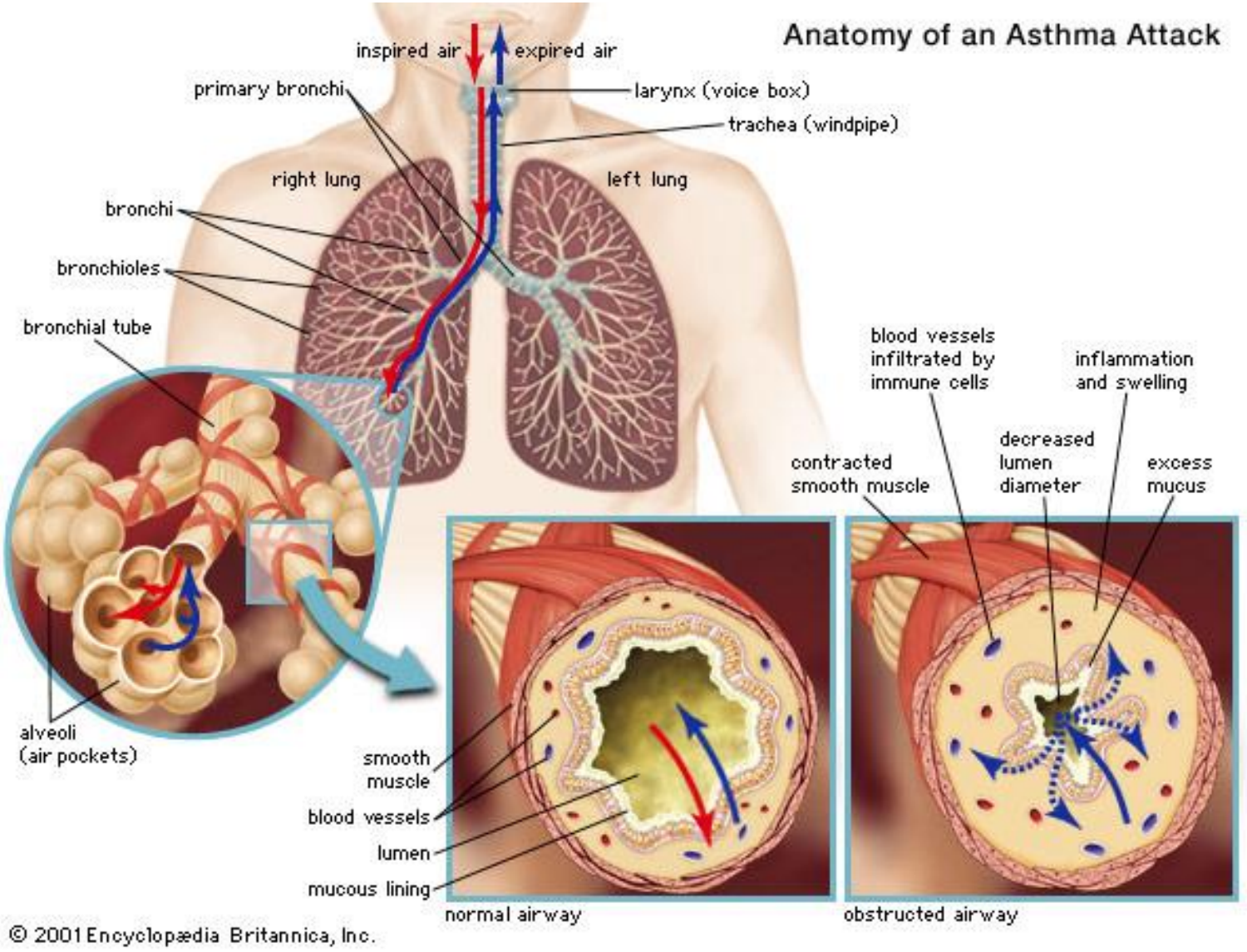
Spergel Ann Asthma All Immunol 2010

The Hygiene Hypothesis

Busse et al. NEJM 2000



What happens to the airway over a lifetime?



“Rhinobronchitis” - Overlap between sinus disease and asthma

- Allergic Asthma and Rhinosinusitis (“Extrinsic”)
- Cough variant asthma
- Chronic cough—GERD or Rhinosinusitis
- Allergic Bronchopulmonary Asthma, Fungal sensitivity
- ASA Exacerbated Respiratory Disease, Nasal Polyposis
- Eosinophilic Granulomatosis with Polyangiitis (Churg Strauss)
- Bronchiectasis, chronic sinopulmonary infections

Severe Asthma: Definition

ATS/ERS Guidelines, Chung et al. ERJ 2014

Asthma which requires treatment with guidelines suggested medications (high dose ICS[#] and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for ≥50% of the previous year to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy

Uncontrolled asthma defined as at least one of the following:

1) Poor symptom control: ACQ consistently >1.5, ACT <20 (or "not well controlled" by NAEPP/GINA guidelines)

2) Frequent severe exacerbations: two or more bursts of systemic CS (>3 days each) in the previous year

3) Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year

4) Airflow limitation: after appropriate bronchodilator withhold FEV_1 <80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal)

Demographics of UBIOPRED cohort

	Severe asthma: non-smoking (308)	Severe asthma: smoking & ex-smoking (110)	Moderate Asthma (98)	Non-asthma (101)	P-value
Age (yr)	50.9	54.5	42.4	38.9	2.9E-17
Female (%)	65.91	50.91	50.00	38.61	5.16E-06
BMI (kg/m^2)	29.08	29.56	25.88	25.31	2.02E-10
Exacerbations in past yr	2.48	2.55	0.37	0	2.51E-26
IgE (IU/ml)	119.5	126	89.4	23.45	5.40E-15
Atopy (%)	69	58	80	38	6.1E-066
Nasal polyps (%)	34.7	33.7	8.3	8.8	1.33E-06
FEV_1 (% pred)	67.42	67.25	88.37	101.76	1.81E-44
Oral corticosteroids (%)	50.68	46.08	1.06	0	9.73E-17
Sputum eosinophils (%)	2.75	4.13	1.05	0.00	2.69E-12
Exhaled NO	27	23.5	25.50	19.00	3.00E-04

Asthma: The Goals of Care

Reduce Symptoms

- Relieve symptoms
- Improve exercise tolerance
- Improve health status

+

Reduce Risk

- Prevent disease progression
- Prevent and treat exacerbations
- Reduce mortality

Asthma management includes both pharmacologic and non-pharmacologic measures

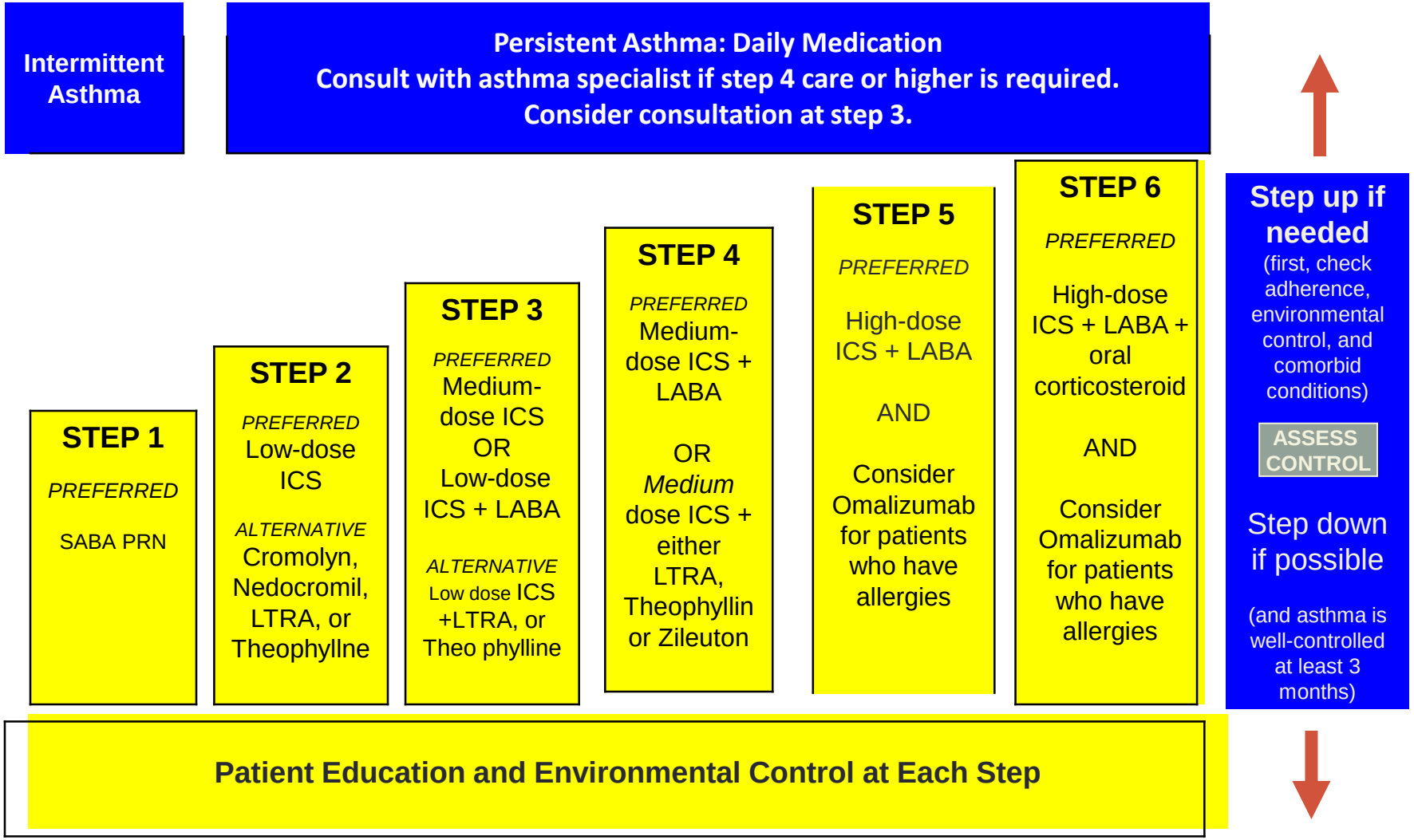
Figure adapted from NHLBI. National Asthma Education and Prevention Program. Full report of the Expert Panel: guidelines for the diagnosis and management of asthma (EPR-3), http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

Approach to Asthma: Classifying Control in Patients ≥12 Years

Components of Control		Classification of Asthma Control (Youths ≥12 years of age and adults)		
		Well-Controlled	**Not Well-Controlled**	**Very Poorly Controlled**
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2x/month	1-3x/month	≥4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting $beta_2$-agonist use for symptom control	≤2 days/week	>2 days/week	Several times per day
	FEV_1 or peak flow	>80% predicted/ personal best	60-80% predicted/ personal best	<60% predicted/ personal best
	Validated questionnaires ATAQ ACQ **ACT**	 0 ≤0.75 **≥20**	 1-2 ≥1.5 **16-19**	 3-4 N/A **≤15**
Risk	Exacerbations	0-1 per year	2-3 per year	>3 per year
	Reduction in lung growth	Evaluation requires long-term follow-up care.		
	Treatment-related adverse effects	Medication side effects vary in intensity. Level of intensity does not correlate to specific levels of control but should be considered in overall assessment of risk.		

NHLBI. National Asthma Education and Prevention Program. Full report of the Expert Panel: guidelines for the diagnosis and management of asthma (EPR-3) Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.

Approach for Managing Asthmatics ≥ 12 Years of Age



NHLBI. National Asthma Education and Prevention Program. Full report of the Expert Panel: guidelines for the diagnosis and management of asthma (EPR-3) DRAFT,

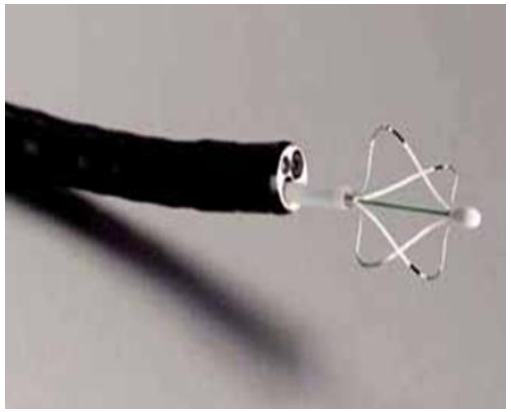
More ‘targeted’ treatments : Asthma vs. COPD

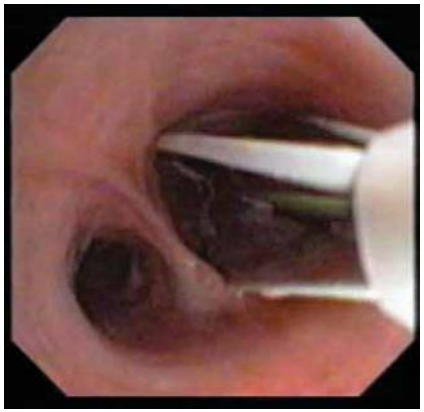
- Leukotriene antagonists
  - Lipoxygenase inhibitor
  - LT receptor antagonist
- Magnesium
- Omalizumab (anti-IgE)

- Bronchial Thermoplasty

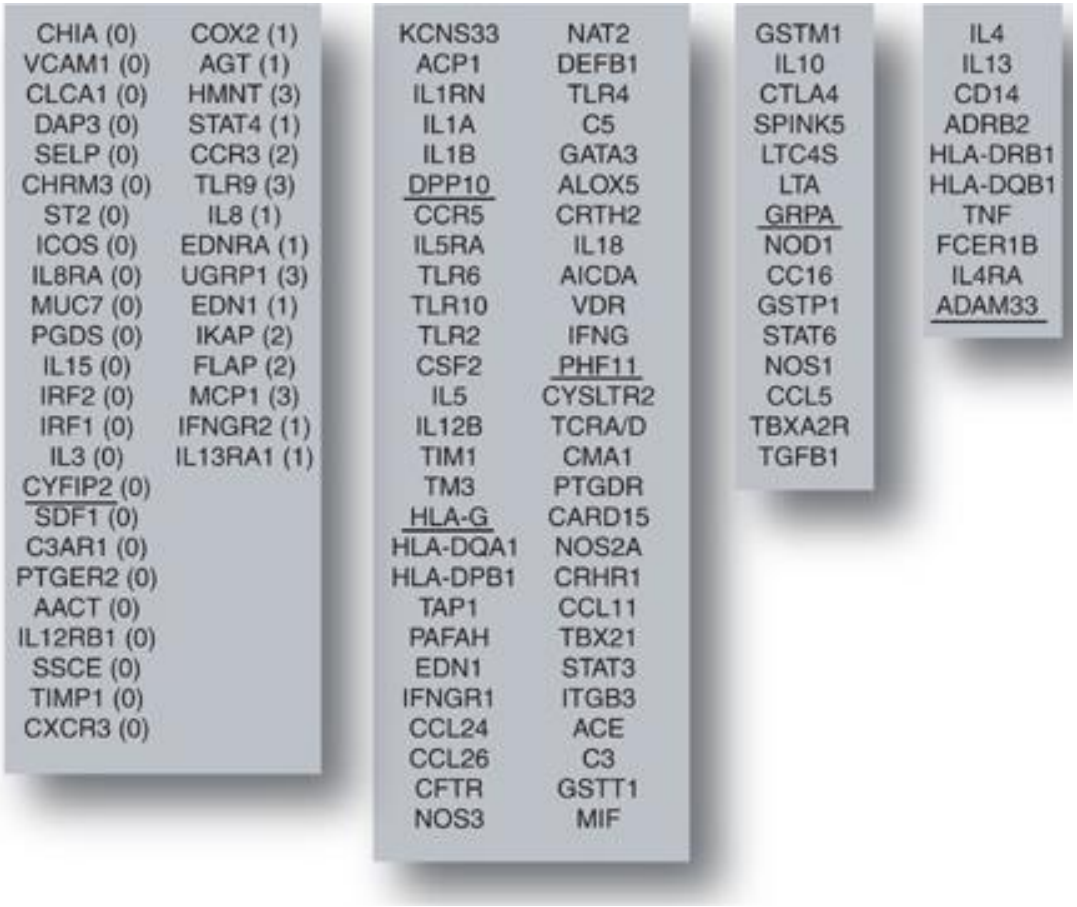
- Roflumilast
- Azithromycin

- Anti-IL5
  - Mepolizumab
- Anti–IL13
  - Lebrikizumab
- Anti-IL4/Anti-IL13
  - Dupilumab





Asthma: Genotyping studies have led to new research avenues, but little change in therapeutics, in asthma.

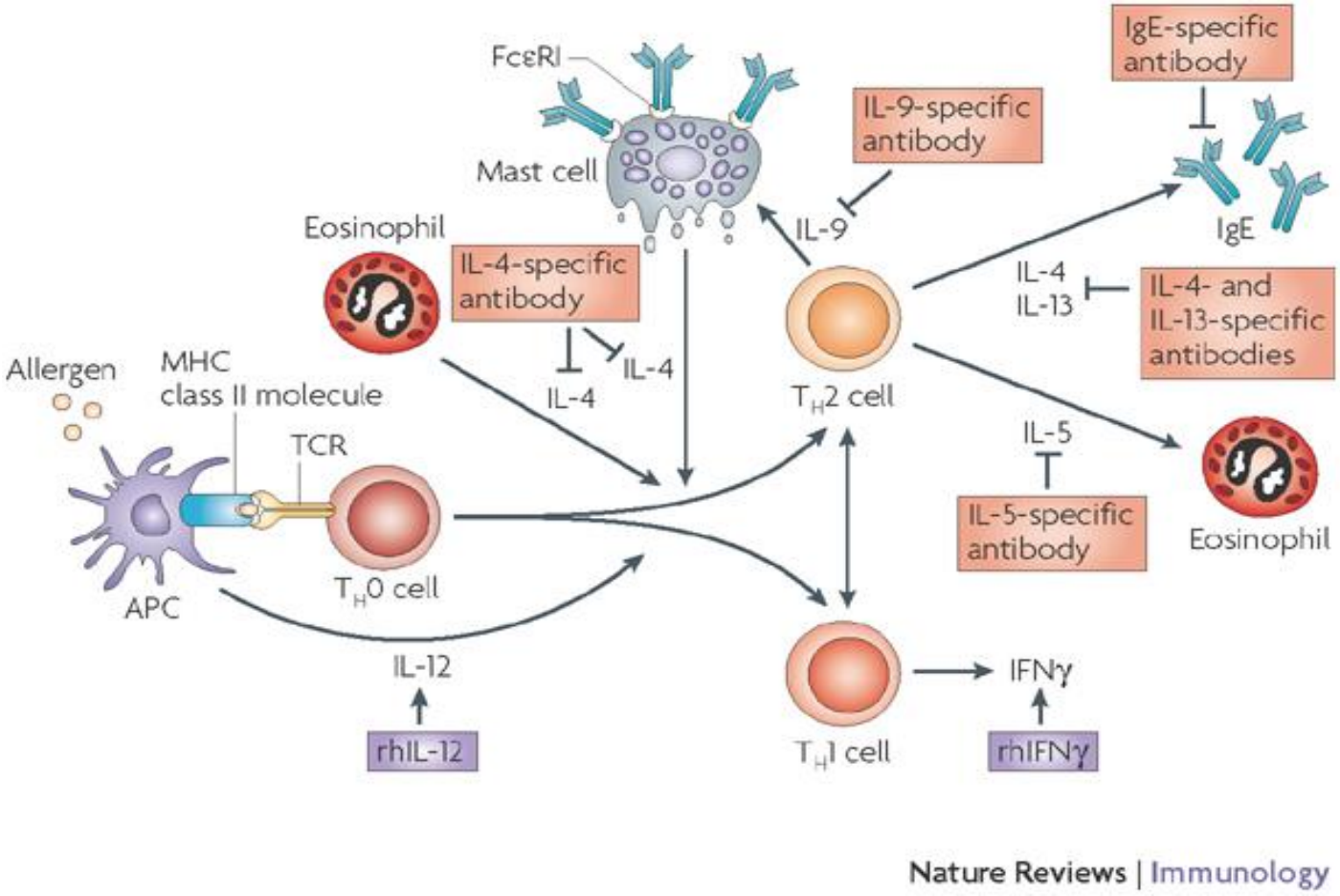


- **>100 genes associated with either asthma or atopy**
- **Most genes are related to either Th2 lymphocyte mediated inflammation or smooth muscle reactivity**

IL4
IL13
CD14
ADRB2
HLA-DRB1
HLA-DQB1
TNF
FCER1B
IL4RA
ADAM33

Ober et al., Genes and Immunity 2007

Cytokines and Effector Cells of Interest in Asthma



Key Cells

Eosinophil

Mast cell

Th2 lymphocyte

Dendritic cell

Key Cytokines

IL-4

IL-5

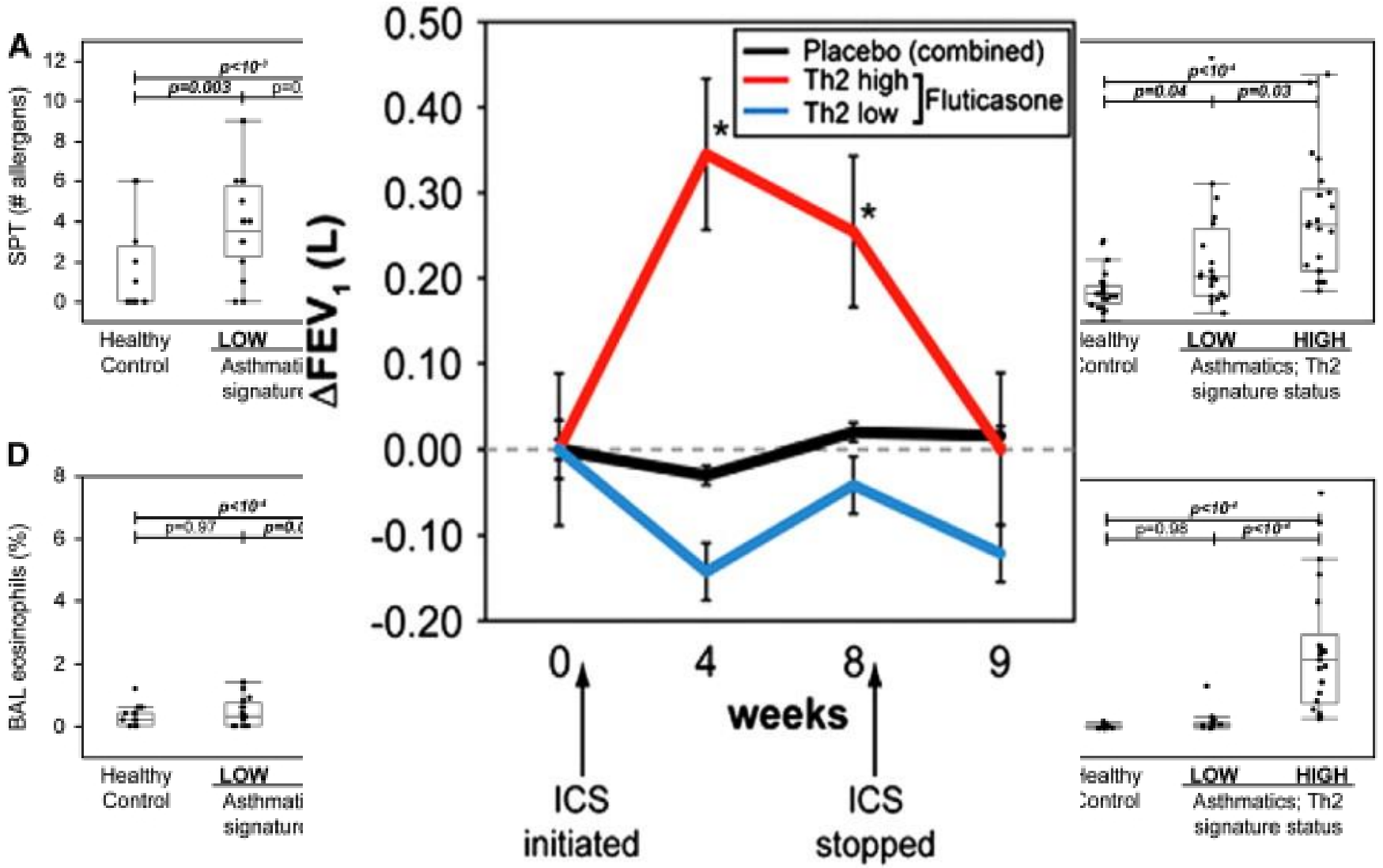
IL-13

IL-17

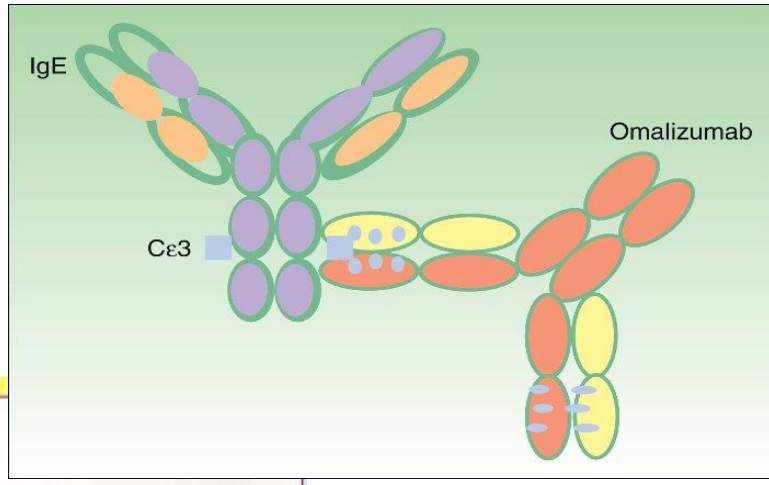
Holgate et al. 2008

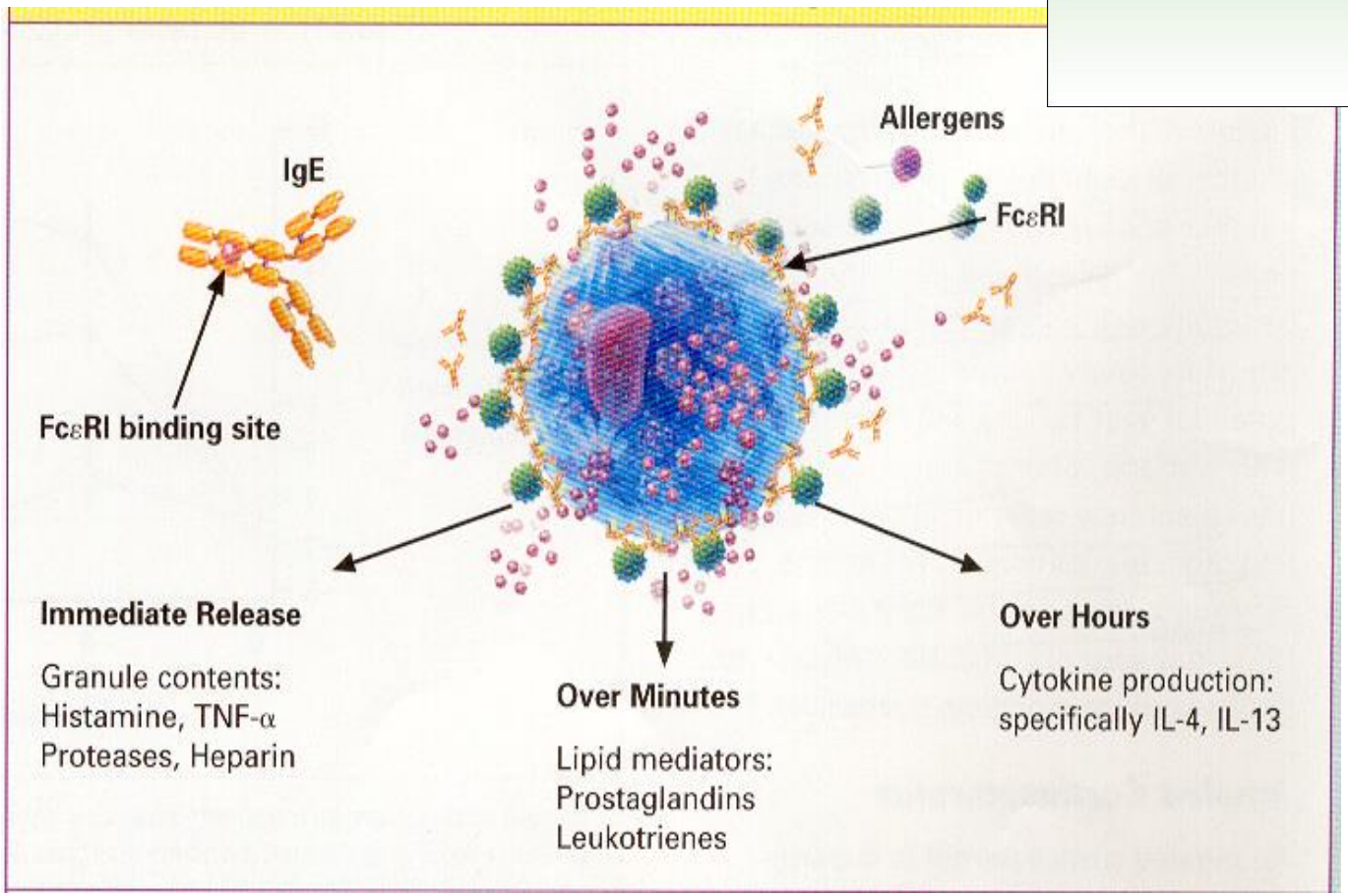
Not all asthmatics respond the same to steroids.
Th2 High vs. Th2 Low Phenotype

Woodruff et al. AJRCCM 2009

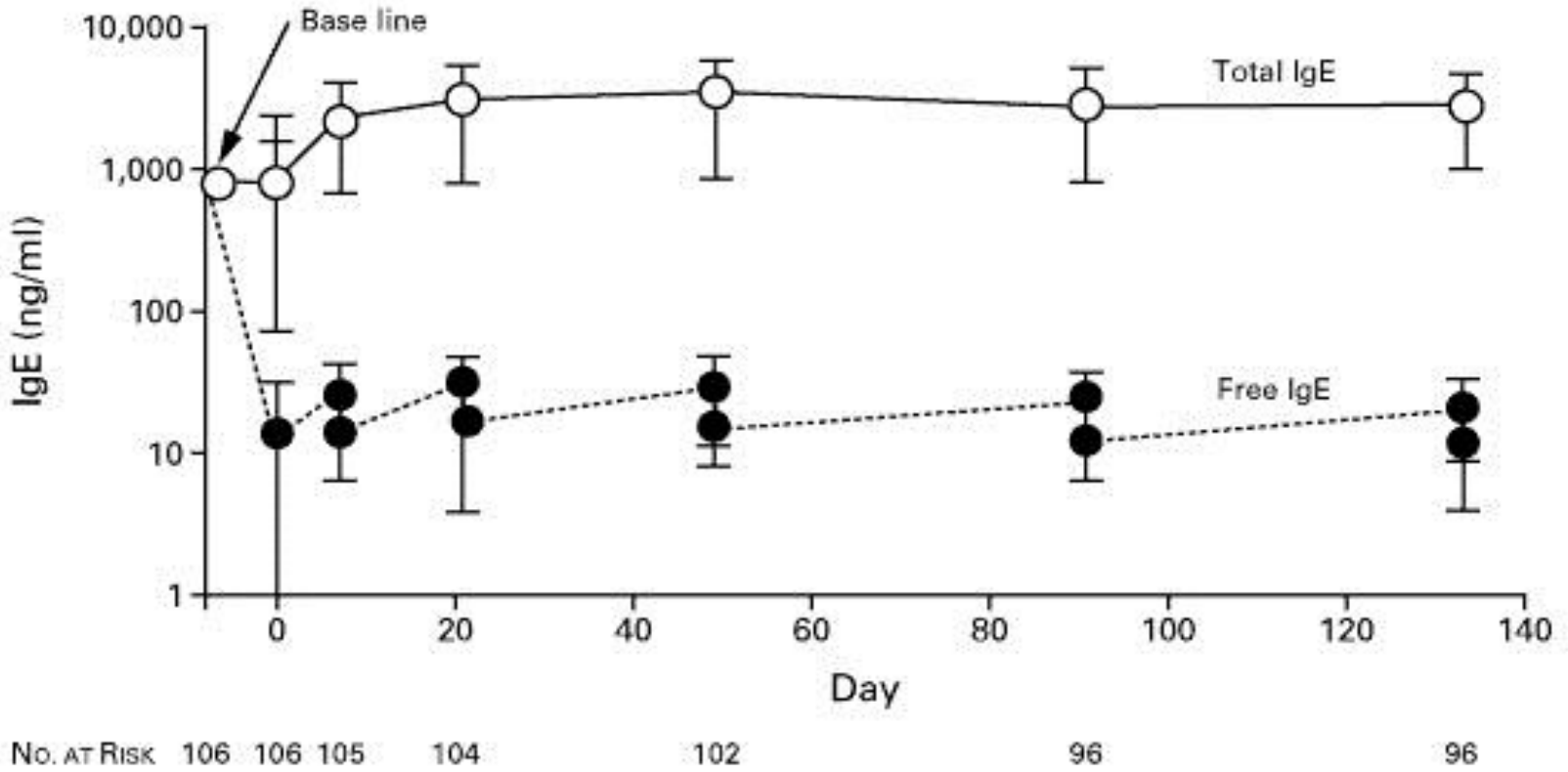


Anti-IgE (Omalizumab, Xolair): Humanized monoclonal anti-IgE antibody





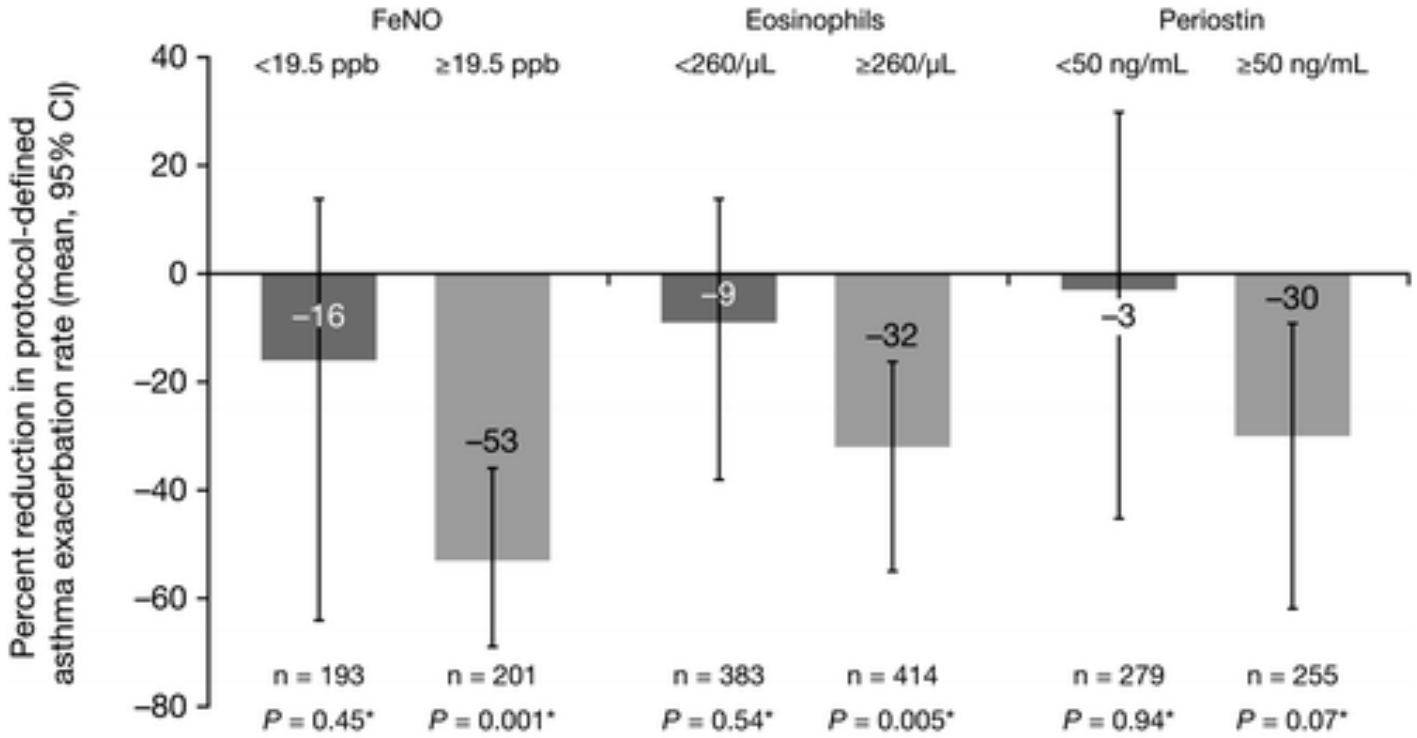
Mean (±SD) Serum Concentrations of Total and Free IgE with low dose omalizumab for 20 Weeks.



Milgrom H et al. N Engl J Med 1999;341:1966-1973.

Omalizumab: Analysis of Biomarkers, 10 yrs experience

Hanania et al AJRCCM 2013



	Exacerbation rates					
	Low FeNO at baseline	High FeNO at baseline	Low eosinophils at baseline	High eosinophils at baseline	Low periostin at baseline	High periostin at baseline
Omalizumab	0.60	0.50	0.65	0.70	0.73	0.66
Placebo	0.71	1.07	0.72	1.03	0.72	0.93

2007 and 2011 Joint Task Force Report on omalizumab - associated anaphylaxis.

TABLE II. Summary of timing of Xolair (omalizumab) adverse reactions

Timing of the reaction	First-third Xolair (omalizumab) dose (no. of events)	Fourth or later Xolair (omalizumab) dose (no. of events)	Total
<30 min	11	5	16
30-60 min	6	1	7
1-2 h	5	0	5
2-12 h	4	1	5
>12 h	3	0	3
Unknown	3	2	5
Total	32	9	41

Summary of the joint task force's 2007 recommendations*

1. **Informed consent**: should be obtained from the patient after discussing the risks, benefits, and alternatives to omalizumab (Xolair).

2. **Anaphylaxis education**: educate the patient on the signs, symptoms, and treatment of anaphylaxis.

3. **Epinephrine auto-injector**: prescribe and educate the patient on the proper use of and advise patients to carry an epinephrine autoinjector before and for 24 hours after omalizumab (Xolair) injection.

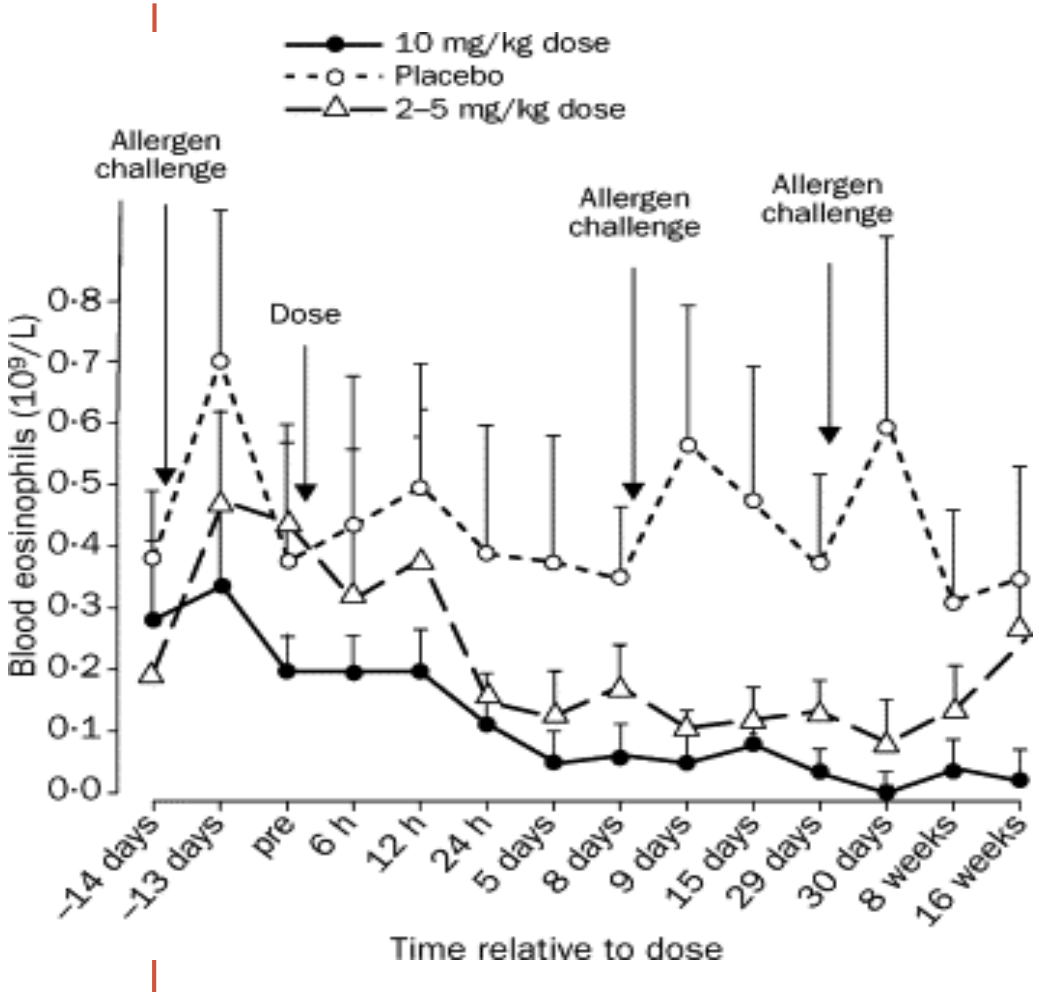
4. **Pre-injection health assessment**: assess health status, including vital signs and some measure of lung function (eg, peak expiratory flow or FEV1).

- 5. **Wait period after injection**: patients should be kept under observation for 30 minutes after each injection. This time should be extended to 2 hours after each of the first 3 injections.

Effects of humanized monoclonal anti-IL5 Ab on blood/sputum eosinophils, airway hyper-responsiveness, late asthmatic response.

Leckie MJ[1], et a al. Lancet. 2000

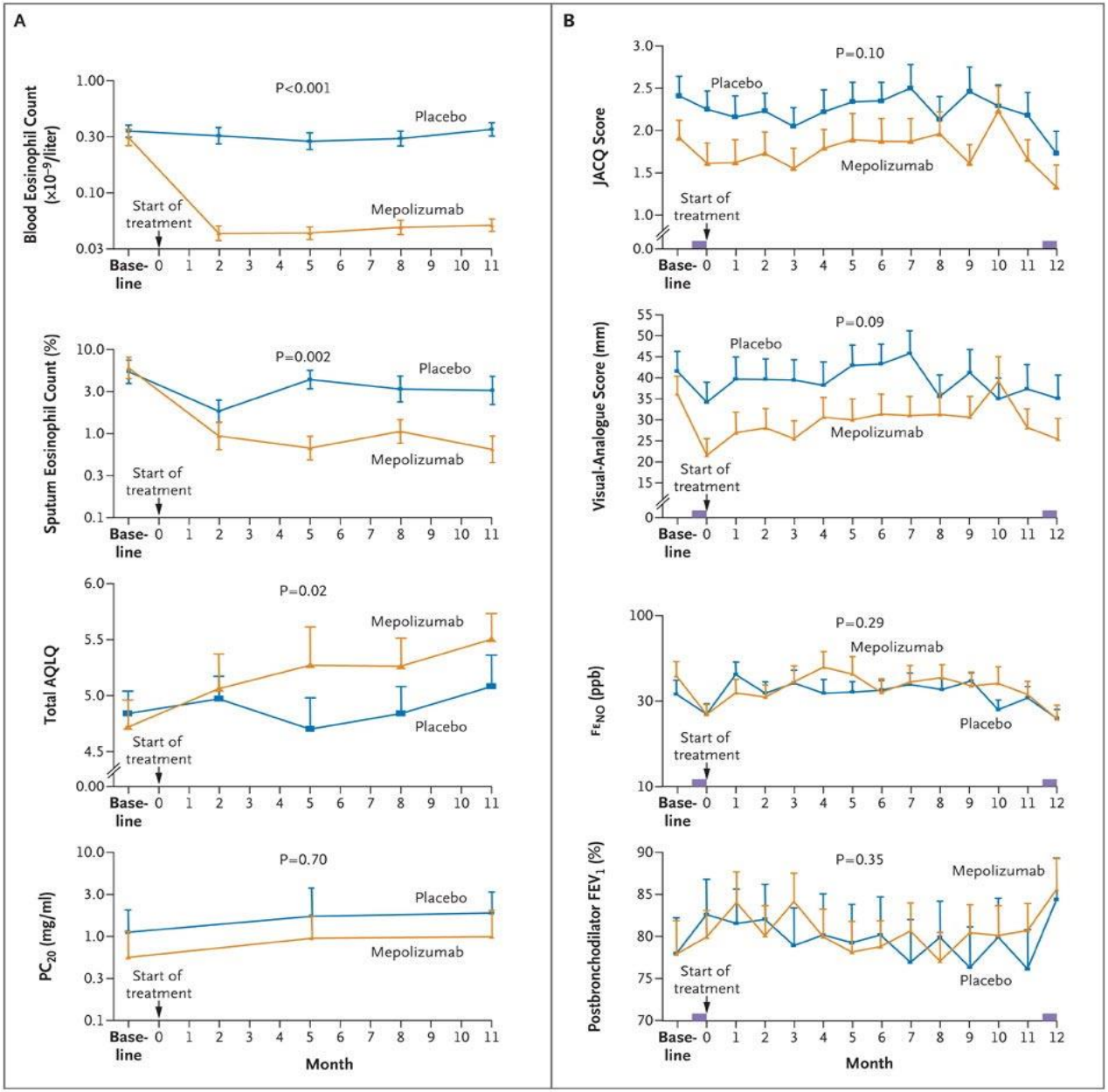
- 24 mild asthmatic subjects given single dose of anti IL5 antibody or placebo
- 3 inhaled allergen challenges were performed to assess EAR and LAR
- Primary endpoint was blood and sputum eosinophil counts after allergen challenge
- No effect on asthma response



Mepolizumab in Refractory Eosinophilic Asthma, NEJM 2009

- Single center, RCT with placebo (Europe)
- 60 asthmatics with refractory asthma and >3% sputum eos despite high-dose ICS
- Mepolizumab 750mg IV monthly or placebo for 1 year
- 40% reduction exacerbations (oral steroids) in mepolizumab group

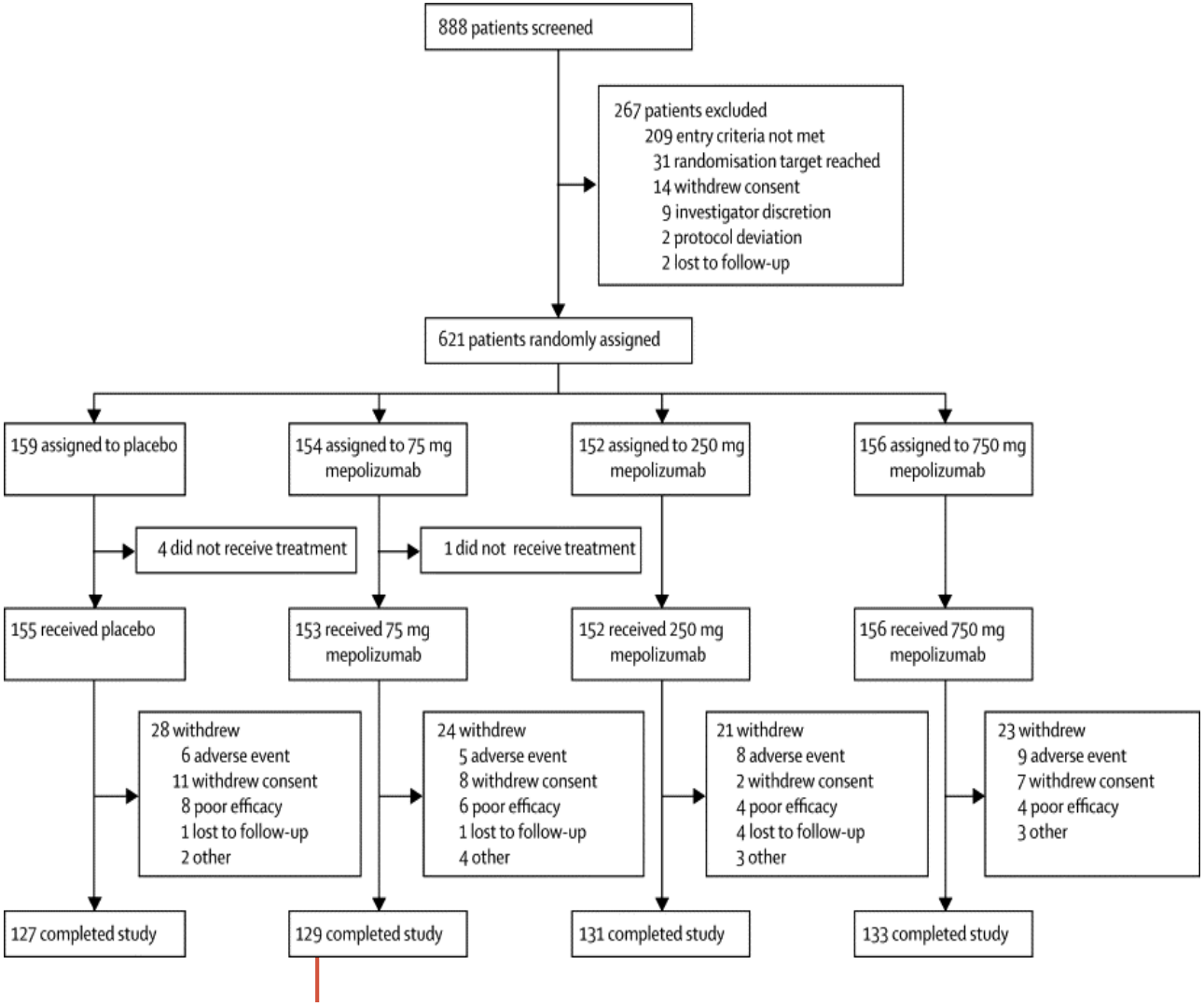
Haldar P N Engl J Med 2009;360:973-9



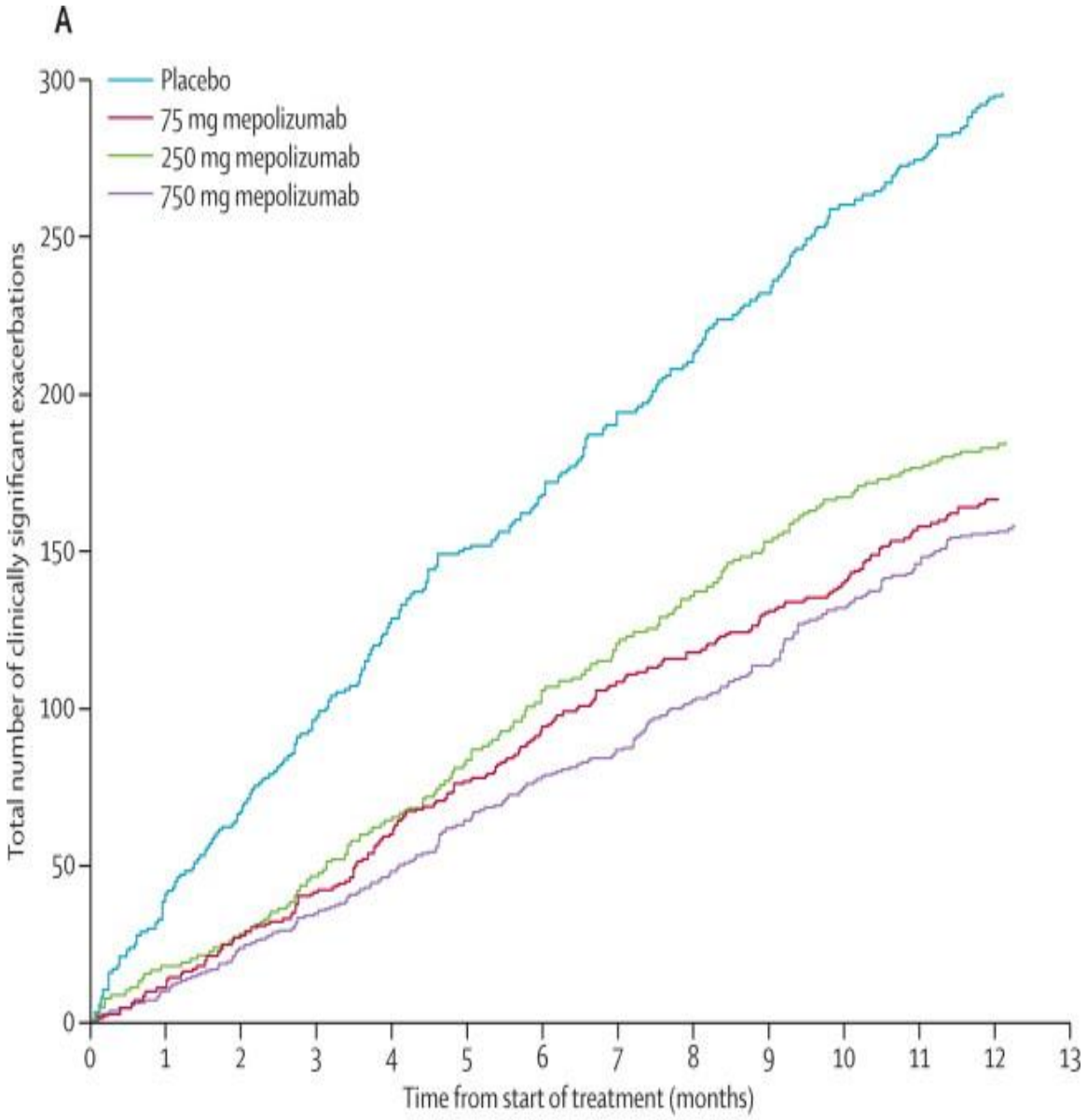
Mepolizumab in severe eosinophilic asthma (DREAM)

Pavord et al. Lancet 2012

- 81 center RCT, 1:1:1:1 randomization
- Severe asthma with 2 oral steroid bursts/yr
- Sputum eos >3% or FeNO > 50 ppb or blood eos >300/ml
- Primary outcome: oral steroid bursts, ED visit, hospital

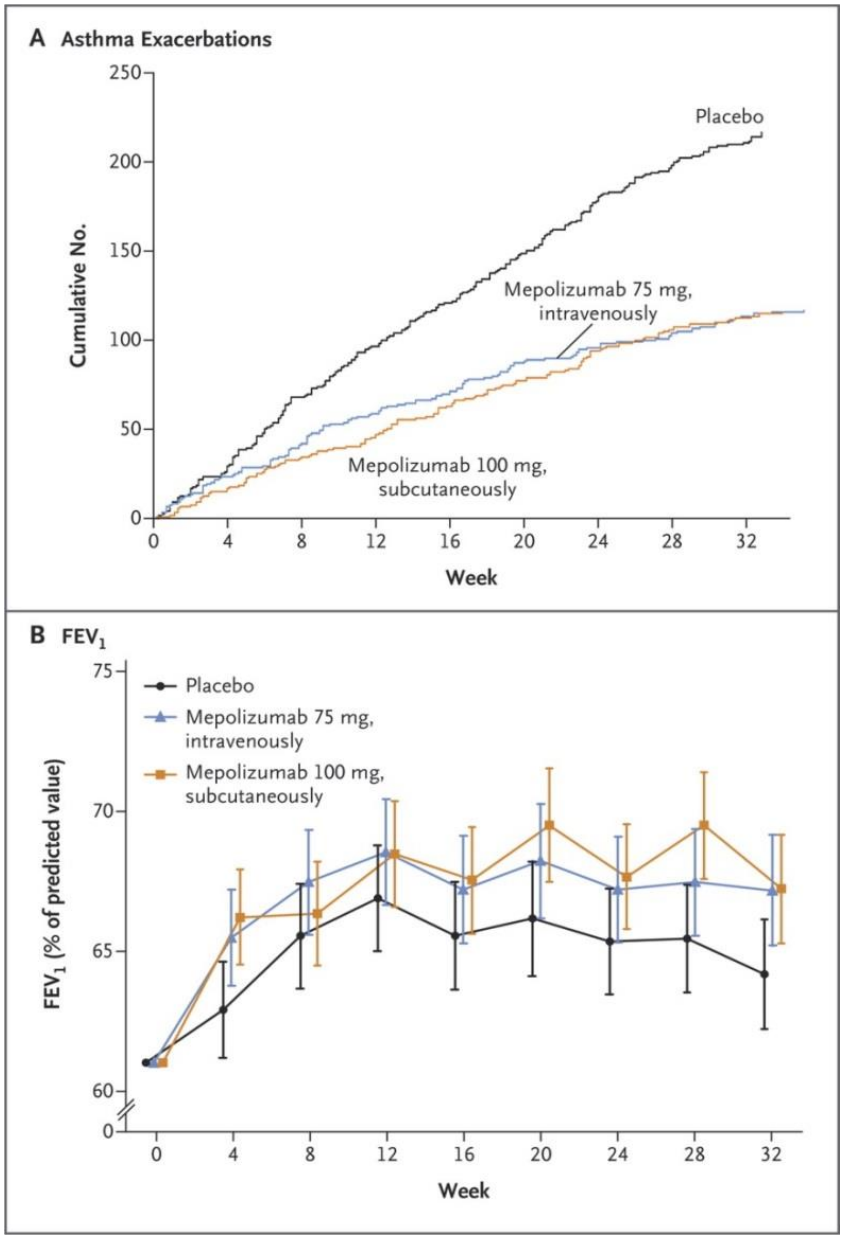


DREAM: All doses of IV mepolizumab decreased asthma exacerbations



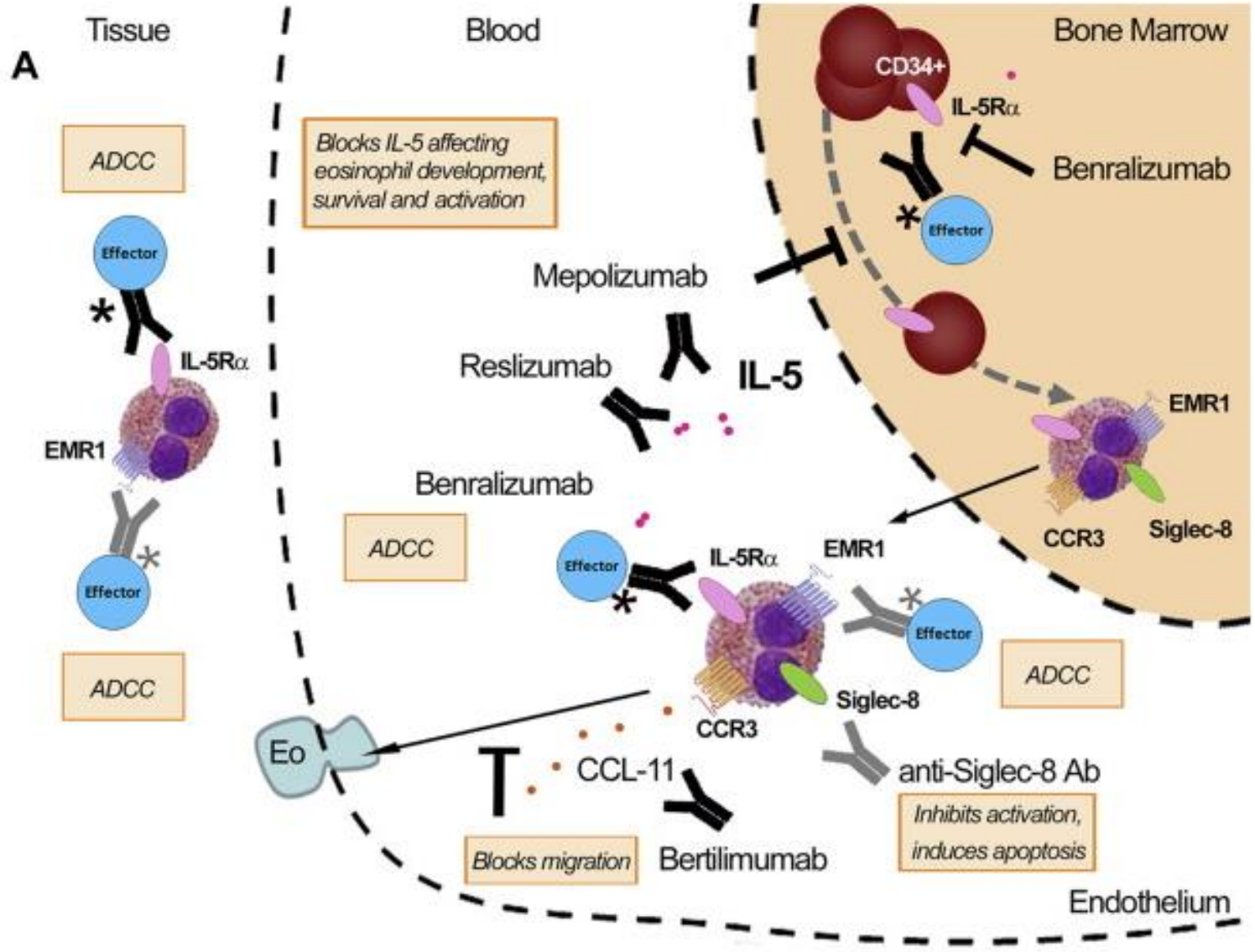
IV vs Subcutaneous Mepolizumab, Asthma Exacerbations and FEV_1

- Multicenter, RCT with 576 asthmatics with high eosinophil counts and recurrent asthma exacerbations despite high dose ICS + LABA, and FEV1 < 80% predicted
- Randomized to 100 mg sq, 75 mg IV, or placebo monthly
- RESULT: The rate of exacerbations was reduced by 47% among patients receiving intravenous mepolizumab and by 53% among those receiving subcutaneous mepolizumab, as compared with those receiving placebo



Ortega HG et al. N Engl J Med 2014;371:1198-1207.

N Engl J Med. 2014 Sep 25;371(13):1189-97. doi: 10.1056/NEJMoa1403291.
Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma.
Bel EH[1], Wenzel SE, et al.

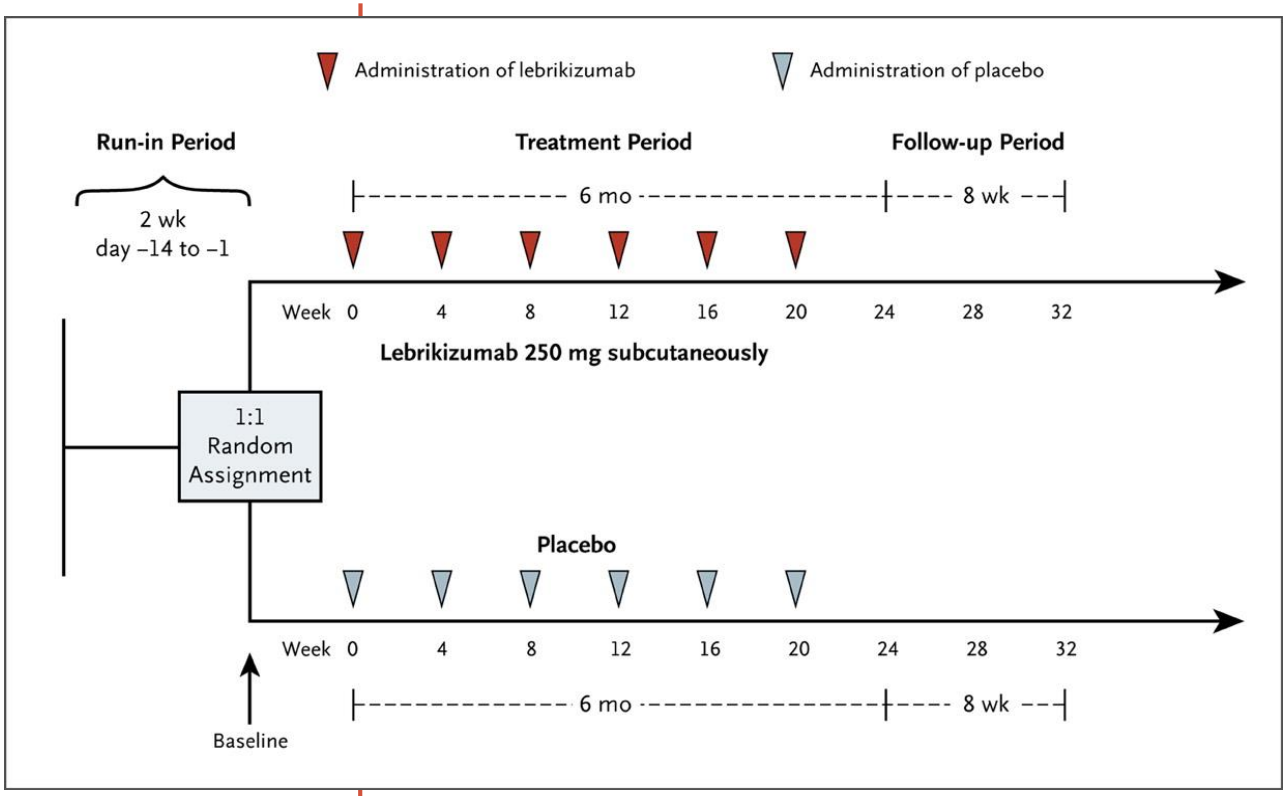


Mechanism of action of biologic therapies for treatment of allergic asthma
Fajt et al JACI 2014

Study Design for Anti-IL13 (lebrikizumab)

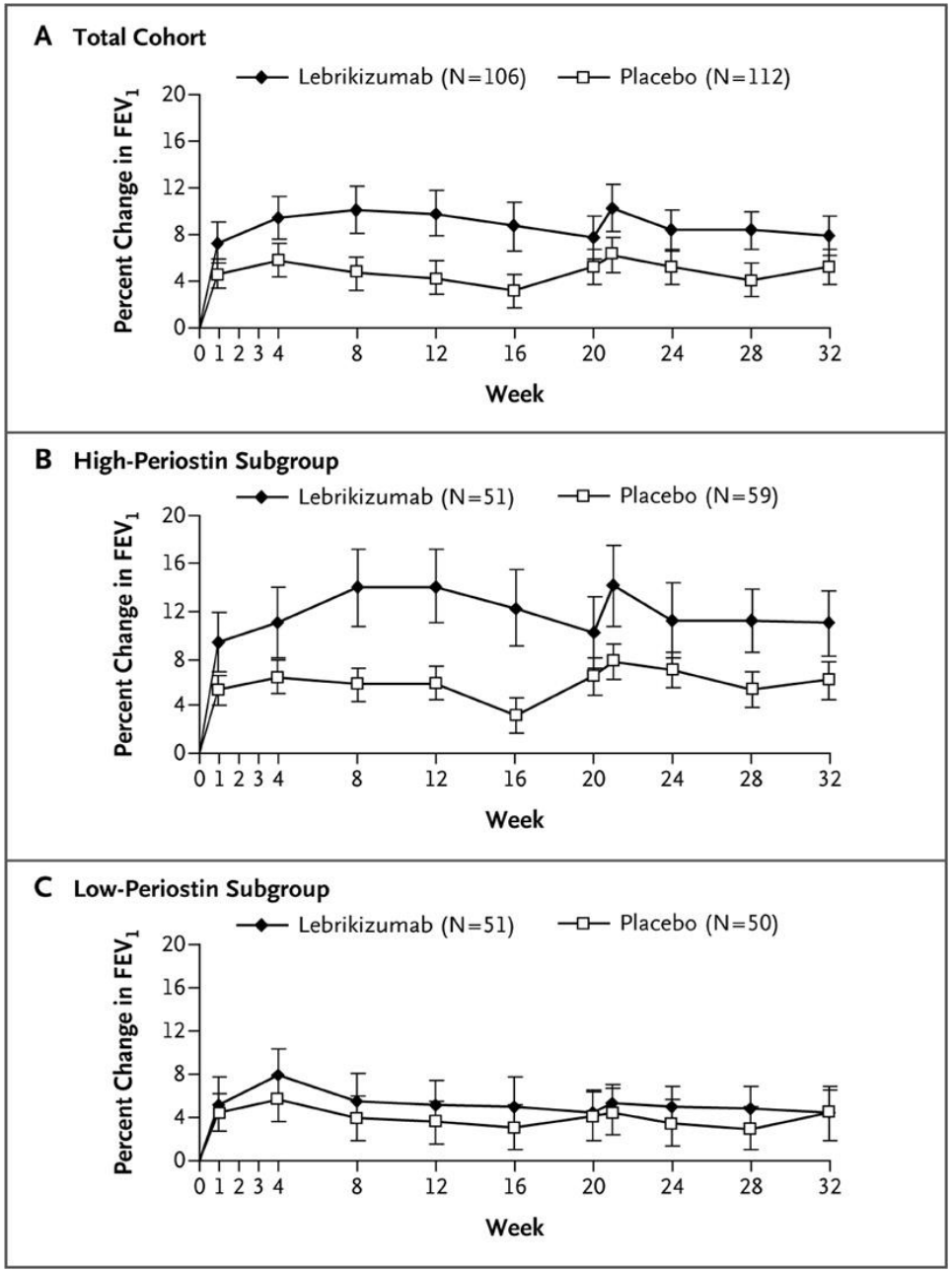
Corren J et al. N Engl J Med 2011;365:1088-1098.

- Multicenter RCT
- 220 uncontrolled asthma subjects had Th2 status assessed by IgE level and blood eosinophils
- Anti-IL13 sq monthly
- Primary outcome was % change in FEV1



Effects of lebrikizumab on FEV1

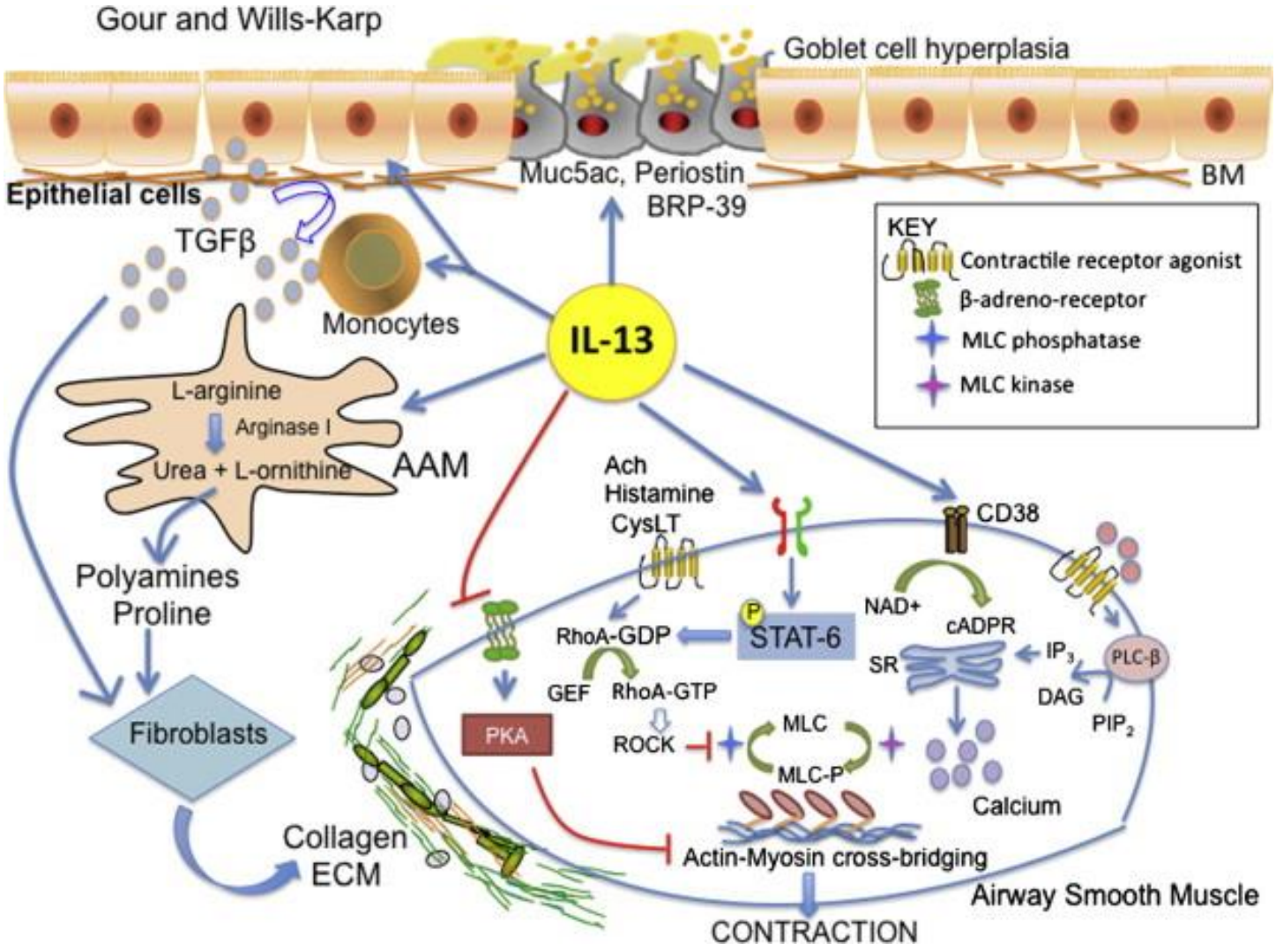
- Periostin is an extracellular matrix protein that is induced by interleukin (IL)-4 and IL-13 in airway epithelial cells and lung fibroblasts. It has also been shown to predict response to treatment with inhaled corticosteroids in patients with these characteristics.



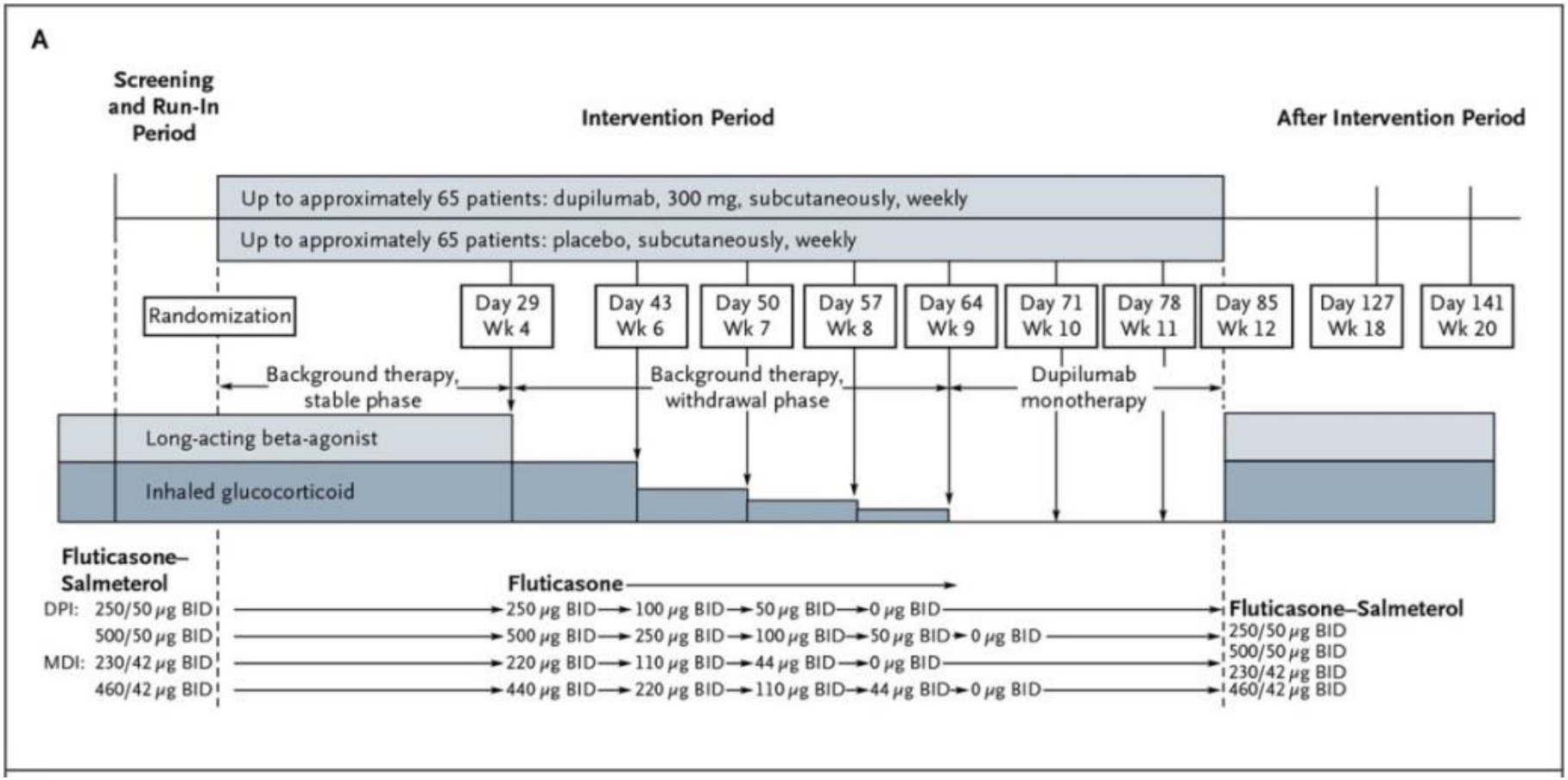
Corren J et al. N Engl J Med 2011;365:1088-1098.

IL-4 and IL-13 signaling in allergic airway disease

Naina Gour, Marsha Wills-Karp Cytokine 2015

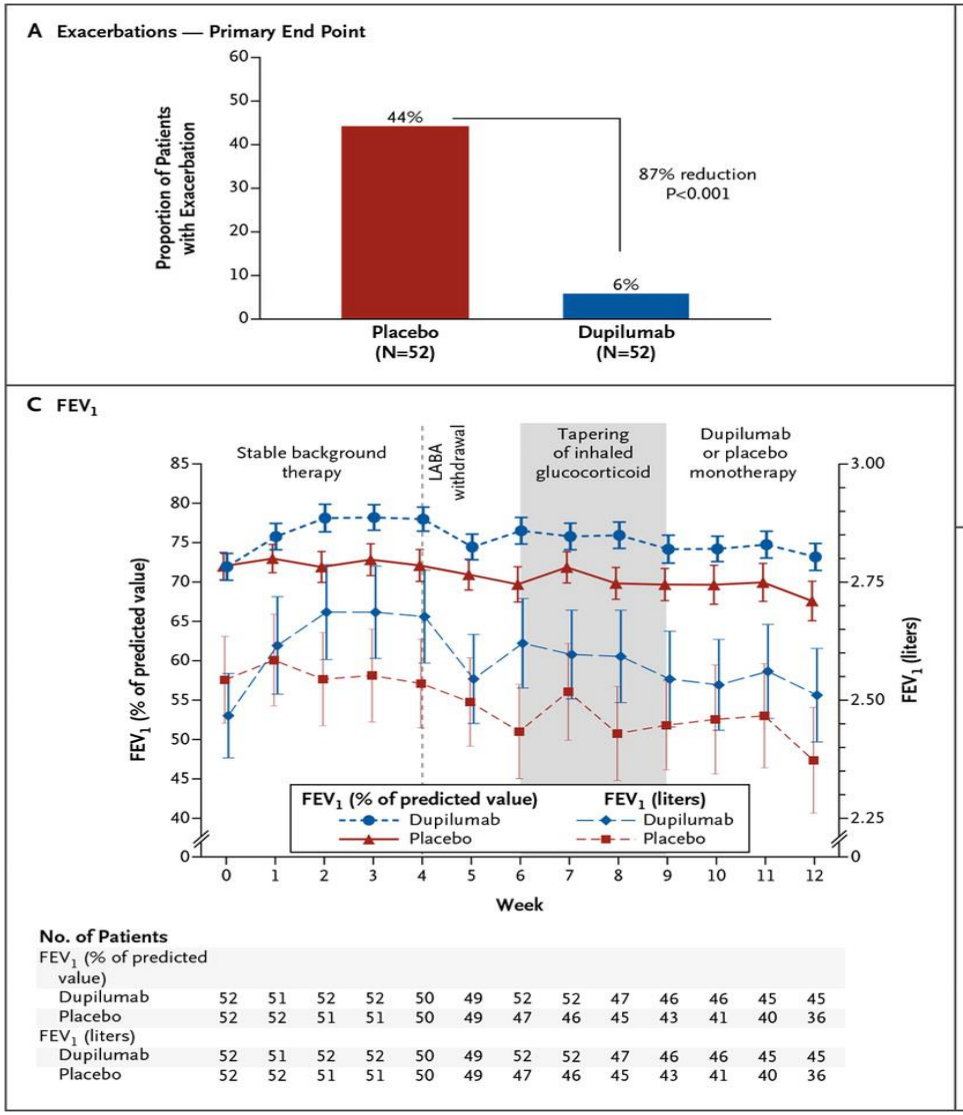


Dupilumab (IL-4Rα/ IL-13Rα1) in persistent asthma with elevated eosinophil level



Wenzel S et al. N Engl J Med 2013;368:2455-2466.

Dupilumab (IL-4Rα/ IL-13Rα1): Primary and Secondary End Points

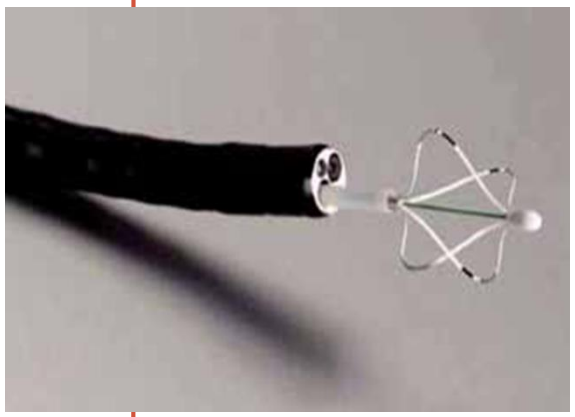


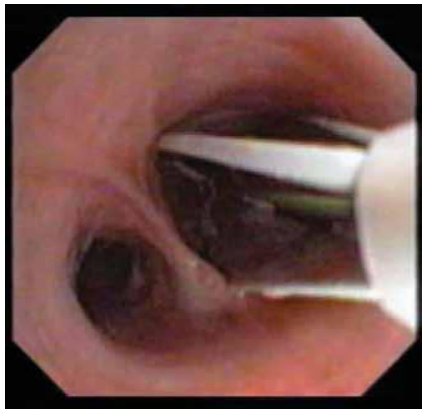
Wenzel S et al. N Engl J Med 2013;368:2455-2466.

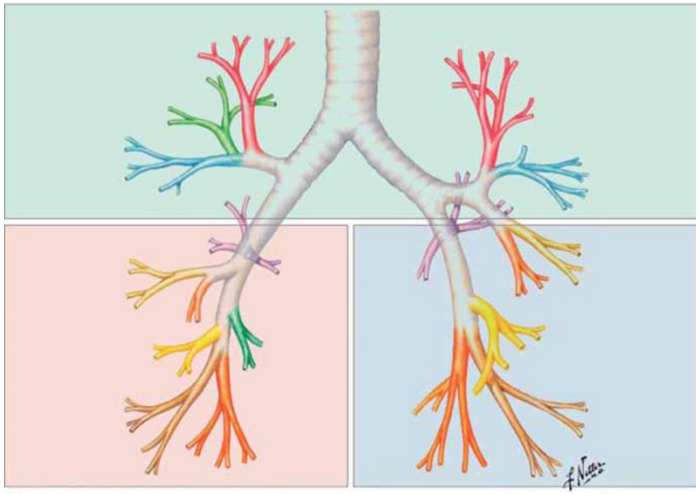
Target	Drug	Mechanism of action	Status
IL-5	Mepolizumab SB-240563	••Block IL-5	••Submitted to the FDA for asthma in November 2014 ••Ongoing trials in asthma, COPD, HES, EoE, EGPA, nasal polyposis, and eosinophilic cystitis
	Reslizumab SCH55700		••Phase 3 trials in asthma and EoE completed and open-label extension ongoing
IL-5Rα	Benralizumab MEDI-563	••Inhibits IL-5 binding to receptor ••Depletes eosinophils through enhanced ADCC	••Ongoing trials in asthma, COPD, and HES
CCL-11	Bertilimumab	••Blocks CCL-11	••Not yet recruiting in ulcerative colitis and bullous pemphigoid; planned in asthma
Siglec-8		••Induces eosinophil apoptosis	••In preclinical development
IgE	Omalizumab *Xolair*	••Blocks IgE	Ongoing trials in mastocytosis, chronic urticaria, asthma, AERD, nasal polyposis, EoE, eosinophil gastroenteritis, and hyper-IgE syndrome
IL-4Rα/ IL-13Rα1	Dupilumab REGN668 AMG 317	••Inhibit binding of IL-4 and/or IL-13 to IL-4Rα	••Ongoing trials in asthma, nasal polyposis, atopic dermatitis, and ulcerative colitis ••Ongoing trials in asthma
IL-13	Lebrikizumab ILR1444A Tralokinumab Anrukinzumab	••Block IL-13	••Ongoing trials in asthma and idiopathic pulmonary fibrosis ••Ongoing trials in asthma, ulcerative colitis, and idiopathic pulmonary fibrosis
IL-4/IL-13	QBX258 VAK694 +QAX576 SAR156597 Bispecific antibody	••Block both IL-4 and IL-13	••Ongoing trials in asthma ••Ongoing trial in idiopathic pulmonary fibrosis
TSLP	AMG 157 MEDI9929	••Blocks TSLP	• Ongoing trials in asthma and atopic dermatitis
IL-17Rα	Brodalumab	••Inhibits IL-17A, IL-17F, and IL-25 binding to receptor	••Ongoing trials in asthma and psoriasis

Advanced treatment options for severe asthma

- Targeted anti-inflammatory therapy
  - Anti-IgE
  - Anti-IL5
  - Anti –IL13
- Smooth muscle hypertrophy
  - Bronchial Thermoplasty

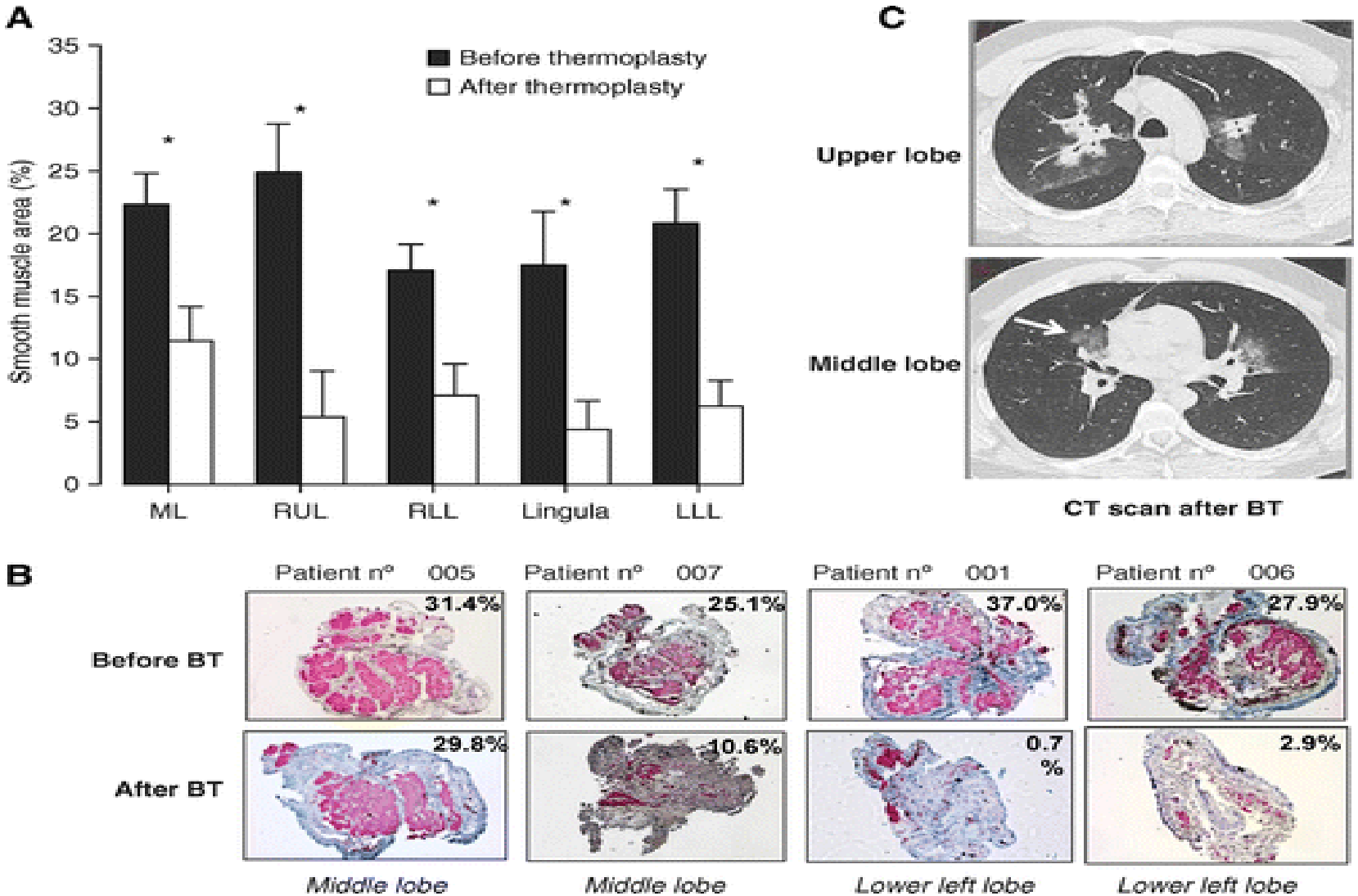






Bronchial Thermoplasty: Effect on Smooth Muscle (13 pts)

Pretolani et al AJRCCM 2015



Effectiveness of Bronchial Thermoplasty in the Treatment of Severe Asthma

Castro et al. 2010

- 18 – 65 years old
- Stable maintenance medications for at least 4 wks
- Lung Function: FEV1 $\geq$ 60% of predicted
- Randomized, double-blind, sham-controlled
- 30 investigational sites in six countries
- 2:1 randomization to bronchial thermoplasty (BT) or sham
- 190 BT and 98 sham control
- Three bronchoscopies performed 3 weeks apart

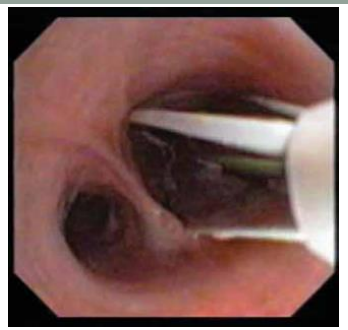
Am J Respir Crit Care Med Vol 181. pp 116-124, 2010

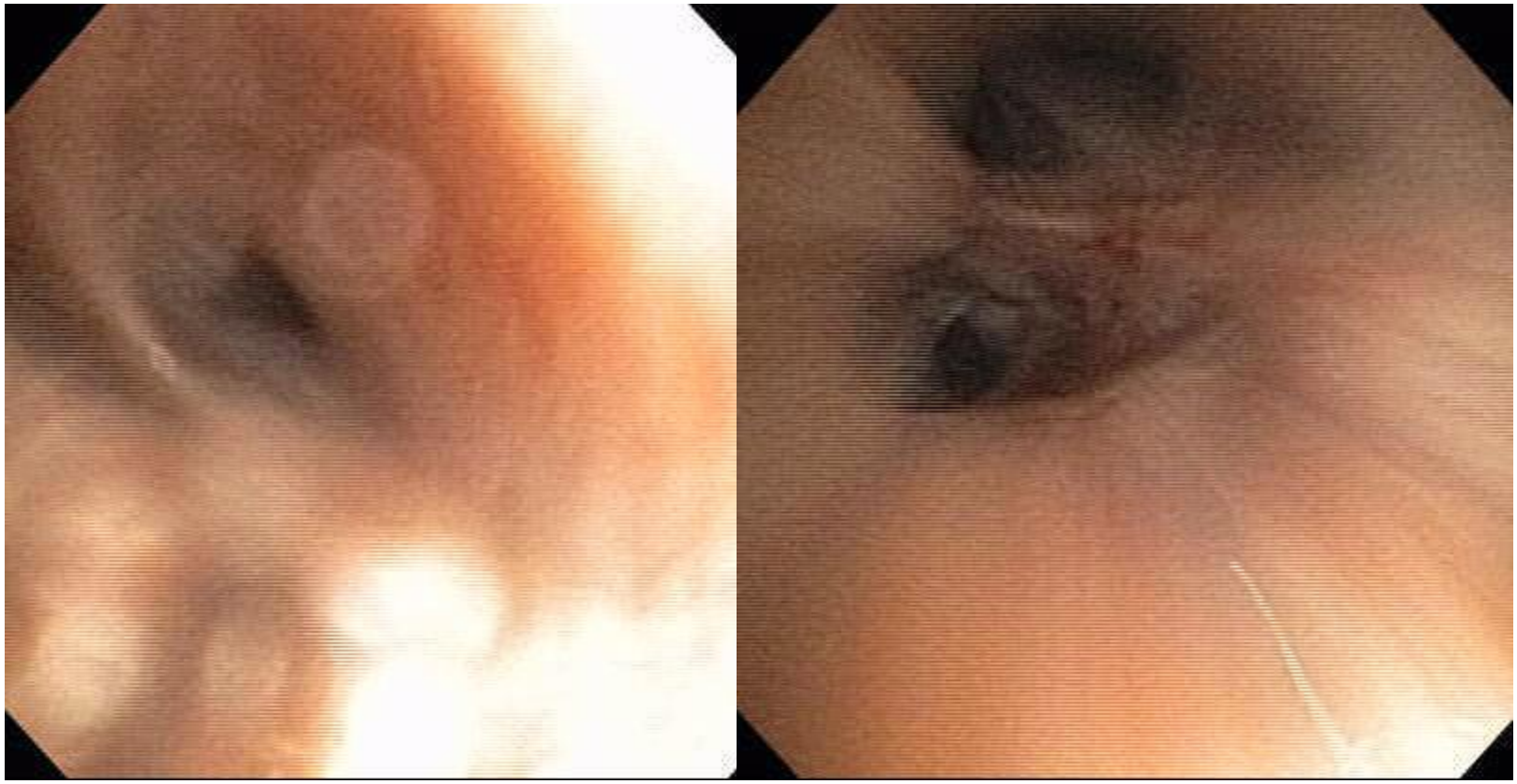
Clinical Outcomes Summary at 1-Yr
Castro et al. 2010

- Improved asthma-related quality of life compared to control (AQLQ score)
  - 79% of BT treated patients achieved ≥ 0.5 increase in symptom score
  - Effect persistent across 6, 9, and 12 months
- Improved clinical outcomes compared to control:
  - 32% decrease in severe exacerbations
  - 84% reduction in ER visits for respiratory symptoms
  - 73% reduction in hospitalization for respiratory symptoms
- No unanticipated device-related adverse events or deaths

- Acceptable safety profile now at 2 yr/5 yr.

Bronchial Thermoplasty #2:
Left: LLL Untreated, Right: RLL Treated



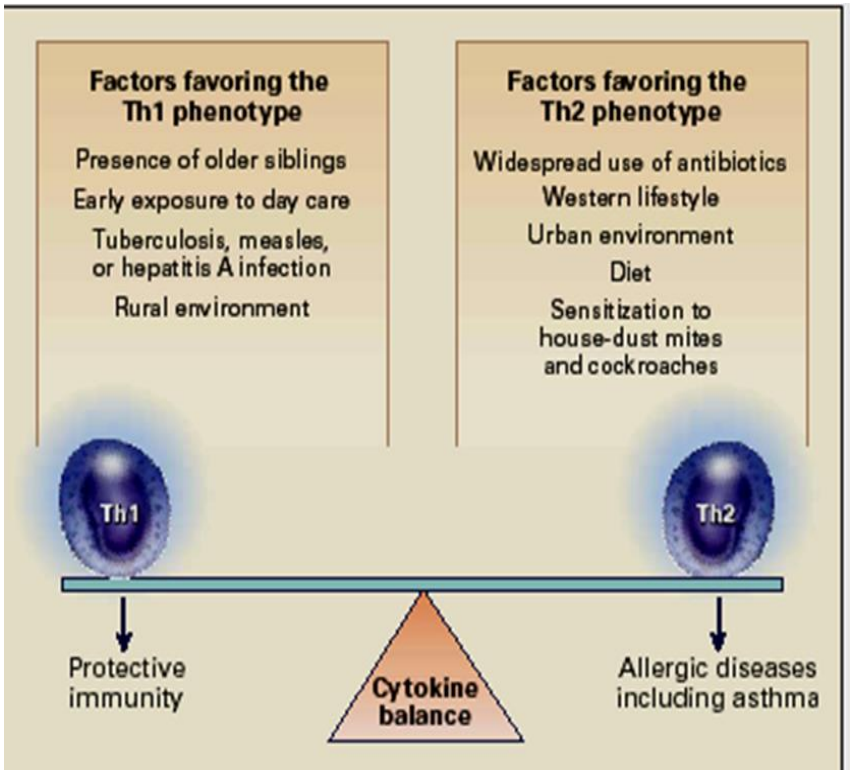


UC Davis Experience (2010-2014)

- To date, patient referrals from California, Washington, Nevada, Hawaii
- ~ 35 referrals in 18 months ; recommended for BT: 16 patients
- 37 procedures on 13 patients
- Completed: 10 patients
  - “Great” result: 4 patients
  - “Good” result: 4 patients
  - “Little change”: 2 patients
- Steroid myopathy in 1 patient

Medicine, Asthma, and the Exposome

The Bathini family has been administering fish to asthma patients for the past 166 years.



Nutritional Supplements and Exercise Trials in Asthma

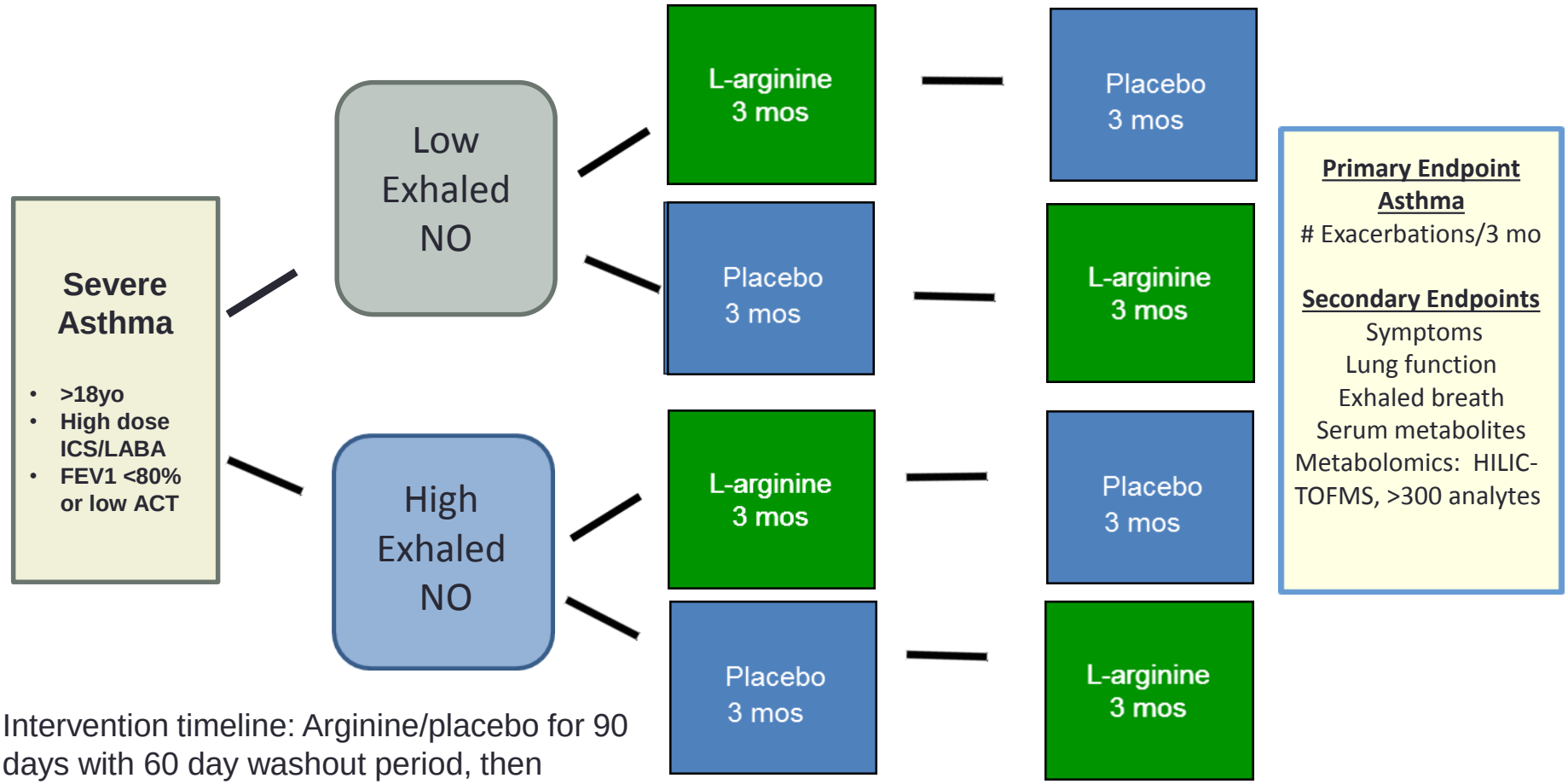
"I am eating much better now!"

- Omega 3 fatty acids
- Essential Amino Acids
  - Creatine
  - L-arginine
  - L-citrulline
  - L-glutamine
- Essential Minerals and Elements
  - Magnesium
  - Selenium
- Anti-inflammatory diets: DASH
- Vitamins
  - A, E, C, D, B

- Yoga
- Naturopathy
- Hypnosis
- Stress reduction interventions
- In-home interventions
- High Efficiency Air Filtration systems

Double-blind, Placebo-controlled, Cross-over intervention Trial

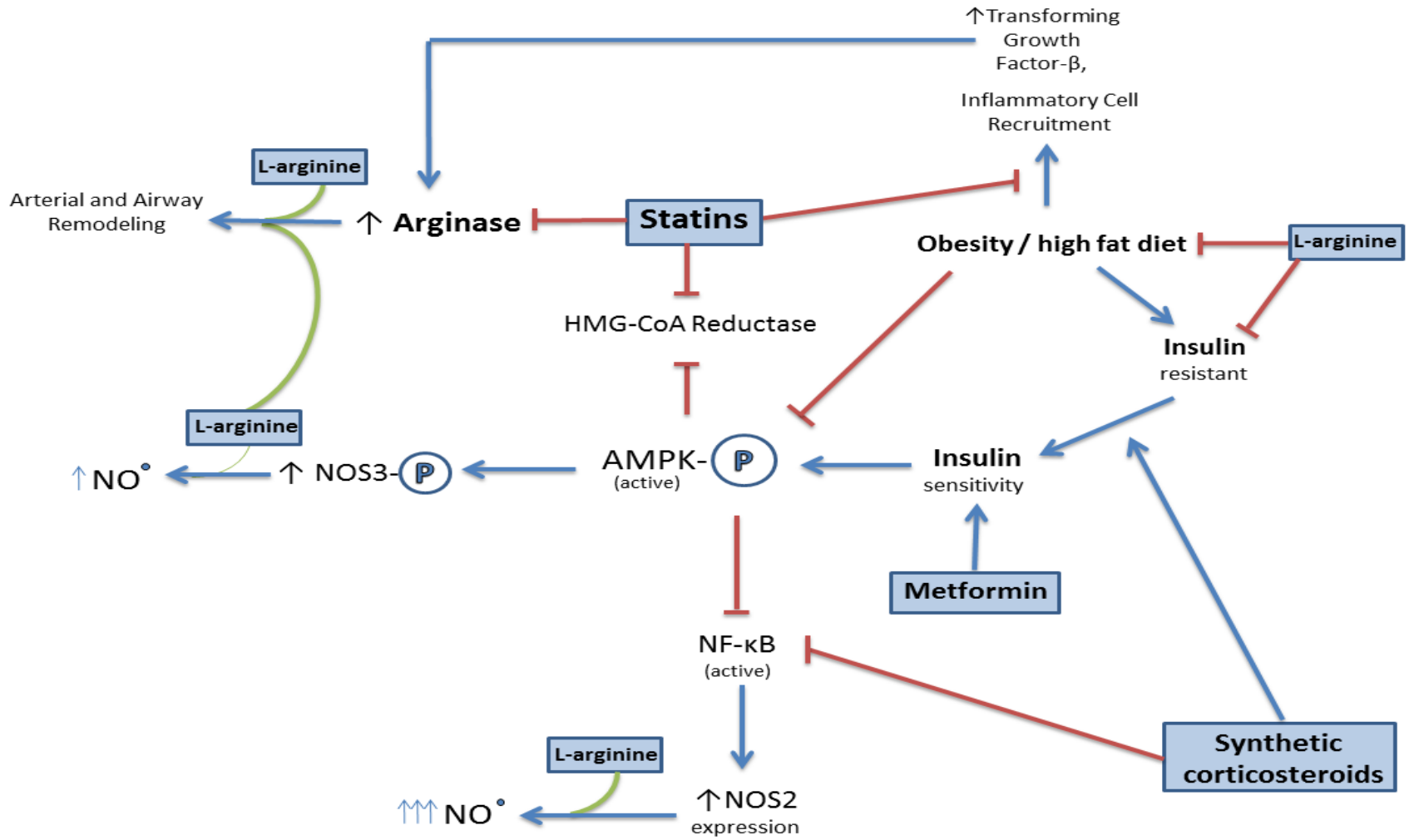
NIH/NHLBI, IND#114120 , NCT#01841281



Intervention timeline: Arginine/placebo for 90 days with 60 day washout period, then arginine/placebo

Dosage: 0.05g/kg L-arginine, twice daily

Working Model for L-arginine and other glucose modulationg therapies for treating asthma



Linderholm et al. Allergy Immunology Clinics, 2015

Biomarkers: Exhaled Nitric Oxide and Breath analysis

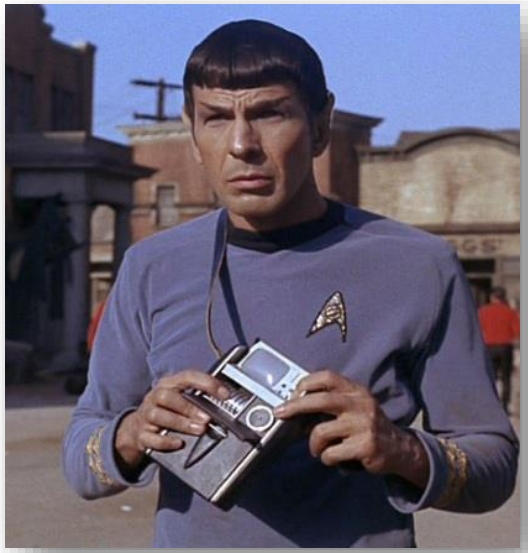
Aerocrine, Inc.

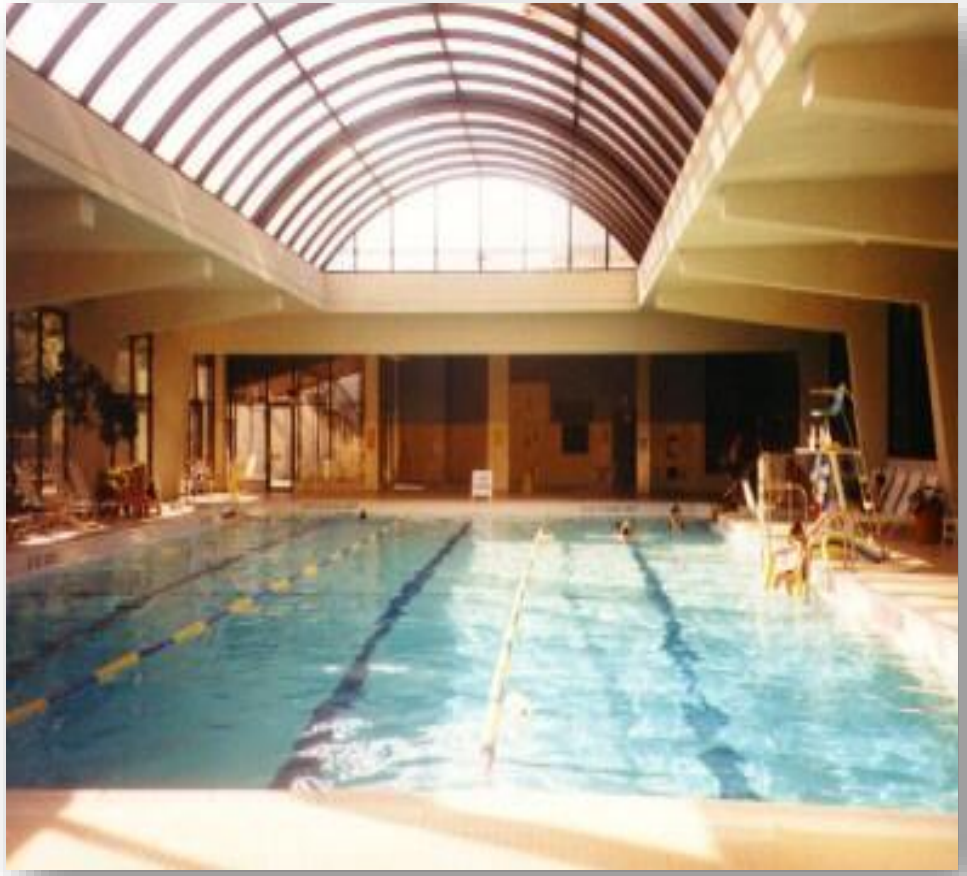
- ATS recommends using FeNO in:
  - diagnosing of eosinophilic airway inflammation
  - determining likelihood of steroid responsiveness
  - supporting the diagnosis of asthma
  - monitoring airway inflammation

Modern technical barriers for breath analysis

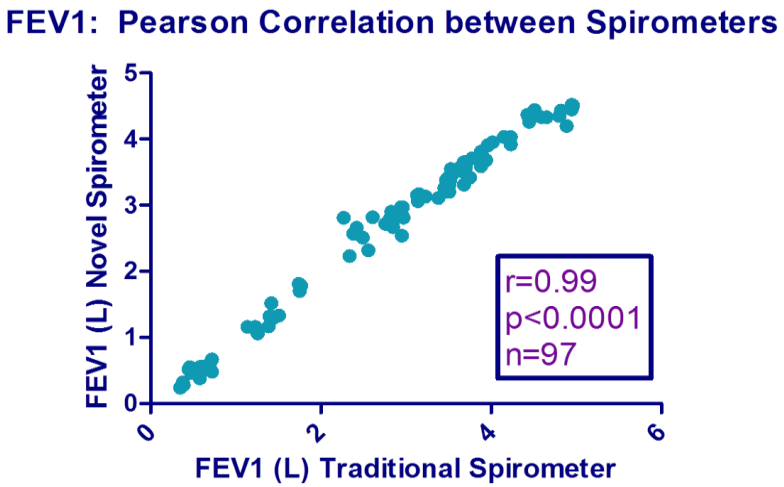
Chemicals present at extremely low concentration levels.

750 Tons water
5 g (1 spoon sugar)
gives 1 part-per-billion (ppb)

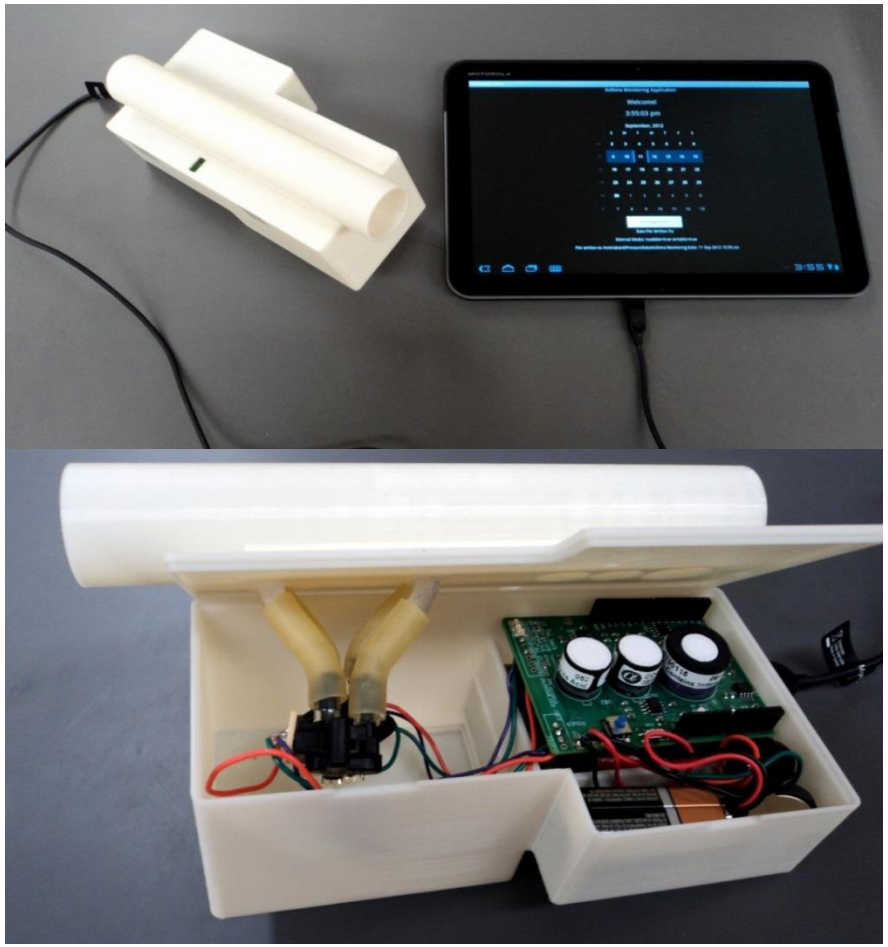




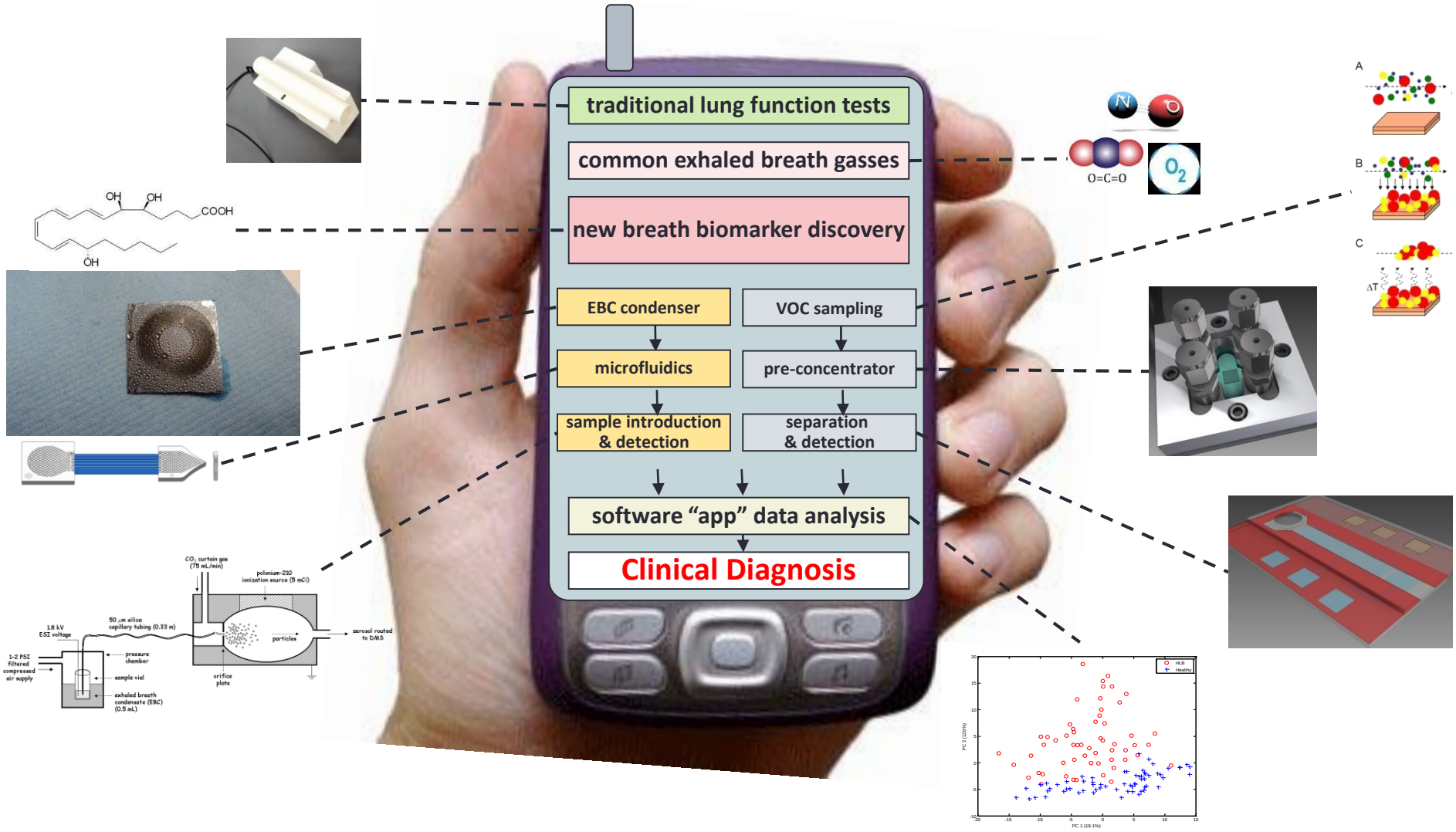
Engineering Advances, Bioinformatics, and Biomarker Development are needed to improve drug development and limit costs.



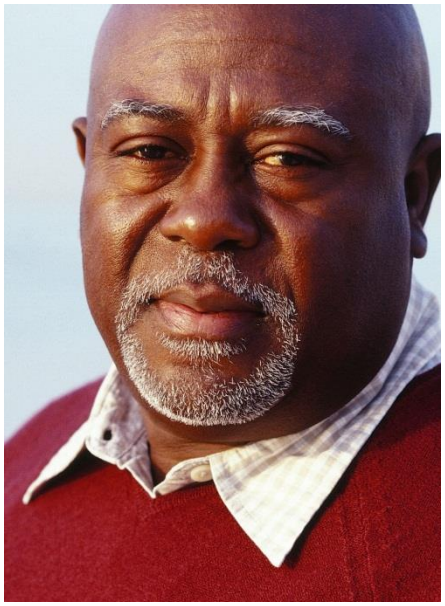
- Forced expiratory volume 1 (FEV1) and FVC can be measured
- Exhaled NO, CO, CO2, can be measured
- Data can be stored, stamped, and transferred electronically



NIH/NIBIB PRISMS Consortium: Pediatric Research Using Integrated Sensor Monitoring (2015-2019)



Asthma v. COPD • Which is it?

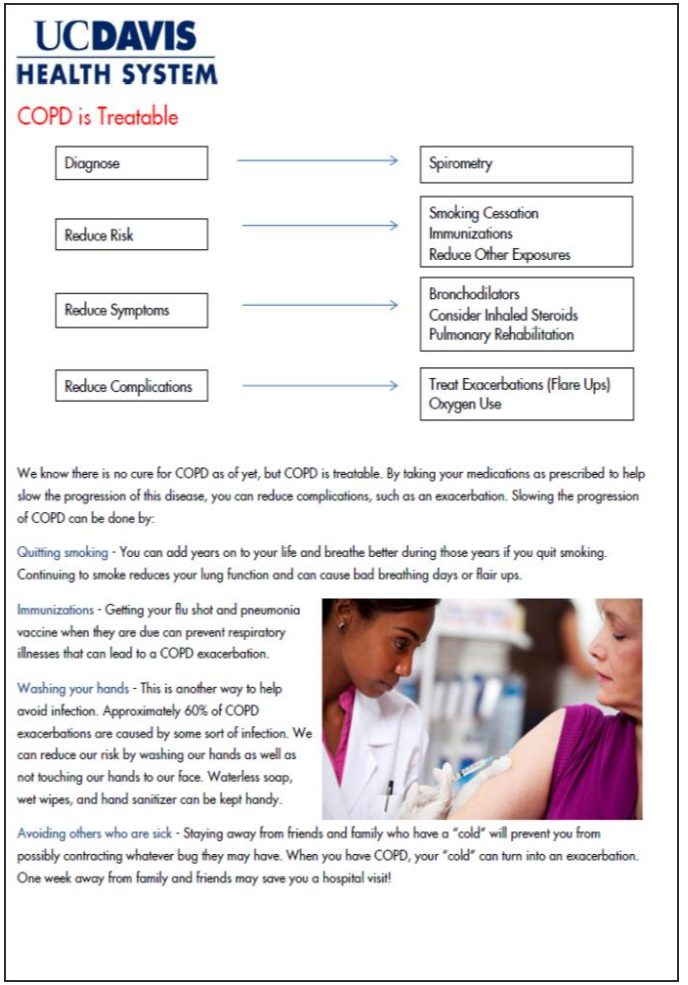


- 55-year-old man
- FEV_1 69% predicted
- Current smoker
- Productive cough in the morning
- No longer can walk up stairs
- ? Osteoporosis, coronary artery disease

- 48-year-old woman
- FEV_1 66% predicted
- 20 pack-year history of smoking
- Increased shortness of breath when gardening
- ? Osteoporosis, coronary artery disease

UCAN Asthma Team

- UC Davis Asthma Network Clinic
  - Three pulmonary asthma specialists
  - Two full time respiratory therapists
  - Two additional bronchoscopists integrated into the UCAN team specifically to perform BT
- 3 one-half day clinics/week
- “UCAN Quit” smoking cessation clinic
- Omalizumab clinic
- Bronchial Thermoplasty clinic
  - Interventional pulmonary laboratory nurses and respiratory therapists specifically trained in BT



UCDAVIS HEALTH SYSTEM

COPD is Treatable

Diagnose	Spirometry
Reduce Risk	Smoking Cessation Immunizations Reduce Other Exposures
Reduce Symptoms	Bronchodilators Consider Inhaled Steroids Pulmonary Rehabilitation
Reduce Complications	Treat Exacerbations (Flare Ups) Oxygen Use

We know there is no cure for COPD as of yet, but COPD is treatable. By taking your medications as prescribed to help slow the progression of this disease, you can reduce complications, such as an exacerbation. Slowing the progression of COPD can be done by:

Quitting smoking - You can add years on to your life and breathe better during those years if you quit smoking. Continuing to smoke reduces your lung function and can cause bad breathing days or flair ups.

Immunizations - Getting your flu shot and pneumonia vaccine when they are due can prevent respiratory illnesses that can lead to a COPD exacerbation.

Washing your hands - This is another way to help avoid infection. Approximately 60% of COPD exacerbations are caused by some sort of infection. We can reduce our risk by washing our hands as well as not touching our hands to our face. Waterless soap, wet wipes, and hand sanitizer can be kept handy.

Avoiding others who are sick - Staying away from friends and family who have a “cold” will prevent you from possibly contracting whatever bug they may have. When you have COPD, your “cold” can turn into an exacerbation. One week away from family and friends may save you a hospital visit!

2012 UC Davis ROAD Inpatient COPD program

1. COPD hospitalizations increased from 459 in 2009 to 587 in 2011.
1. Average cost per case increased nearly 2-fold from $14,259 to $26,355
2. Average LOS increased from 6.27 to 7.57 days in FY 2011.
3. Total direct cost in FY 2011 for inpatient COPD care was 587 patients = $15,470,385

Summary and Acknowledgements

1. Phenotyping patient with difficult to control asthma is becoming clinically relevant.
2. New biologic therapies will become the norm in severe asthma.
3. Tools for biomarker development in asthma are available.
4. Care of patients for severe asthma will benefit over the next 10 years.

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West Coast Metabolomics Center
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Loma Linda University
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