

Asthma and Its Many Unmet Needs: Directions for Novel Therapeutic Approaches

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Disclosure Slide

- **Employment**
 - University of Wisconsin
- **Financial Interests**
 - Advisory Boards: GSK, Merck, Wyeth, Pfizer, Centocor, Amgen, Johnson & Johnson
 - Consultant: Novartis, Genetech, Boehringer Ingelheim
- **Research Interests**
 - NHLBI, NIAID, Novartis, Ception, MedImmune, GSK, AstraZeneca
- **Organizational Interests**
 - AAAAI, ATS, AAP, ACAA, AAI
- **Gifts**
 - Nothing to Disclose
- **Other Interests**
 - Nothing to Disclose

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Objectives:

- Review current approaches to asthma treatment
- Review the effectiveness of guideline approaches to asthma
- Introduce the concept of asthma phenotypes
- Discuss approaches to personalized asthma treatment and development of novel therapeutic to meet these needs

What characterizes asthma?

- Asthma is characterized by episodes of wheezing, cough, chest tightness and dyspnea
- The great majority of asthma patients have:
 - Allergies (e.g. HDM, cat, molds, cockroach)
 - Exercise-induced asthma (cold air)
 - Nocturnal asthma
- Airway obstruction in asthma is typically reversible
- Nonspecific airway hyperresponsiveness can be demonstrated in the vast majority of patients with asthma

How have guidelines for asthma treatment benefitted care of this disease?

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Components of Severity		Classification of Asthma Severity (Youths ≥12 years of age and adults)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment Normal FEV ₁ /FVC: 8-19 yr 85% 20-39 yr 80% 40-59 yr 75% 60-80 yr 70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime Awakenings	≤2x/month	3-4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting beta ₂ -agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not >1x/day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung Function	<ul style="list-style-type: none"> • Normal FEV₁ between exacerbations • FEV₁ >80% predicted • FEV₁/FVC normal 	<ul style="list-style-type: none"> • FEV₁ >80% predicted • FEV₁/FVC normal 	<ul style="list-style-type: none"> • FEV₁ >60% but <80% predicted • FEV₁/FVC reduced 5% 	<ul style="list-style-type: none"> • FEV₁ <60% predicted • FEV₁/FVC reduced >5%
Risk	Exacerbations (consider frequency and severity)	0-2/year	>2/year		
		Frequency and severity may fluctuate over time for patients in any severity category			
		Relative annual risk of exacerbations may be related to FEV ₁			

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How are these concepts incorporated into the Guidelines?

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Risk	Exacerbations (consider frequency and severity)	0–2/year			
		>2/year	Frequency and severity may fluctuate over time for patients in any severity category		
		Relative annual risk of exacerbations may be related to FEV ₁			
Recommended Step for Initiating Treatment		Step 1	Step 2	Step 3	Step 4 or 5
(See figure 4–5 for treatment steps)		and consider short course of systemic oral corticosteroids In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

Does this approach work?

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**Can Guideline-Defined
Asthma Control Be
Achieved?**

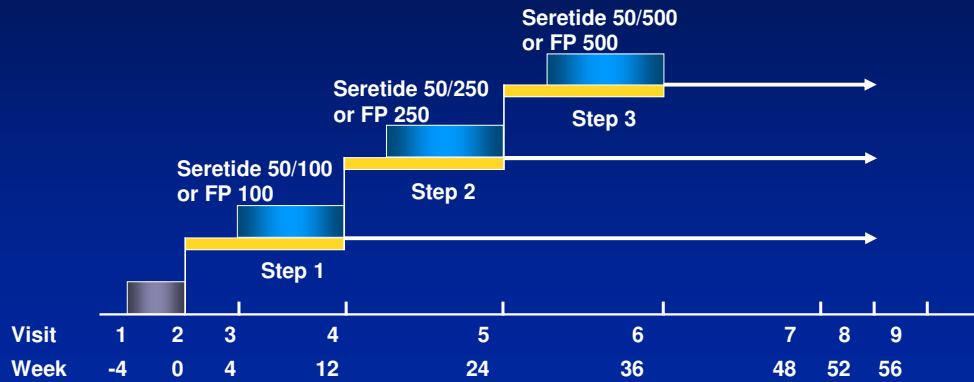
The Gaining Optimal Asthma ControlL
(GOAL) Study

E.D. Bateman et al. Am J Respir Crit Care Med
2004; 170:836-844.

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GOAL Design—Phase I

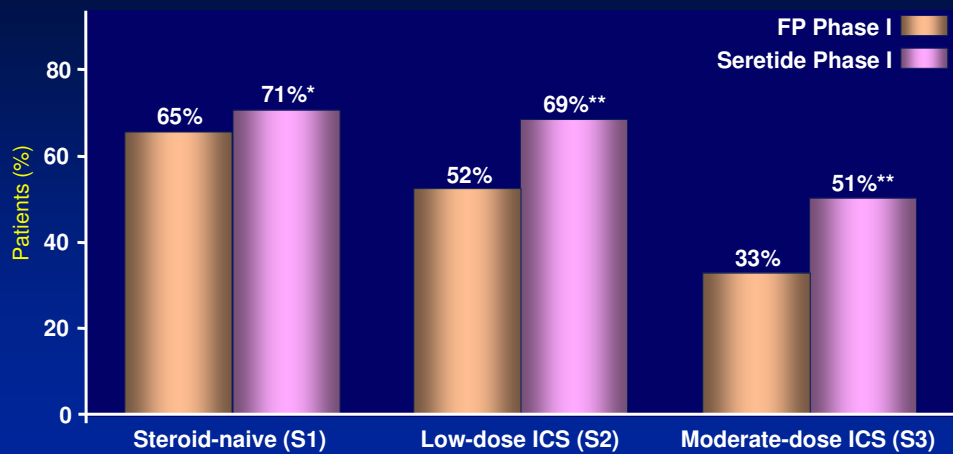
Phase I 8- week control assessment



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GOAL Study

WELL CONTROLLED Asthma During Phase I



* $P = 0.039$

** $P < 0.001$

GOAL Study, Bateman E, et al ARJCCM 2004; 170:836

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Given that asthma control is not universally achieved, what can be the next steps?

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Arthritis, anemia and asthma

- How are they all alike?
 - They all are *nonspecific and general* characteristics of disease, describing swelling, low RBC numbers or reversible airway obstruction
 - They shed almost no light on what caused these characteristics to develop

Sally Wenzel, ATS 2010

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Arthritis

- In rheumatology, no one would ever “ultimately” diagnose a patient with arthritis as the natural history, genetics, inflammatory processes and response to therapy will differ by “which” arthritis the patient has
 - i.e., the understanding and treatment of RA will be vastly different from treatment of OA
 - The same is likely true in asthma

Sally Wenzel, ATS 2010

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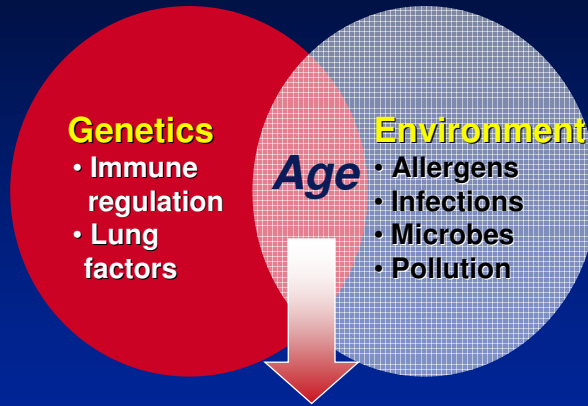
What is a phenotype?

The relatively *stable* and *observable* characteristics of an organism resulting from interaction between its *genetic* make-up and *environmental* influences

Peter Sterk, ATS 2010

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Pathogenesis of Asthma



Asthma
(Many Phenotypes)

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What about other approaches to identify asthma phenotypes?

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Cluster Analysis

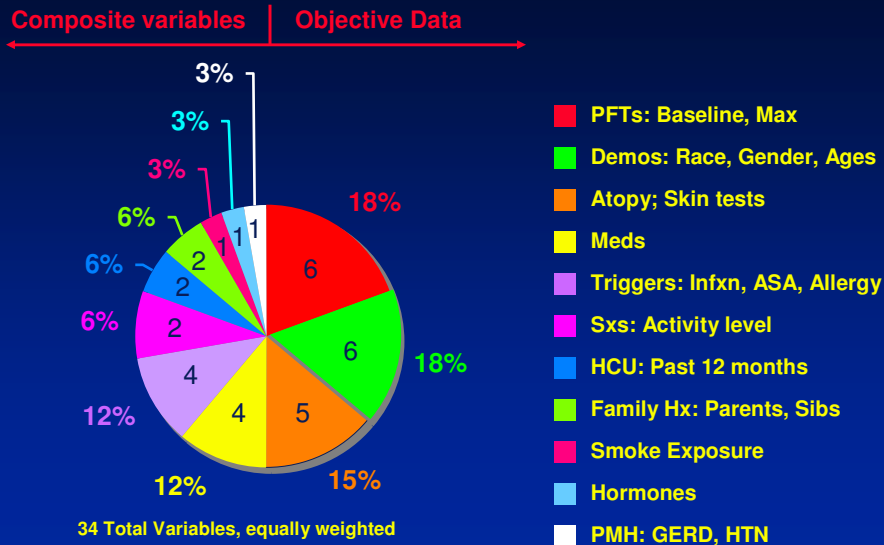
- Perform a multivariate cluster analysis to identify asthma groups who share similar phenotype profiles (defined by the factor scores identified in the variable reduction step)

Moore et al. AJRCCM 2010; 181:315-323.

Population studied in our cluster analysis

- Severe Asthma Research Program
- Started in 2000
- Determine how severe asthma differs from non-severe asthma

Distribution of Variables



Moore et al. AJRCCM 2010; 181:315-323.

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CLUSTER ANALYSIS: 5 CLUSTERS

	Cluster 1 n=110	Cluster 2 n=321	Cluster 3 n=59	Cluster 4 n=120	Cluster 5 n=116	P-value
Age at Enrollment	27	33	50	38	49	<0.0001
Gender (%female)	80	67	71	53	63	0.0006
Race (% Cauc/AAOther)	62/29/9	63/30/7	73/22/5	62/33/5	68/20/12	0.17
Body Mass Index (BMI)	27	28	33	31	31	<0.0001
Age of Asthma Onset (yrs)	11	11	42	8	21	<0.0001
Asthma Duration (yrs)	15	22	9	30	29	<0.0001
Baseline Lung Function*						
FEV1 % Predicted	102	82	75	57	43	<0.0001
FVC % Predicted	112	93	80	72	60	<0.0001
FEV1/FVC	0.78	0.74	0.74	0.64	0.57	<0.0001
Maximal Lung Function†						
FEV1 % Predicted	113	94	84	76	58	<0.0001
FVC % Predicted	117	100	87	89	75	<0.0001
Atopy: % with ≥ 1 pos skin test	85%	78%	64%	83%	66%	0.0008

*Pre-bronchodilator values (>6 hours withhold of bronchodilators). † Post-bronchodilator values after 6-8 puffs of albuterol. Moore et al. AJRCCM 2010; 181:315-323.

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CLUSTER ANALYSIS: 5 CLUSTERS

	Cluster 1 n=110	Cluster 2 n=321	Cluster 3 n=59	Cluster 4 n=120	Cluster 5 n=116	P-value
Corticosteroid Use (%)						<0.0001
None	45%	31%	14%	15%	5%	
Low-moderate dose ICS	38%	40%	37%	18%	16%	
High dose ICS*	10%	28%	49%	63%	78%	
Oral or Systemic CS**	11%	10%	17%	39%	47%	
Total Controllers(%)						<0.0001
None	41%	26%	10%	12%	4%	
≤ 2	41%	46%	35%	33%	28%	
≥ 3	19%	29%	54%	56%	67%	
Health Care Utilization Pst Yr †						<0.0001
None	67%	61%	41%	38%	32%	
≥ 1 Urgent Visit and/or ED	20%	25%	34%	39%	42%	
≥ 3 Oral CS burst/yr	11%	19%	36%	46%	42%	
Hospitalization	7%	9%	15%	23%	28%	

* High dose ICS dose equivalent to ≥ 1000 fluticasone propionate daily; **Chronic oral corticosteroids (OCS) ≥ 20 mg daily or other systemic steroids in the past 3 months. †Controllers include LTRA, ICS, LABA, theophyllines, OCS, omalizumab. P value from Chi-Square Analysis of ranked ordinal composite variables.

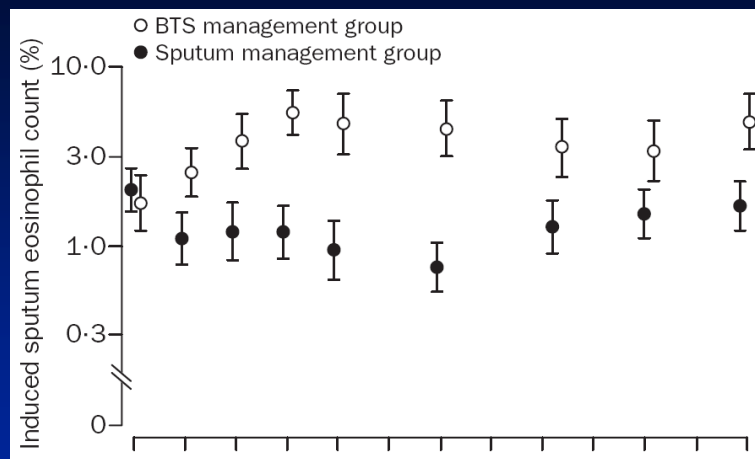
Moore et al. AJRCCM 2010; 181:315-323.
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What about inflammatory markers, like eosinophils

Asthma Exacerbations and Sputum Eosinophil Counts: A Randomized Controlled Trial. Green et al. Lancet 2002; 360:1718-1721

- Evaluated whether inhaled corticosteroid treatment directed towards reducing the sputum eosinophils was more effective than “standard guideline” care.

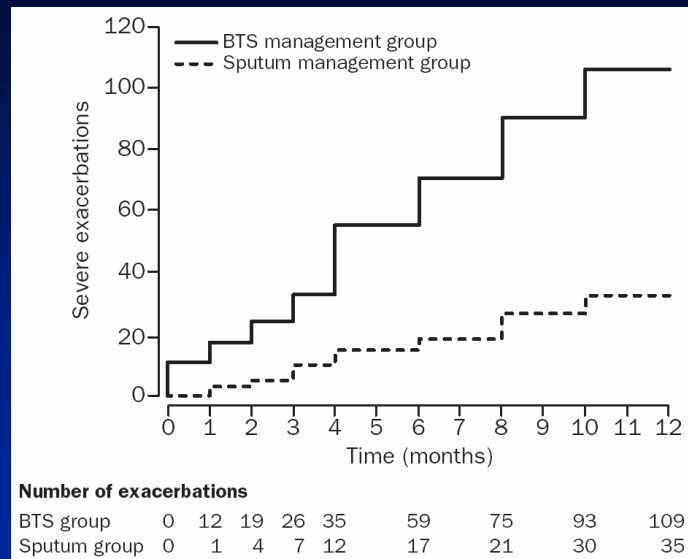
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Green et al. Lancet 2002; 360:1718-1721.

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Cumulative Asthma Exacerbations in the BTS Management Group and the Sputum Management Group



Green et al. *Lancet* 2002; 360:1718-1721.
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Haldar et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009; 360:973-984.

- Evaluate the effect of reducing sputum eosinophils in patients refractory to usual asthma treatment
- Recruited subjects with persistent airway eosinophils despite aggressive anti-inflammatory treatment

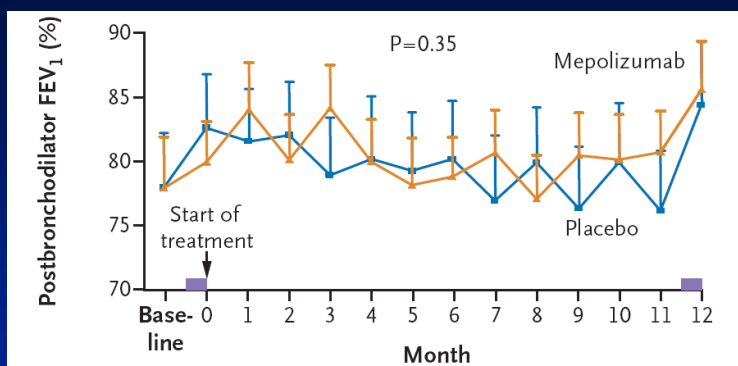
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Baseline Characteristics of Subjects in the Intention-to-Treat Population

Characteristic	Mepolizumab (N=29)	Placebo (N=32)	P Value
Age (yr) Mean	48	50	
Severe exacerbations per subject in previous year (no.)	5.5	5	0.71
FEV ₁ after bronchodilator use (% of predicted value)	78.1±20.9	77.6±24.1	0.93
Eosinophil count in sputum (%)	6.84 ±0.64	5.46 ±0.75	0.60
Eosinophil count in blood (x10 ⁻⁹ /liter)	0.32 ±0.38	0.35 ±0.30	0.57
Dose of inhaled corticosteroid – beclomethasone dipropionate – equivalent (µg) Daily dose	2038	1711	
Use of oral prednisolone Regular use (% of subjects)	57.1	53.1	0.80

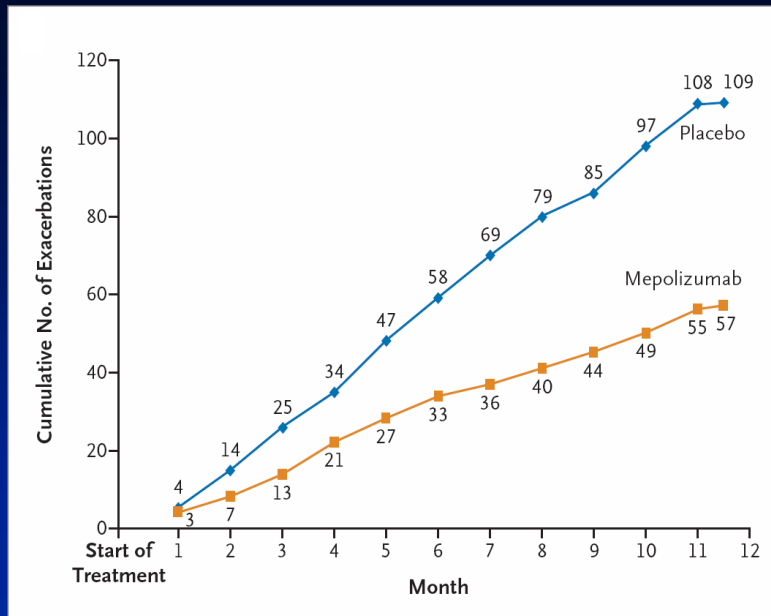
Haldar, et al. NEJM 2009; 360:973-984.

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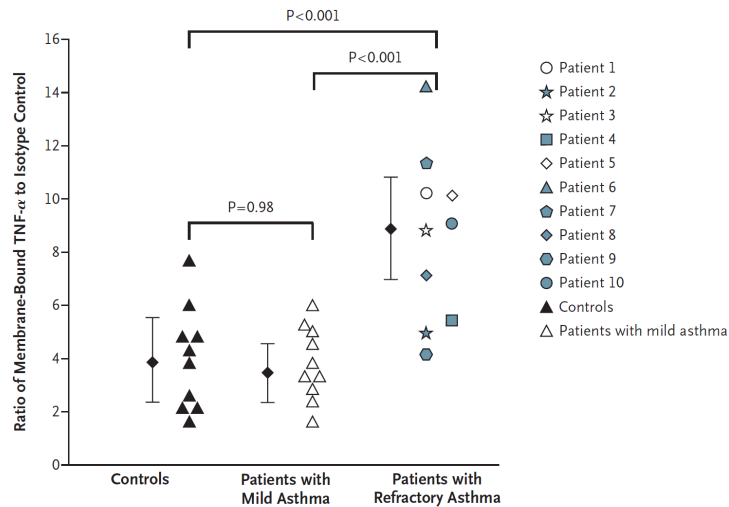
**How can phenotypic features
be used to select patients
more likely to respond to a
specific treatment?**

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MA Berry et al. Evidence of a role of tumor necrosis factor- α in refractory asthma. *N Eng J Med* 2006; 354:697-708.

- Objective – to evaluate the potential role of TNF- α in asthma
- Identified patients with treatment refractory asthma
- Selected normal subjects and asthma patients with low and high peripheral blood mononuclear cell expression of TNF- α receptor

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Berry et al. *N Engl J Med* 2006; 354:697-708.

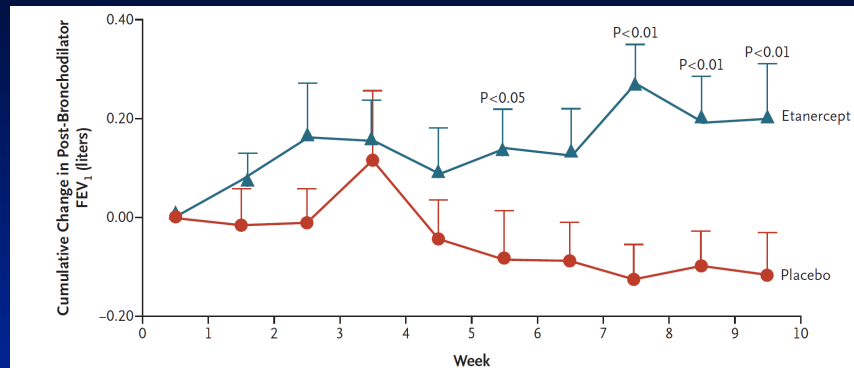
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Baseline Characteristics of the Subjects

Characteristic	Controls (N = 10)	Patients with Mild-to-Moderate Asthma (N = 10)	Patients with Refractory Asthma (N = 10)
% of predicted value	97±18	94±23	62±21†
FEV ₁ :FVC ratio (%)	80±25	78±21	65±17†
Eosinophils (%):‡	0.3±0.2	4.1±0.7	5.6±0.8†
Neutrophils (%)	57±25	55±26	62±27
Total cells (×10 ³ /mg):‡	0.6±0.2	0.9±0.4	1.6±0.2
Plasma IgE (IU/ml):‡	16±0.6	172±1.1	77±0.9
PC ₂₀ (mg of methacholine/ml):‡	>16	0.4±0.6	0.14±0.1
TNF-α receptor 1 — ratio§	2.3±0.3	3.1±0.2	5.5±0.6¶
TNF-α-converting enzyme — ratio§	2.8±0.4	3.5±0.5	6.5±0.5¶

Berry et al. N Engl J Med 2006; 354:697-708.

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Berry et al. N Engl J Med 2006; 354:697-708.

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Phenotypic characteristics based upon gene activation profiles

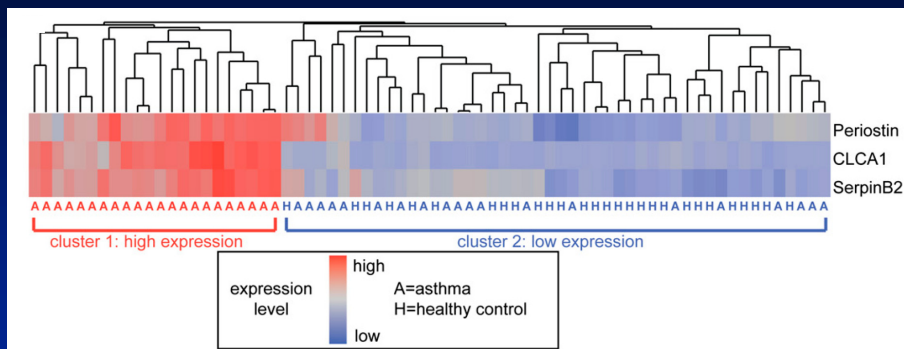
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PG Woodruff et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. Am J Respir Crit Care Med 2009; 180:388-395.

- To determine whether clinical heterogeneity is reflected in the heterogeneity of molecular mechanisms related to Th2 inflammation
- Using molecular approaches (microarrays and PCR), IL-13 inducible genes from bronchial brushings were determined

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Gene expression microarray

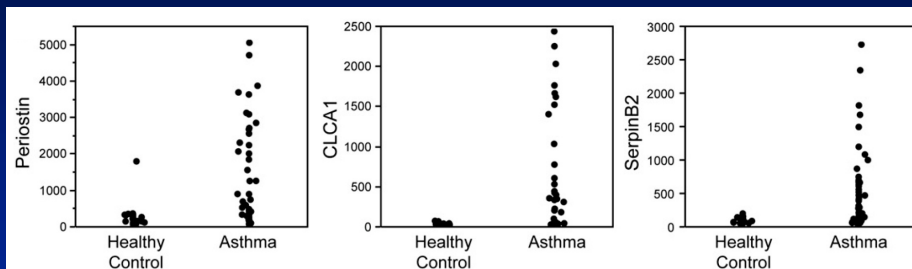


Heatmap depicting unsupervised hierarchical clustering of POSTN (periostin), CLCA1 (chloride channel regulator), and SERPINB2 (serpin peptidase inhibitor, clade) following IL-13 activation of epithelial cells.

Woodruff et al. Am J Respir Crit Care Med 2009; 180:388-395

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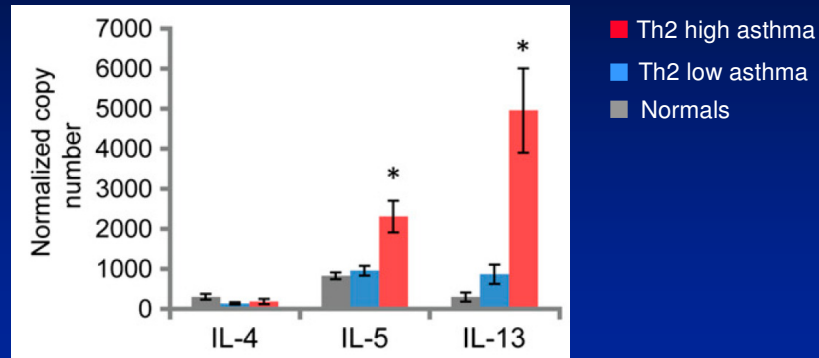
Relative expression of three genes induced by IL-13



Woodruff et al. Am J Respir Crit Care Med 2009; 180:388-395

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Expression levels of the Th2 cytokines, IL-4, IL-5, IL-13, in bronchial biopsy homogenates



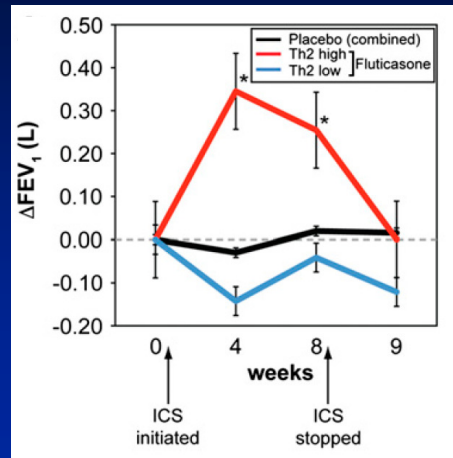
Woodruff et al. Am J Respir Crit Care Med 2009; 180:388-395

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Do patients with “Th2-high asthma” respond differently to inhaled corticosteroids?

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Responsiveness of Th2-high asthma to inhaled steroids



Woodruff et al. Am J Respir Crit Care Med 2009; 180:388-395

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Subject characteristics and bronchoscopic features by a Th2-asthma phenotype

	Health Control Subjects	Subjects with Asthma		P value
		Th2 Signature Low	Th2 Signature High	
Sample size	28	20	22	—
Age, years	36	36	37	0.98
FEV ₁ % predicted	107	89	85	0.85
Methacholine PC ₂₀	64	0.93	0.27	<0.001
IgE, IU/ml	27	125	244	0.031
BAL eosinophil %	0.26	0.42	1.9	0.001
ΔFEV_1 with fluticasone at 4 wk, L	N/A	0.03 ± 0.12	0.35 ± 0.2	0.004
ΔFEV_1 with fluticasone at 8 wk, L	N/A	0.04 ± 0.12	0.25 ± 0.23	0.05

Woodruff et al. Am J Respir Crit Care Med 2009; 180:388-395

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What is the future for treatment of asthma based upon individual patient characteristics?

- Determine associations between phenotype characteristics and genotype
- Develop patient profiles to detect
 - Disease course
 - At risk factors (exacerbations, loss of lung function)
 - Treatment selection
- This approach promises to have greater specificity, predictability, effectiveness, and efficiency