Cluster Analysis of Inflammatory Biomarker Expression in the International Severe Asthma Registry

Eve Denton, David B. Price, Trung N. Tran, G. Walter Canonica, Andrew Menzies-Gow, J. Mark FitzGerald, Mohsen Sadatsafavi, Luis Perez de Llano, George Christoff, Anna Quinton, Chin Kook Rhee, Guy Brusselle, Charlotte Ulrik, Njira Lugogo, Fiona Hore-Lacy, Isha Chaudhry, Lakmini Bulathsinhala, Ruth B. Murray, Victoria A. Carter, Mark Hew

Denton E., et al. *JACI In Pract* 2021:Article In press

The ISAR Initiative

- **A large observational registry with pooled data from multiple countries has the statistical power to better understand severe asthma epidemiology, clinical management and outcomes across international populations.**

The Broad Inclusion Criteria For Enrolment Captures a Diverse Patient Population Rarely Represented in RCTs

Inclusion

- Adult ≥18 years old with severe asthma
- Undergoing GINA Step 5 treatment OR uncontrolled on GINA Step 4 treatment
  - Uncontrolled as defined by ERS/ATS guidelines
- Poor symptom control where ACQ is consistently > 1.5, ACT <20
- Airflow limitation where pre-bronchodilator FEV_1 <80% predicted, with reduced FEV_1/FVC
- Serious exacerbations with ≥1 hospitalization, ICU stay or mechanical ventilation in the previous year
- Frequent severe exacerbations with ≥2 bursts of SCS with each course >3 days in the previous

- ✓ Smokers
- ✓ ACO
- ✓ Moderate-to-severe asthma

Exclusion

- Lack of informed consent for participation

Fitzgerald JM, Price DB et al. BMC Med Res Methodol 2020;20:212

BRISAR: Background & Aim

Inflammatory pathway in severe asthma	Associated biomarker
Allergy	Serum IgE
Eosinophilic inflammation	Blood eosinophil count
Airway epithelial dysregulation	FeNO

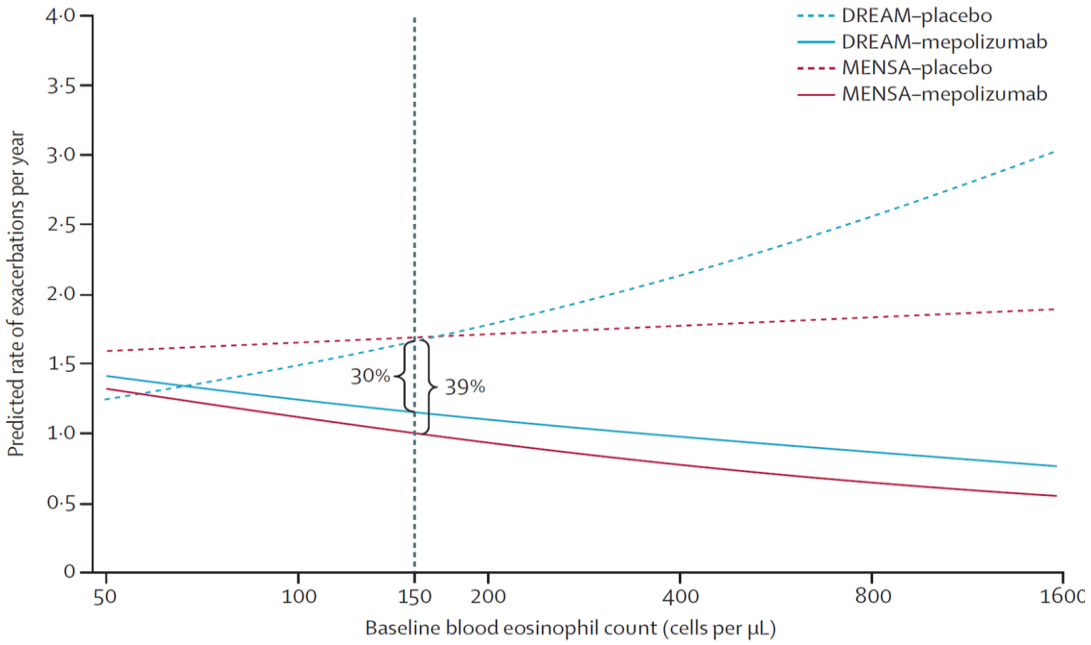
- Severe asthma is a heterogenous disease – a variety of cellular pathways are activated and differentially expressed
- Inflammatory biomarkers are used to characterize severe asthma phenotypes and guide the delivery of precision medicine; however, little is known about the overlap and relatability of these biomarkers in severe asthma

The aim of this study is to therefore describe the interrelation between inflammatory biomarker expression in severe asthma to characterize the activation of underlying inflammatory pathways using a large, international cohort

Denton E., et al. *JACI In Pract* 2021:Article In press

Differential Expression of Biomarkers Can Predict Treatment Response to Different Therapies

DREAM/MENSA: Increased blood eosinophil count associated with better response to Mepolizumab:



Patients with low eos and high FeNO respond to Dupilumab:

	AER relative risk in dupilumab vs placebo			
FeNO (ppb)		**<25**	**25 to <50**	**≥50**
Baseline Eos levels (cells/µL)	**<150**	1.154	0.643	0.551
	150 to <300	0.601	0.494	1.182
	≥300	0.564	0.347	0.194

Differential activation of inflammatory pathways → **Differential expression of biomarkers** → **Manifestation of associated clinical characteristics**

Ortega HG, et al. Lancet Respir Med 2016;4(7):549-556
Pavord ID et al. Presented at AACI 2020
Denton E., et al. *JACI In Pract* 2021:Article In press

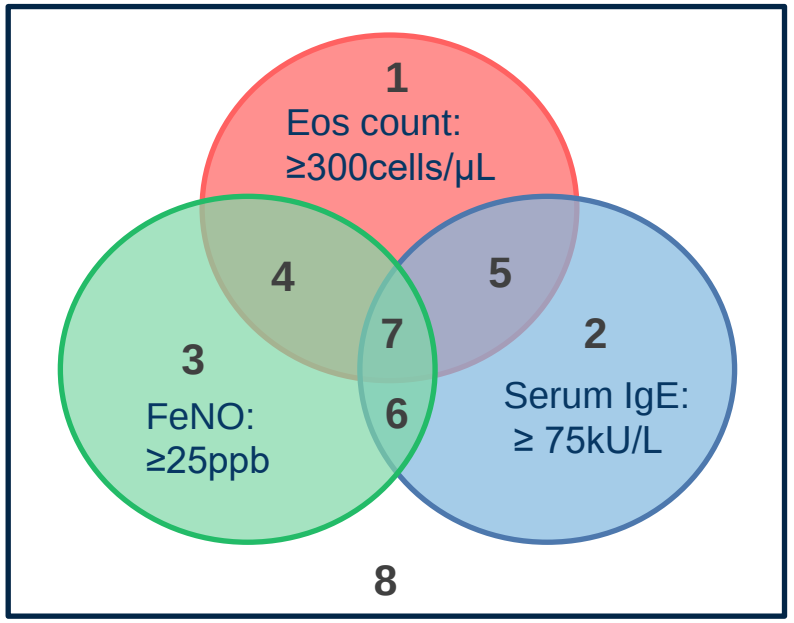
A Cross-Sectional Study: Design

Objective 1
To distinguish patient groups with different patterns of biomarker activation

Objective 2
To compare the clinical characteristics of the patient subgroups derived from these analyses

Inclusion:
- **ISAR population**
- **At least one measurement of each biomarker**

Categorized according to biomarker positivity*:



Outcomes:
- **Demographics**
- **Lung function**
- **Asthma symptoms**
- **Exacerbations**
- **Allergic comorbidities**
- **Asthma medications**

Index date: Date of enrolment in ISAR

Biomarker levels measured pre-biologic initiation

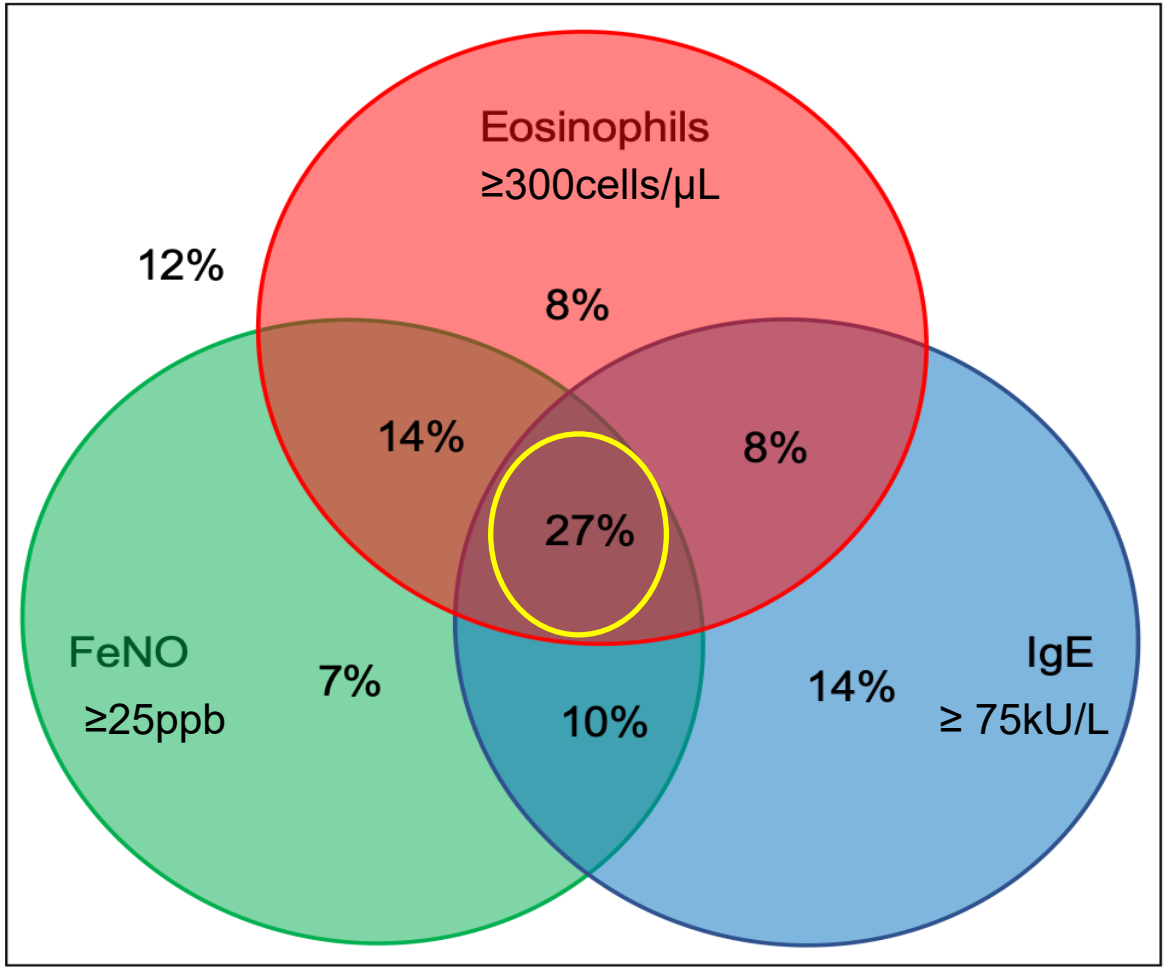
*Biomarkers were measured at baseline; the highest measurement was used in cases of multiple baseline measurements

Denton E., et al. *JACI In Pract* 2021:Article In press

Triple Positivity Was The Most Common Biomarker Overlap Group

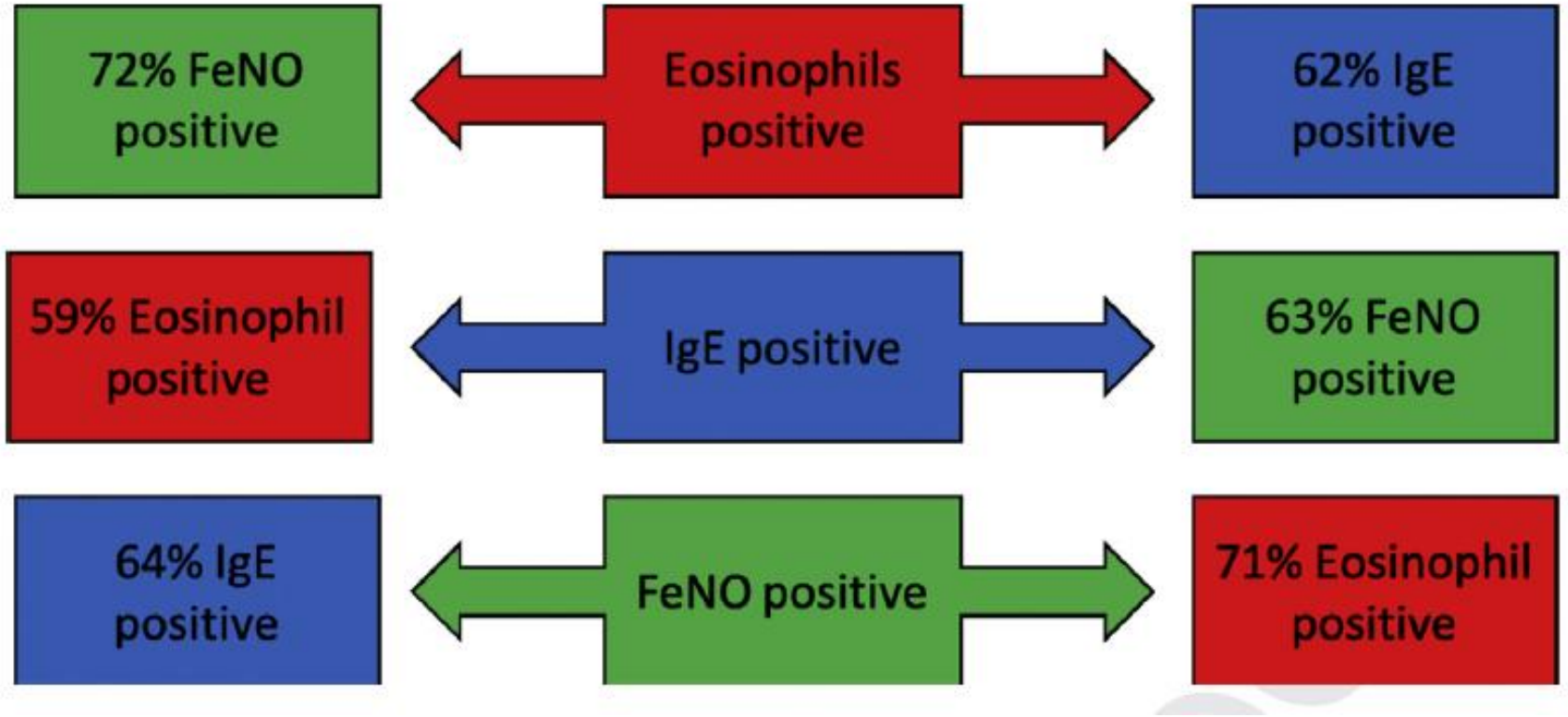
n=1175

- There is substantial overlap between biomarker positivity groups
- A greater overlap was observed with eosinophils and FeNO than with IgE
- Overall:
  - 57% were positive for eosinophils
  - 58% were positive for FeNO
  - 59% were positive for IgE



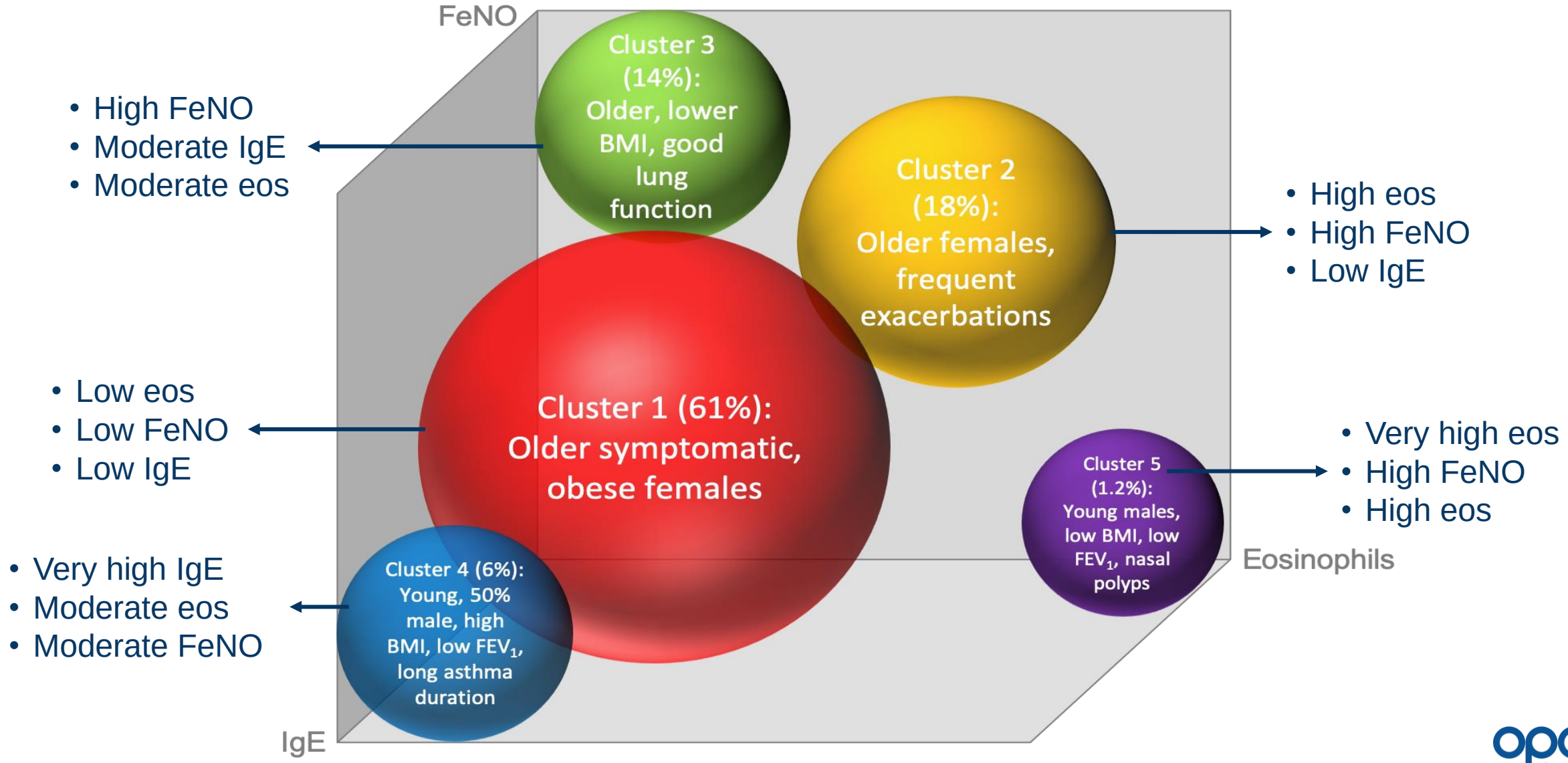
Denton E., et al. *JACI In Pract* 2021:Article In press

Likelihood of alternate biomarker positivity



Denton E., et al. *JACI In Pract* 2021:Article In press

Five Distinct Clusters Based on Biomarker Profiles



- High FeNO
- Moderate IgE
- Moderate eos

- High eos
- High FeNO
- Low IgE

- Low eos
- Low FeNO
- Low IgE

- Very high eos
- High FeNO
- High eos

- Very high IgE
- Moderate eos
- Moderate FeNO

Denton E., et al. *JACI In Pract* 2021:Article In press

Clinical Characteristics Associated With Each Patient Subgroup

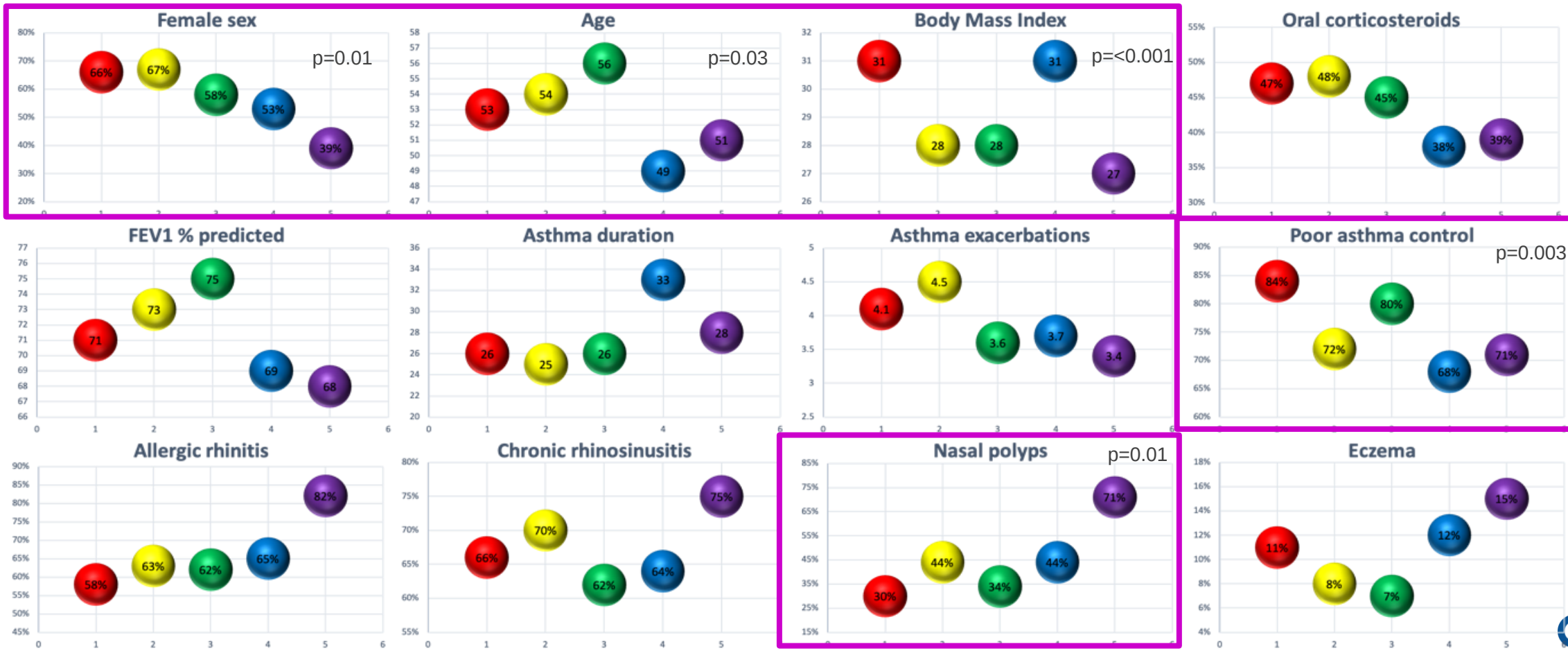
Cluster 1:
- Low eos
- Low FeNO
- Low IgE

Cluster 2:
- High eos
- High FeNO
- Low IgE

Cluster 3:
- High FeNO
- Moderate IgE
- Moderate eos

Cluster 4:
- Very high IgE
- Moderate eos
- Moderate FeNO

Cluster 5:
- Very high eos
- High FeNO
- High eos



Denton E., et al. *JACI In Pract* 2021:Article In press

Implications for Clinical Practice

- New methods are required to determine the most appropriate choice of targeted therapy – simply relying on biomarker positivity is not appropriate due to the significant overlap groups
- There is an urgent unmet need in severe asthma, where patients negative for all three biomarkers cannot be appropriately treated by currently available biologics
- Discrete clusters of severe asthma phenotypes based on specific combinations of biomarker profiles can be identified – future research can use these patient sub-populations as a basis to better understand severe asthma disease mechanisms

Conclusion

- Many patients have an overlap in biomarker positivity, which may assist in delivering precision medicine
- Specific combinations of inflammatory pathway activation predominate in severe asthma
- Distinct inflammatory endotypes underpin clinically recognizable phenotypes