

Asthma Phenotypes, Heterogeneity and Severity: The Basis of Asthma Management

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Translational Research and Personalized Medicine in Asthma

- **Team Science that integrates disease heterogeneity (phenomics), genomics, functional biology and individualized therapeutics**
- **These approaches are critically important to the effective development of “biologic” therapies**
- **This approach is a departure from “few drugs treat all” approach and tailors therapies to individual patients**

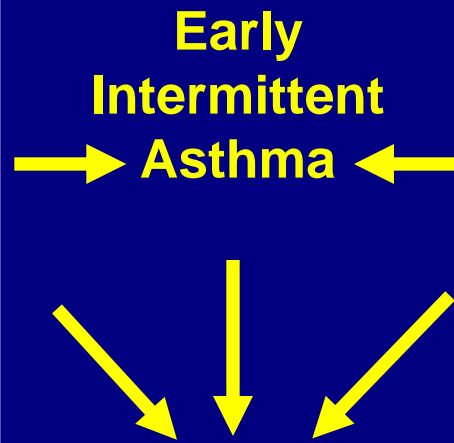
Examples of Stratified (Personalized) Approaches

- **Disease heterogeneity and asthma severity phenotypes**
- *Pulmonary function and asthma severity*
- *Early onset Th2 phenotypes and severity*

Gene-Environment Interactions in Susceptibility and Severity of Asthma

Genetics

Susceptibility:
Associated Phenotypes:
(atopy, BHR)
Expression and Progression:
Severity,
Pharmacogenetics



Environment /Epigenetics

Prenatal influences (prematurity), allergens, respiratory infections, tobacco smoke, air pollutants, diet, lung development etc.

Chronic Persistent Progressive

(reversible and irreversible changes in lung structure and function)

Disease Heterogeneity & Severity

Asthma is a Heterogeneous Disease

Some Important Issues:

- **Are there phenotypes of persistent bronchial inflammation?**
 - Are some associated with airways remodeling?
 - Is there an exacerbating phenotype?
- **Is severity determined by poor response to medications?**
 - Are there biochemical/ biologic mechanisms?
 - Are there pharmacogenetic interactions?
- **What are the associations between nonsmoking asthma with COPD as well as smoking asthma and COPD?**

Characterizing Asthma Heterogeneity

Phenotypes (Hypothesis) Based

- Age of Onset
- Atopic/Allergic
- Shorter vs Longer Disease Duration
- Elderly
- Gender
- Ethnicity
- Obesity
- Exacerbations

Characterizing Asthma Heterogeneity

Phenotypes (Hypothesis) Based

- **Inflammatory**
 - Eosinophilic
 - Neutrophilic
 - Mast Cell
 - Combinations as well as other cellular/morphologic
- **Physiologic**
 - Sinusitis/Upper Airways
 - Small Airways Disease
 - Fixed Airways Obstruction (Remodeling)
- **Pharmacologic**
 - Corticosteroid Resistance
 - Pharmacogenetic

Severe Asthma Research Program (SARP)

- **NHLBI** funded 5 (now 10) year program to investigate the pathobiology of severe asthma

- **Eight individual R01 awards**

Brigham and Women's Hospital

Imperial College, London

University of Pittsburgh

University of Texas-Galveston

Cleveland Clinic

University of Virginia

Emory University

University of Wisconsin

Wake Forest University

Washington University

Elliot Israel, M.D.

K. Fan Chung, M.D.

Sally E. Wenzel, M.D.

William J. Calhoun, M.D.

Serpil C. Erzurum, M.D.

Ben Gaston, M.D.

W. Gerald Teague, M.D.

William W. Busse, M.D.

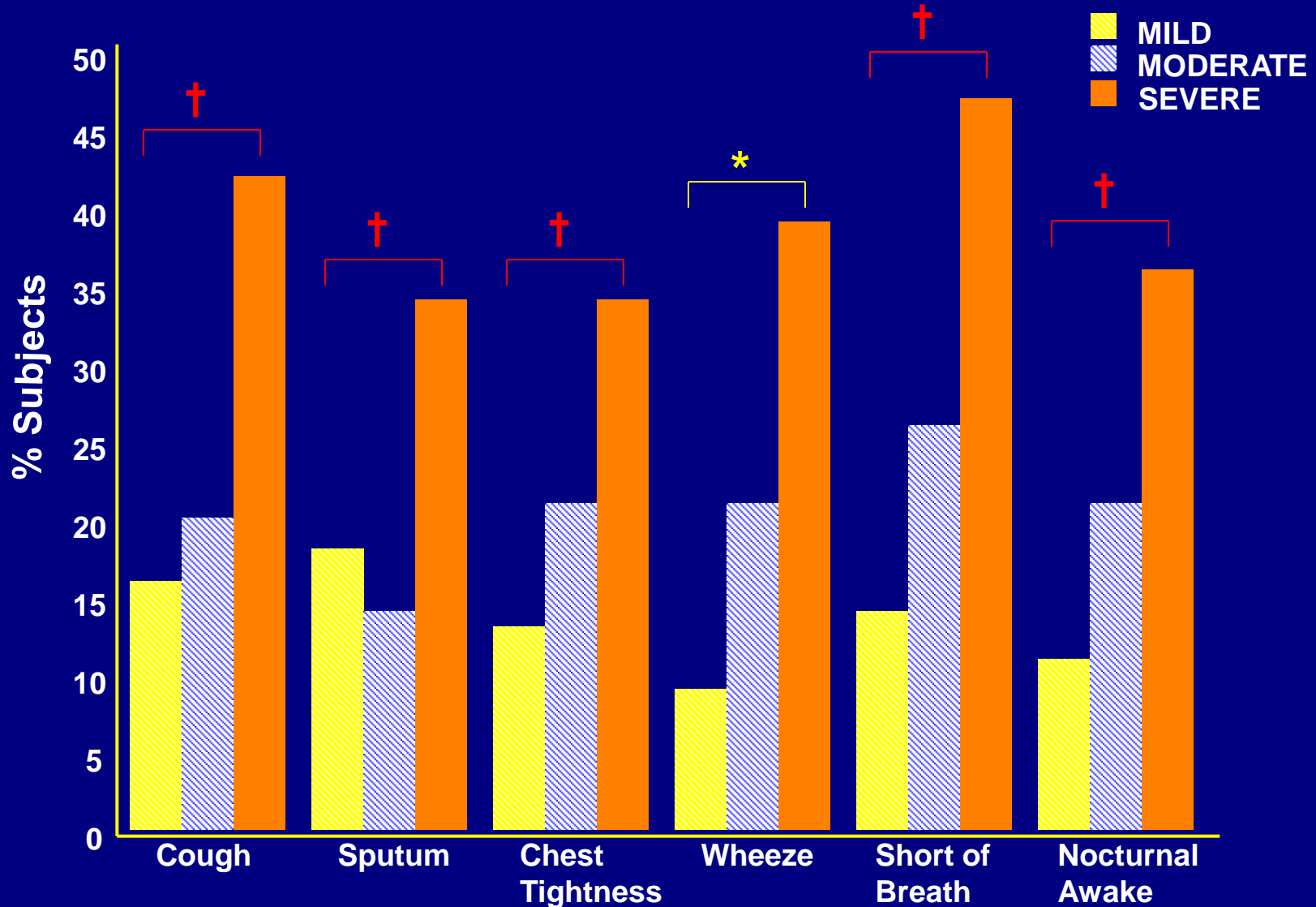
Eugene R. Bleeker, M.D.

Mario Castro, M.D.

Subject Characterization

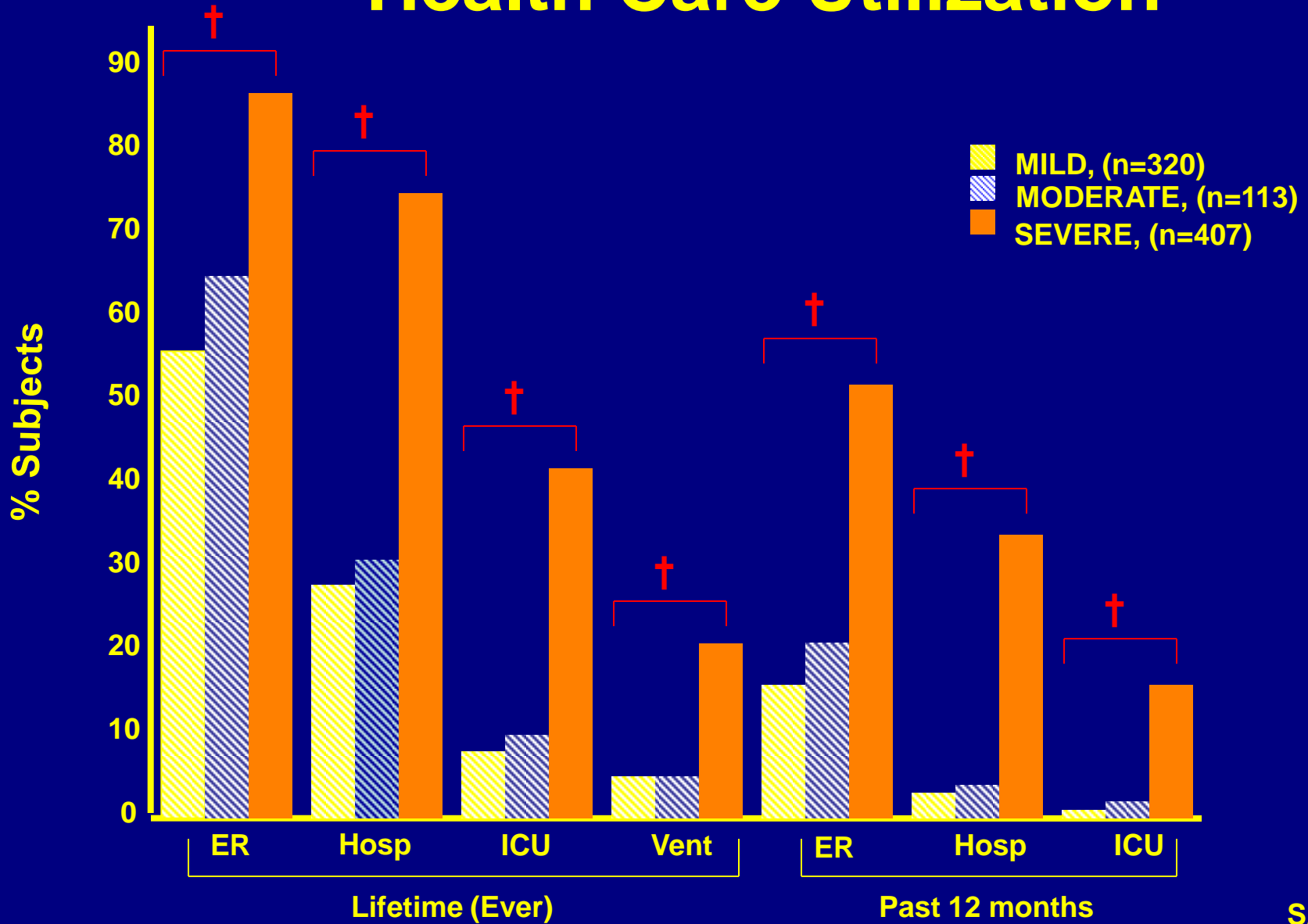
- **Staff administered questionnaires**
- **Phlebotomy for DNA, serum IgE, blood eosinophils**
- **Atopy skin testing**
- **Pulmonary function assessment**
 - Bronchodilator reversibility
 - Airway hyperresponsiveness to methacholine
- **Collection of noninvasive biomarkers**
 - Exhaled nitric oxide
 - Exhaled breath condensate
 - Hypertonic sputum induction
- **Investigative bronchoscopy (subset)**
 - Bronchoalveolar lavage
 - Endobronchial brushings and biopsies

Daily Asthma Symptoms



* all groups differ, † severe group differs from others

Health Care Utilization



† severe group differs from others (p<0.0001)

Subject Characteristics: SARP

	Mild (n=320)	Moderate (n=113)	Severe (n=407)	P value
Demographics				
Current Age (yrs)	29 13	38 13	38 17	<0.0001 [‡]
Age of asthma onset (yrs)	12 12	17 14	14 15	0.005 [‡]
Asthma duration (yrs)	17 12	21 14	24 15	<0.0001*
Gender (% females)	69%	61%	62%	NS
Race (% Caucasian)	65%	66%	60%	NS

* all groups differ, † severe group differs from others, ‡ mild group differs from others

Physiology and Biomarkers

	Mild (n=320)		Moderate (n=113)		Severe (n=407)		P value
Baseline Lung Function							
FEV1% predicted	94	11	66	12	65	23	<0.0001 [‡]
FVC % predicted	100	12	80	13	80	21	<0.0001 [‡]
FEV1/FVC %	80	8	68	10	66	13	<0.0001 [‡]
Best Lung Function							
FEV1% predicted	103	11	80	13	80	22	<0.0001 [‡]
FVC % predicted	105	12	91	14	93	19	<0.0001 [‡]
Max % change in FEV1	11	8	19	17	22	21	<0.0001 [‡]
PC20 Methacholine (log)	.18	.64	-.05	.63	-.07	.80	0.0004 [‡]
Blood eosinophils (log)	-.70	.46	-.56	.45	-.66	.54	NS
Serum IgE (log)	2.0	.71	2.1	.65	2.1	.74	NS
≥ 1 positive skin test (%)	79%		77%		63%		0.0007 [†]

* all groups differ, † severe group differs from others, ‡ mild group differs from others

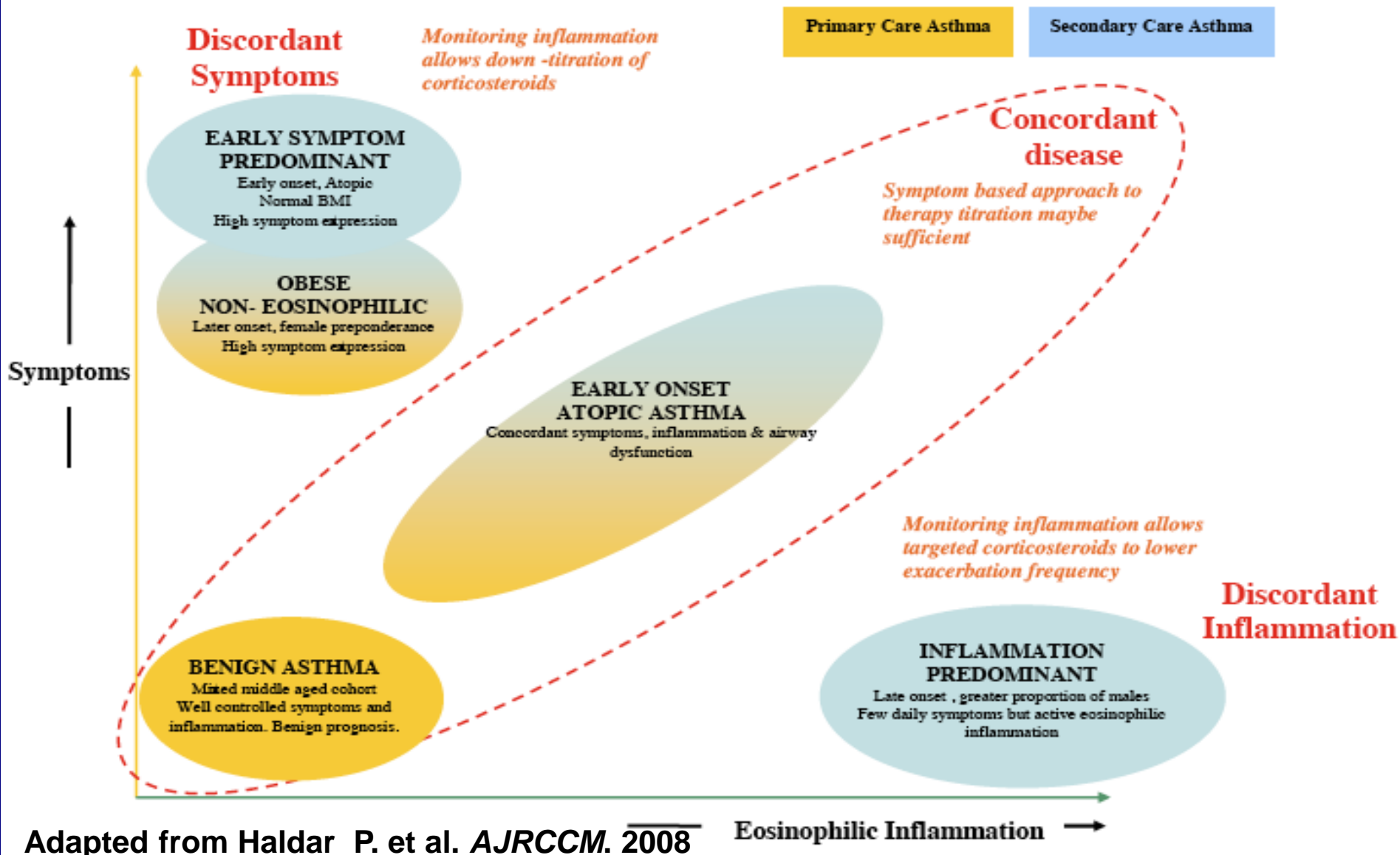
Mild, Moderate, and Severe:

Is this the best we can do?

Phenotypes of Severe Asthma: Biased and Unbiased Approaches

- “Hypothesis Based”: (Age of Onset, Allergic, Eosinophilic, Exacerbations etc)
- **“Model Free”**: Cluster Approaches
 - Haldar et al AJRCCM (2008)
 - Weatherall et al ERJ (2009)
 - SARP NHLBI – Moore et al AJRCCM (2010)

Asthmas Cluster Approaches and Eosinophilic Inflammation

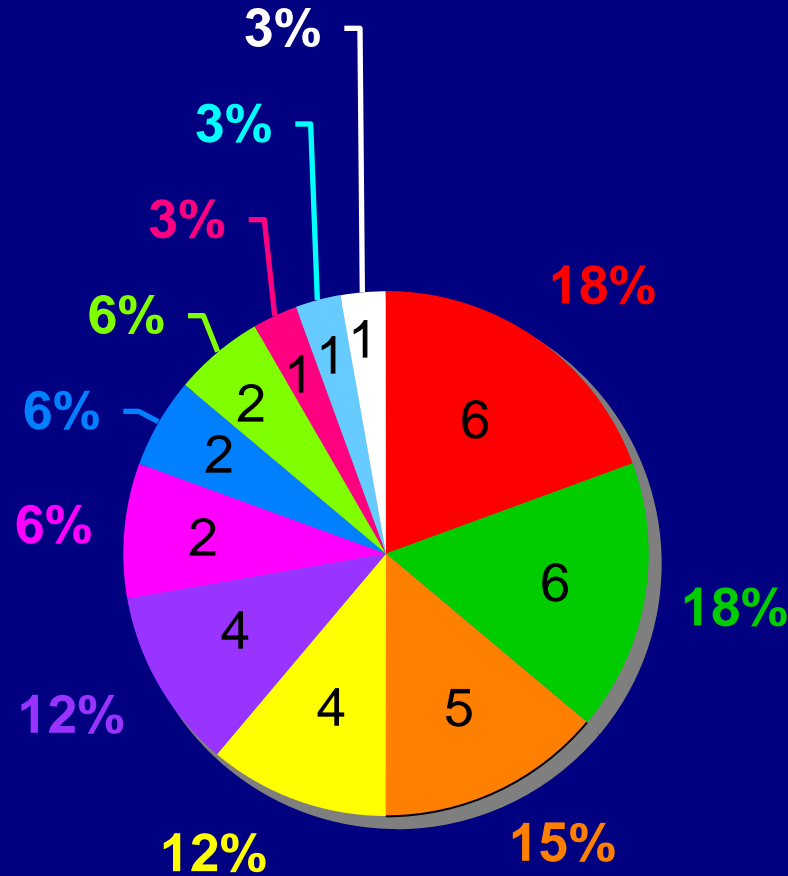


SARP: Cluster Analysis

- **Perform an unbiased multivariate cluster analysis to identify asthma groups who share similar phenotypic profiles and to define asthma heterogeneity and severity**

Distribution of Variables

Composite variables | Objective Data

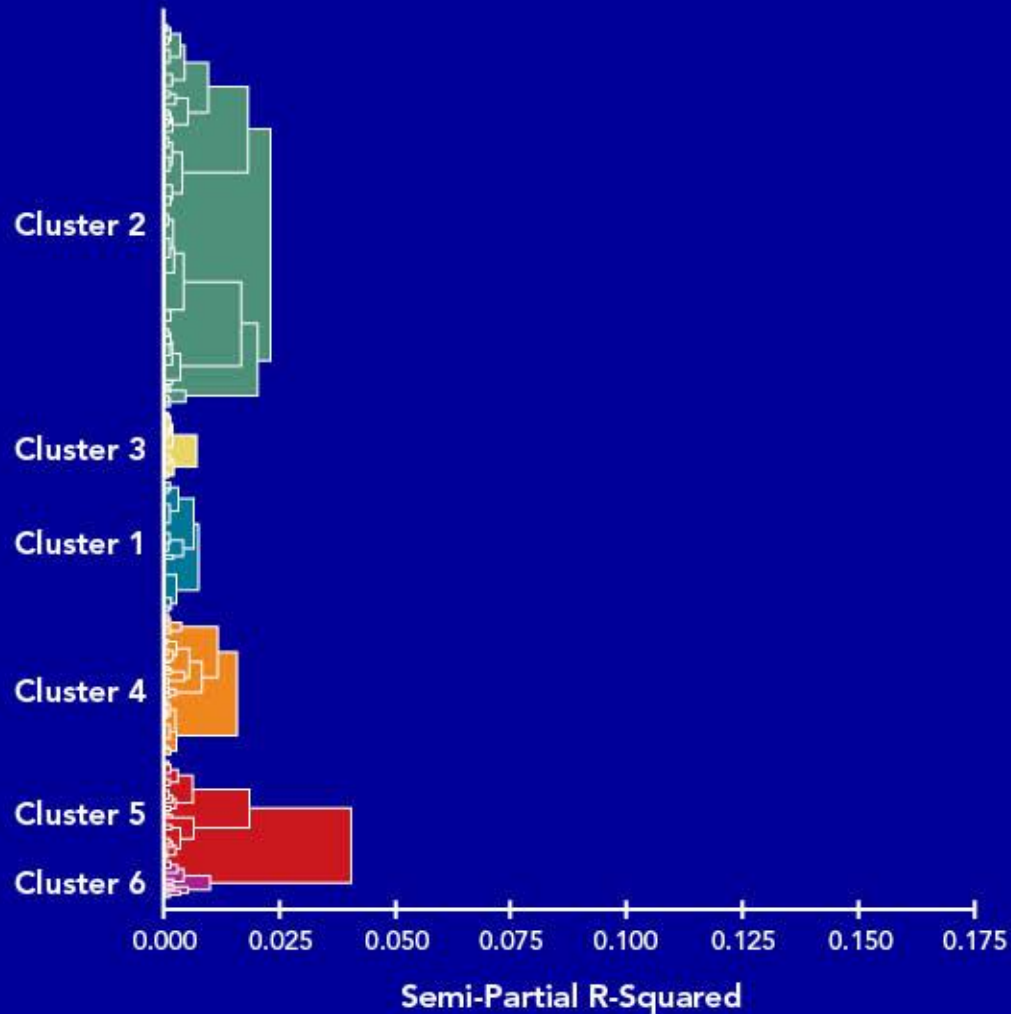


- PFTs: Baseline, Max
- Demos: Race, Gender, Ages
- Atopy; Skin tests
- Meds
- Triggers: Infxn, ASA, Allergy
- Sxs: Activity level
- HCU: Past 12 months
- Family Hx: Parents, Sibs
- Smoke Exposure
- Hormones
- PMH: GERD, HTN

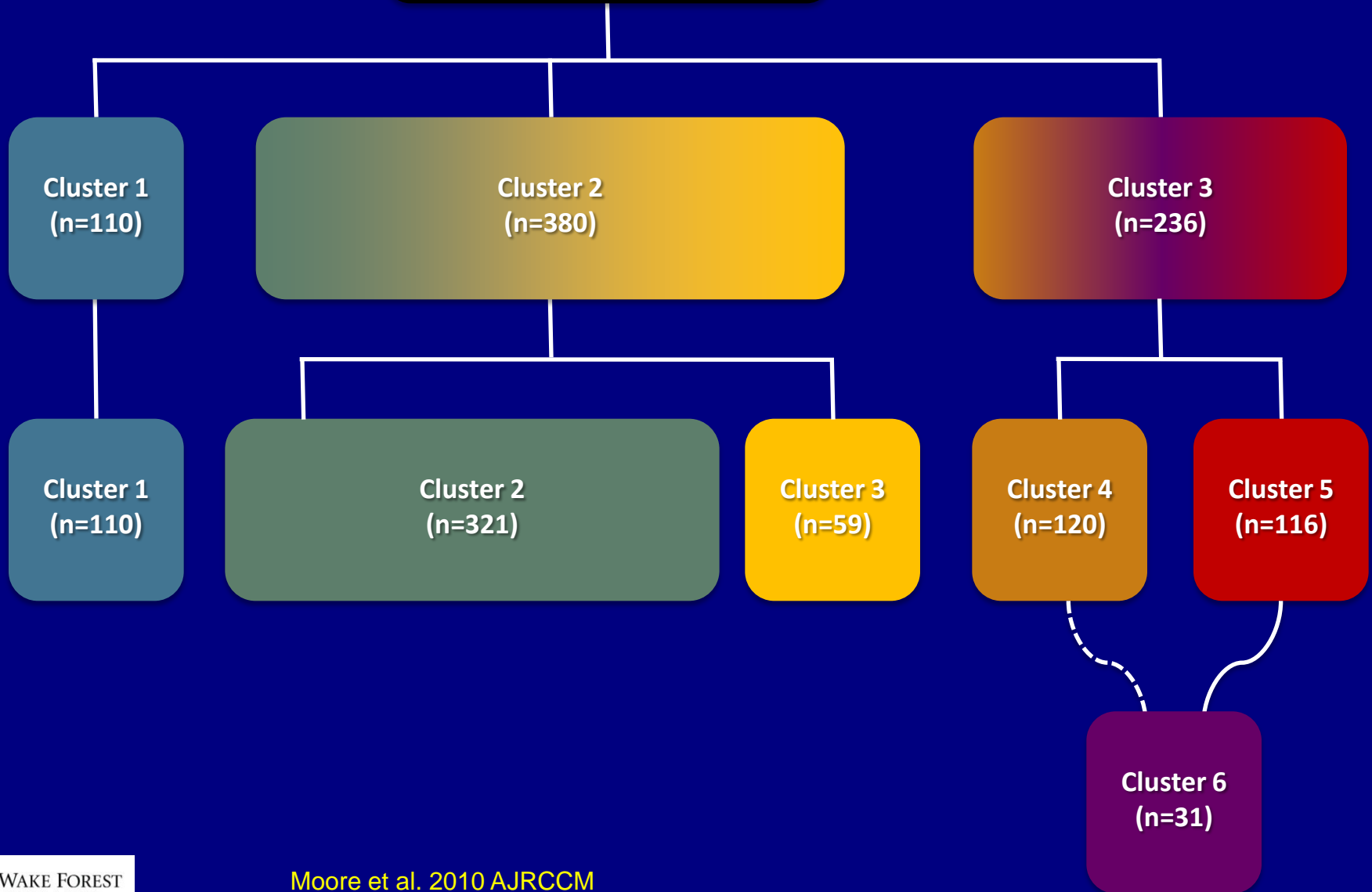
34 Total Variables, equally weighted

Dendrogram

Wald's minimum-variance hierarchical clustering method



726 Subjects in Cluster Analysis



Moore et al. 2010 AJRCCM

Asthma Cluster Analysis: 5 Clusters

1 Mild Allergic Asthma

Early onset asthma (EOA); Normal lung function; atopic
<= 2 Controller (medication use); Minimal Health Care Utilization (HCU): decreased sputum eosinophils (Eos)

2 Mild-Moderate Allergic Asthma

Most common cluster; EOA; Borderline normal FEV1 but reverses to normal; Atopic; <= 2 Controllers; Very low HCU, but some oral steroid bursts (OCS); (decreased EOS)

3 More Severe Older Onset Asthma

Older; Late onset (LOA); higher BMI; Less atopic; Moderately low FEV1 with some reversibility; Higher dos ICS; > 3 Controllers, but despite this more OCS bursts (increased sputum EOS)

4 Severe Variable Allergic Asthma

EOA; 53%; Severely decreased FEV1, but very reversible to near normal; Atopic OCS; "Variable" with need for frequent OCS; High beta agonist use; HCU and global symptoms (GS): (increased EOS)

5 Severe Fixed Airflow Asthma ("COPD similarities")

Older; (longest duration); 63% female; Less atopic; Severely decreased FEV1 less reversibility; On OCS; higher BMI; more GERD.HTN; High HCU, Beta use & GSS; (increased PMN, EOS)

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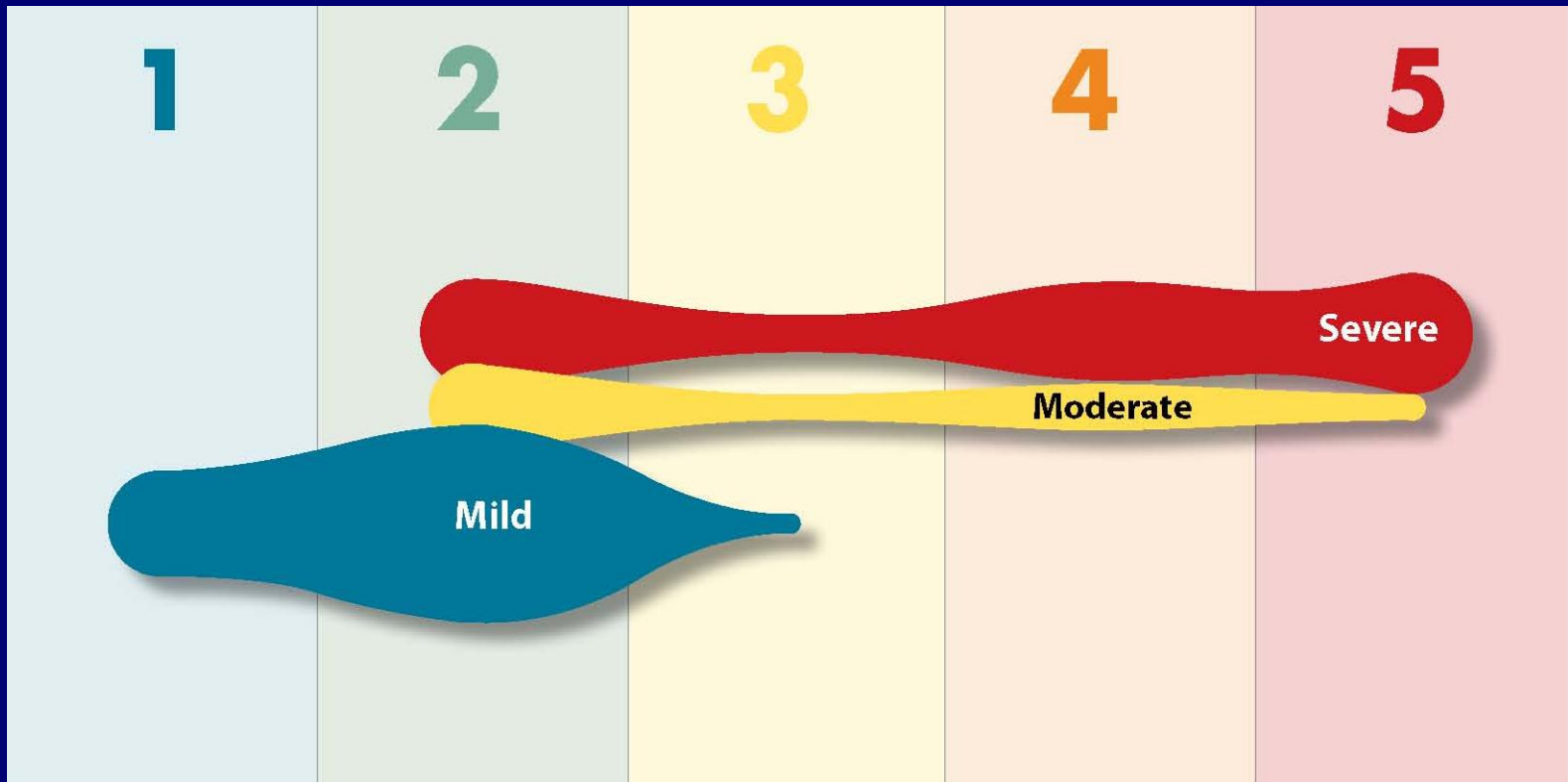
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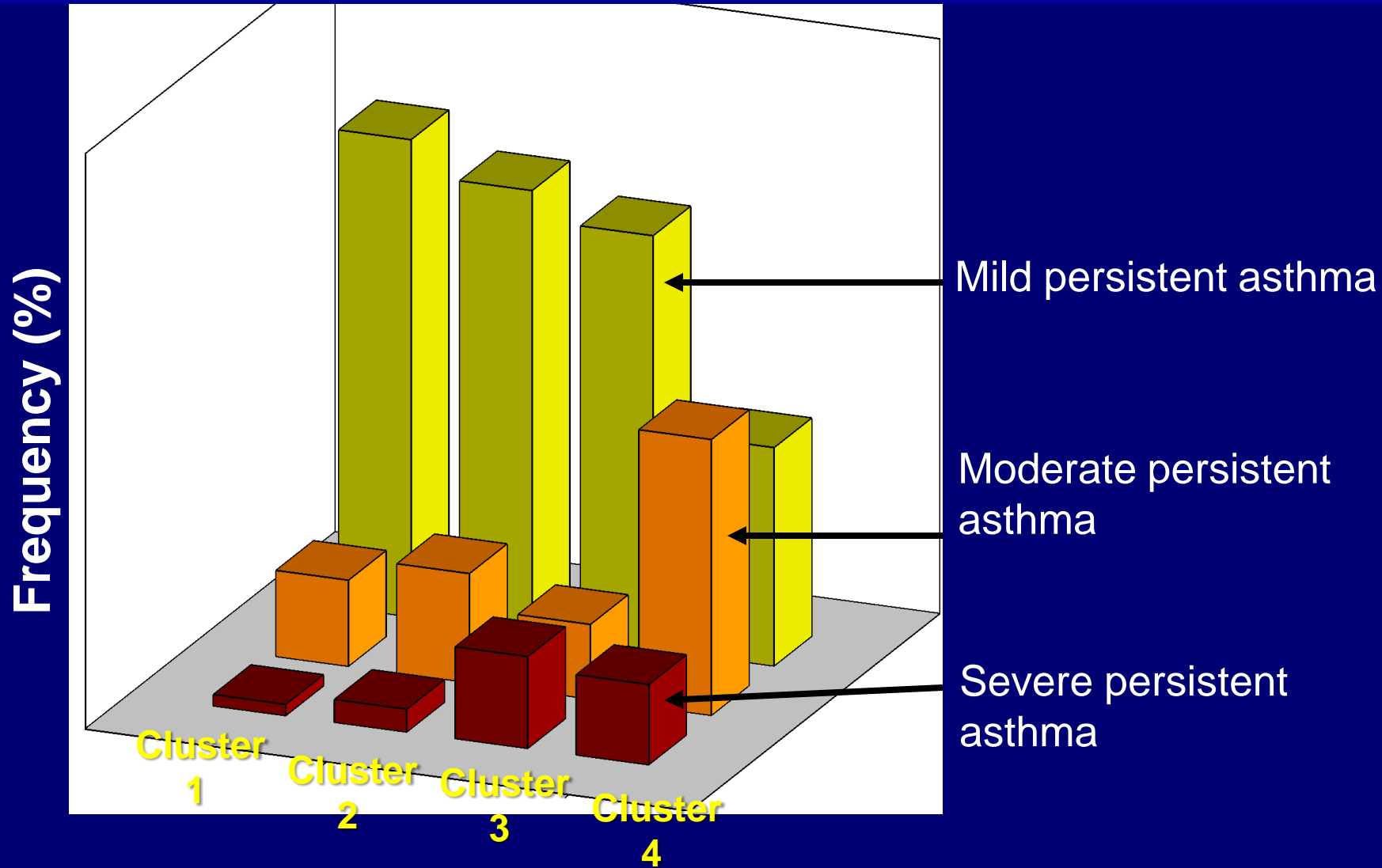
Is There a Cluster 6?

Cluster	“5”	“6”
N	85	31
Race (%CC/AA/Oth)	69/18/13	65/26/10
Age of asthma onset (yrs)	23	15
Gender (% female)	62	65
Asthma duration	30	27
BMI	31	32
Baseline FEV₁ pp (%)	43	45
Baseline FVC pp(%)	59	62
FEV₁/FVC(%)	57	58
MAX FEV₁ pp(%)	55	65
Fev₁ pp diff (%reversibility)	12	19
IgE (GM)	93	115

Relationship of Guideline Asthma Severity Classification and Cluster Assignment (Clusters 1-5)



Asthma Cluster Assignments Do Not Agree with NAEPP EPR-3 Definitions of Asthma Severity



Discriminant Variables for Cluster Assignment (Clinical)

- **Demographics**
 - Sex
 - Age of Asthma Onset
 - Asthma Duration
- **Pulmonary Function**
 - Baseline (drug withheld)
 - FEV₁ pp
 - FVC pp
 - FEV₁/FVC %
 - Maximum (post bronchodilator)
 - FEV₁ pp
 - FVC pp
 - % change in FEV₁
- **Medication**
 - Frequency of beta agonists use
 - Dose of corticosteroids

Important Questions About the Cluster Analyses

Do these phenotypic subgroups have different genetic or molecular phenotypes (biomarkers)?

Do these subgroups respond the same or differently to current and future (biologic) therapeutic regimens?

What are the implications of overlapping phenotypes with COPD in nonsmoking asthma?

**How well do sputum cell counts
characterize asthma severity?**

Identifying Phenotypic Subgroups of Subjects with Asthma:

Can Less Invasive Biomarkers
Predict Airway Inflammation?

(SARP)

Summary

Subjects with asthma stratified by sputum granulocytes show significant differences in lung function and healthcare utilization

Subjects with asthma stratified by blood eosinophils show some differences in lung function and atopic measures, but no associations with healthcare utilization

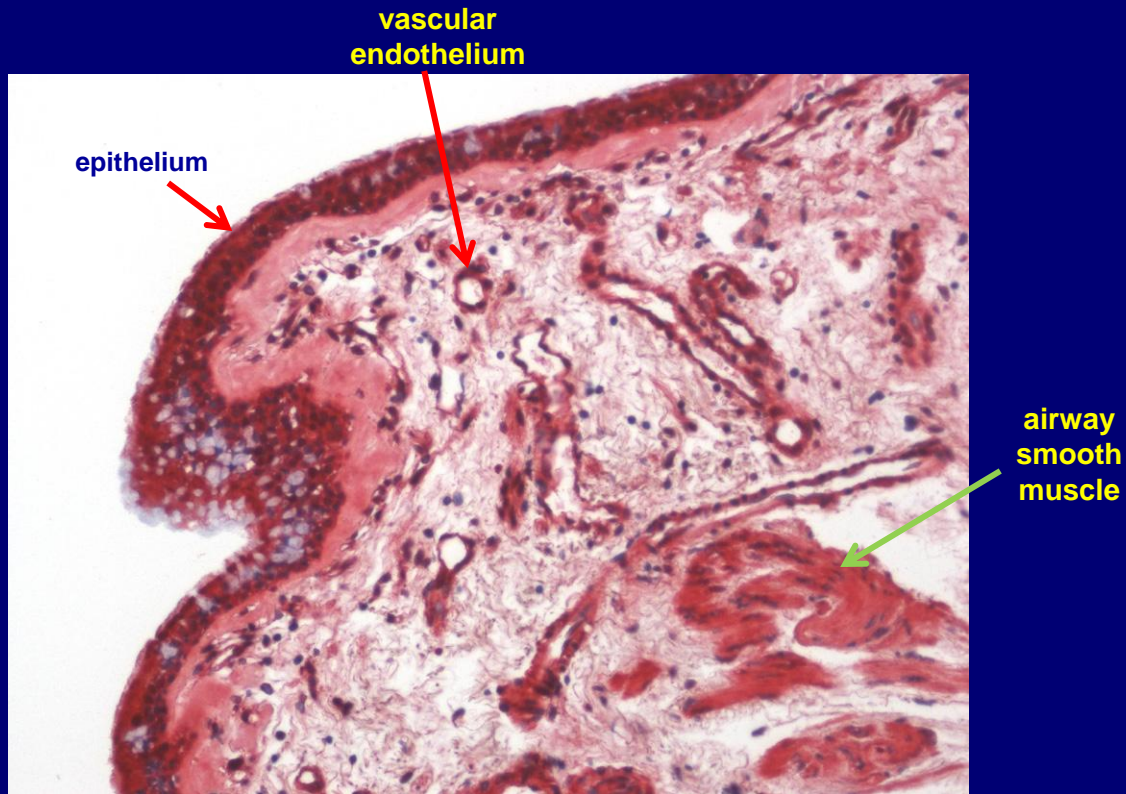
FeNO, blood eosinophils and IgE do not accurately predict sputum eosinophils ; additional criteria do not improve predictive value or accuracy

Both sputum eosinophils and neutrophils are important for associations with lung function and healthcare utilization

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Bronchial Biopsy Immunostaining with Anti-IL6 Receptor



IL6R and Lung Function in Severe Asthma

- Relationships of gene variation, serum IL6R levels and decreased lung function
- Evidence for IL6R in bronchial biopsies
- **New data from epithelial cell gene expression (NHLBI GO grant) shows correlation of increased IL6R RNA expression with decreased FEV1**

Question: Should available anti-IL6R therapies be evaluated in specific severe asthma phenotypes?

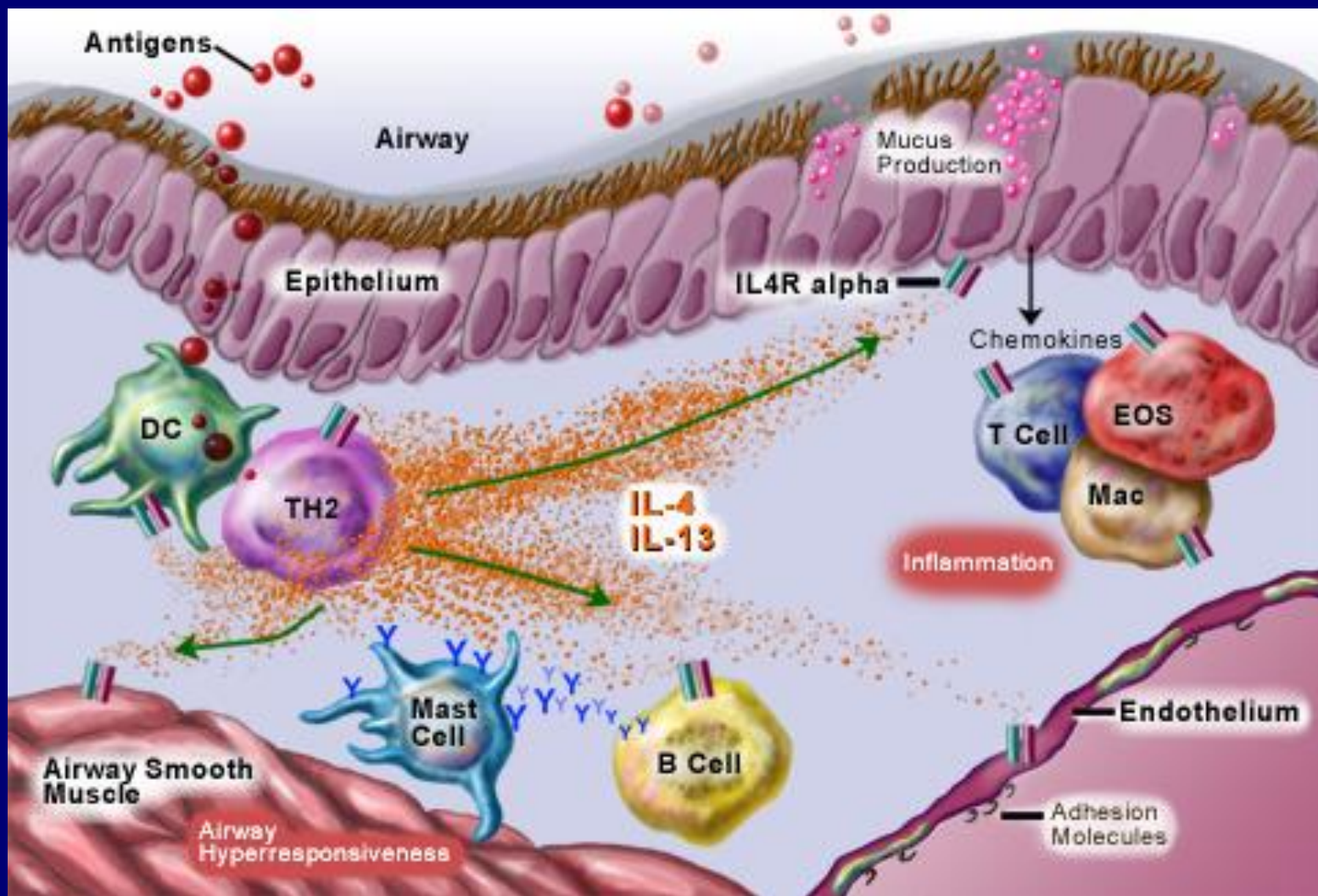
Lung Function: Summary

- Will this additive genetic approach be useful to identify patients with at risk asthma in early life for specific therapeutics interventions?
- Additional studies are needed for replication and longitudinal outcomes (SARP III)

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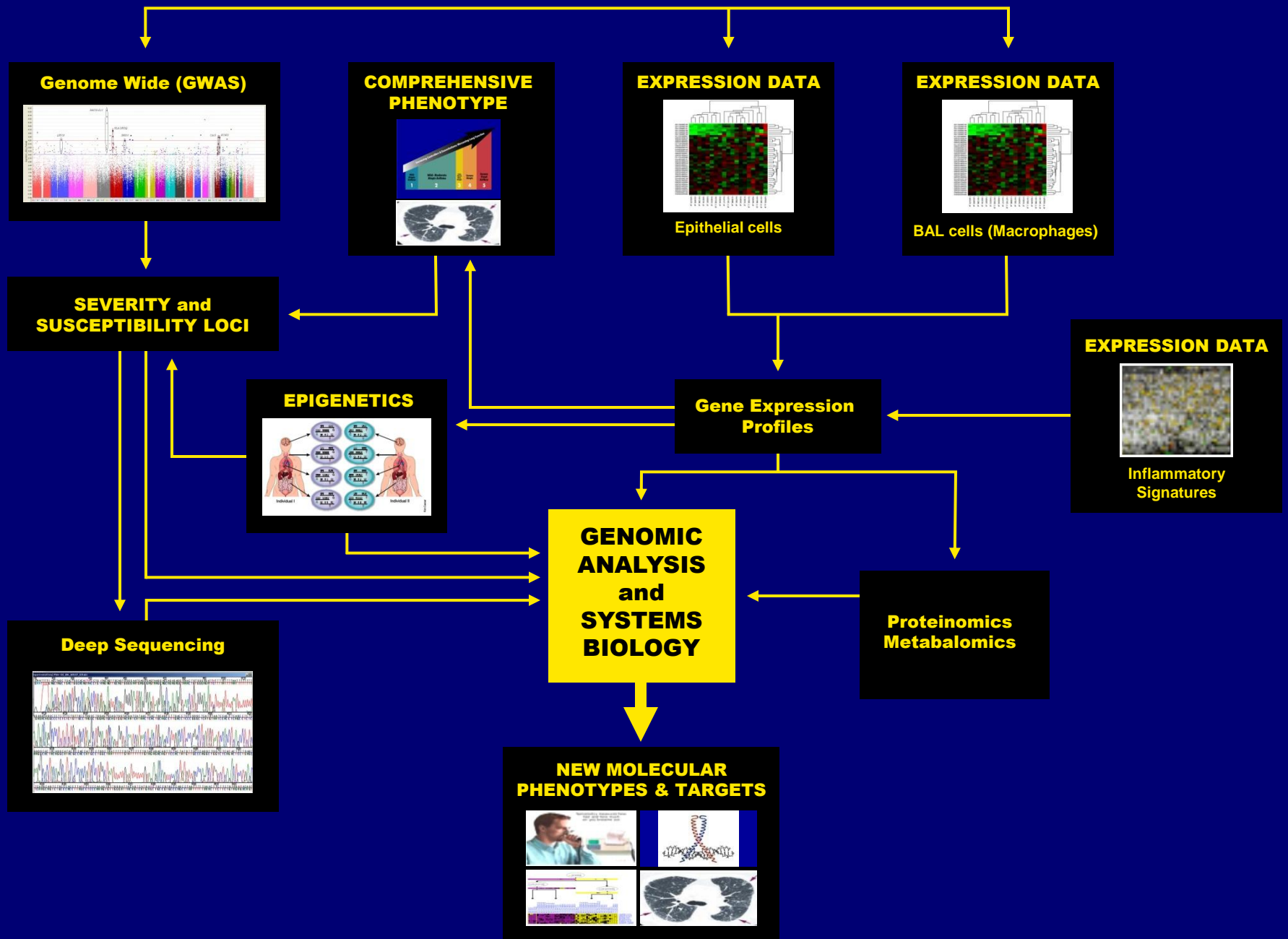
T helper 2 (Th2) Pathway in Asthma



Rational Therapeutic Targeting in Patients with Relevant IL4/IL13 Pathway Variation



Genomic Approaches in Severe Asthma



Advantages of Personalized Medicine: Everyone Can Win

- **Patients:** Identify the right drug for the right patient at the right time with improved compliance and better outcomes
- **Physicians:** More choices and more specific therapies
- **Government/Payers:** Better outcome driven return on investments
- **Regulators:** Increased confidence to approve earlier (licensing)
- **Pharma:** Better investment strategies for novel therapies