Biomarker Relatability in Severe Asthma

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Speaker Disclosure

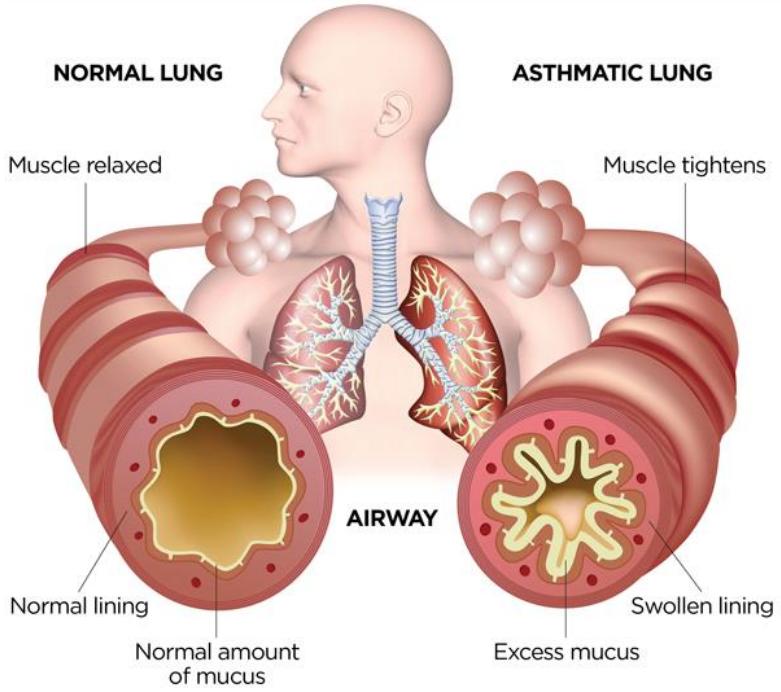
- In accordance with the policy of the Thoracic Society of Australia and New Zealand the following presenter has indicated that they have a relationship which could be perceived as a real or apparent conflict of interest. The nature of the conflict is listed:

- **This project was funded by Optimum Patient Care Global Ltd. and AstraZeneca, all data analysis and writing was conducted independently.**

- **No other conflicts of interest to report related to this project.**

Introduction

- 339 million people worldwide[1]
- Up to 1 in 10 asthma patients have severe asthma[2]
- Severe asthma is clinically heterogeneous [3]
- Many patients have evidence of 'Type 2' airway inflammation



Type 2 inflammation

- Eosinophilic inflammation
- Allergic inflammation
- Epithelial dysfunction

Biomarker

-> elevated blood eosinophils

-> elevated serum Immunoglobulin E (IgE)

-> elevated exhaled nitric oxide (FeNO)

Targeted therapy[4]

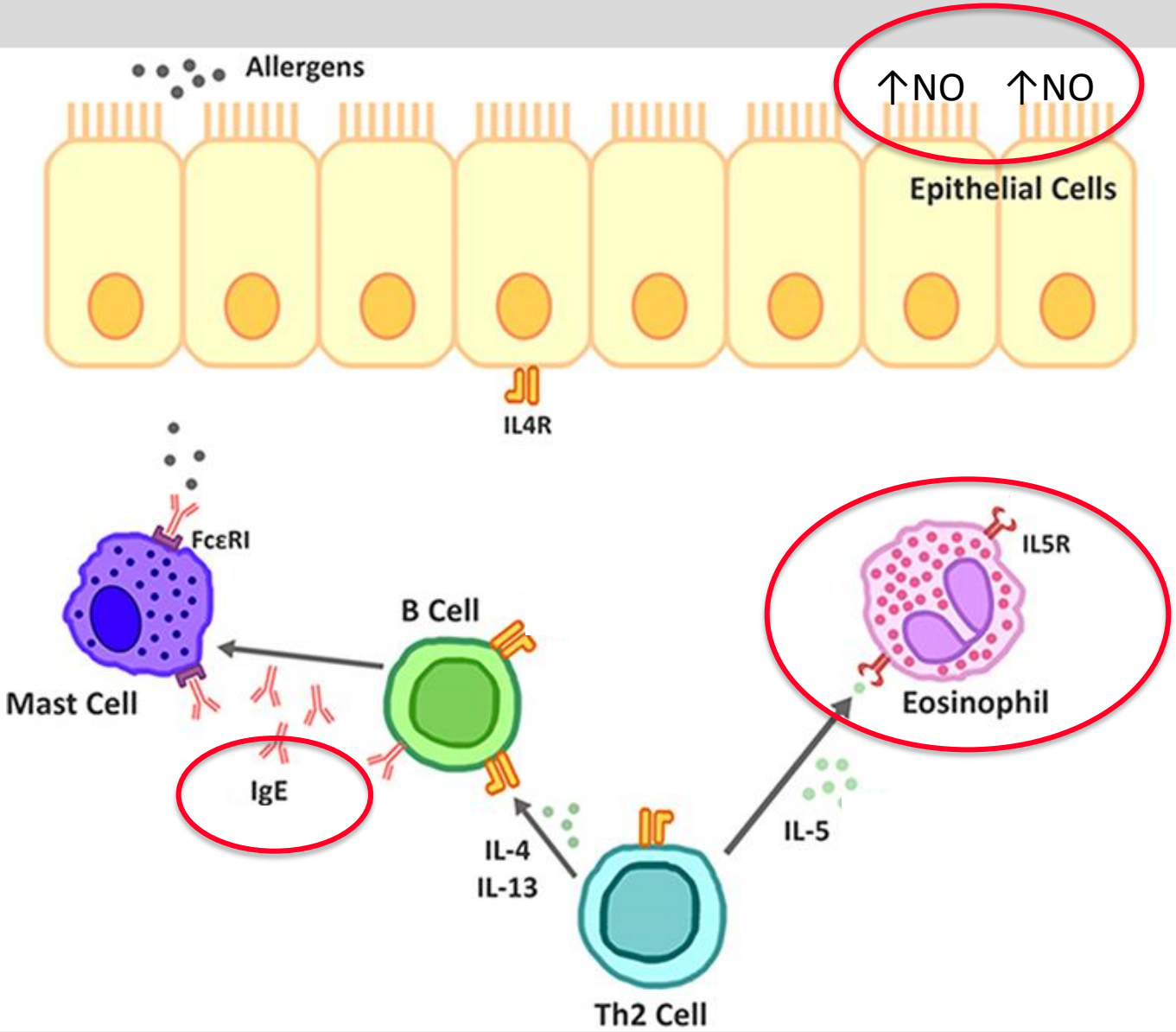
-> Anti IL5/R, anti IL4/13R

-> Anti IgE

-> Anti IL4/13R

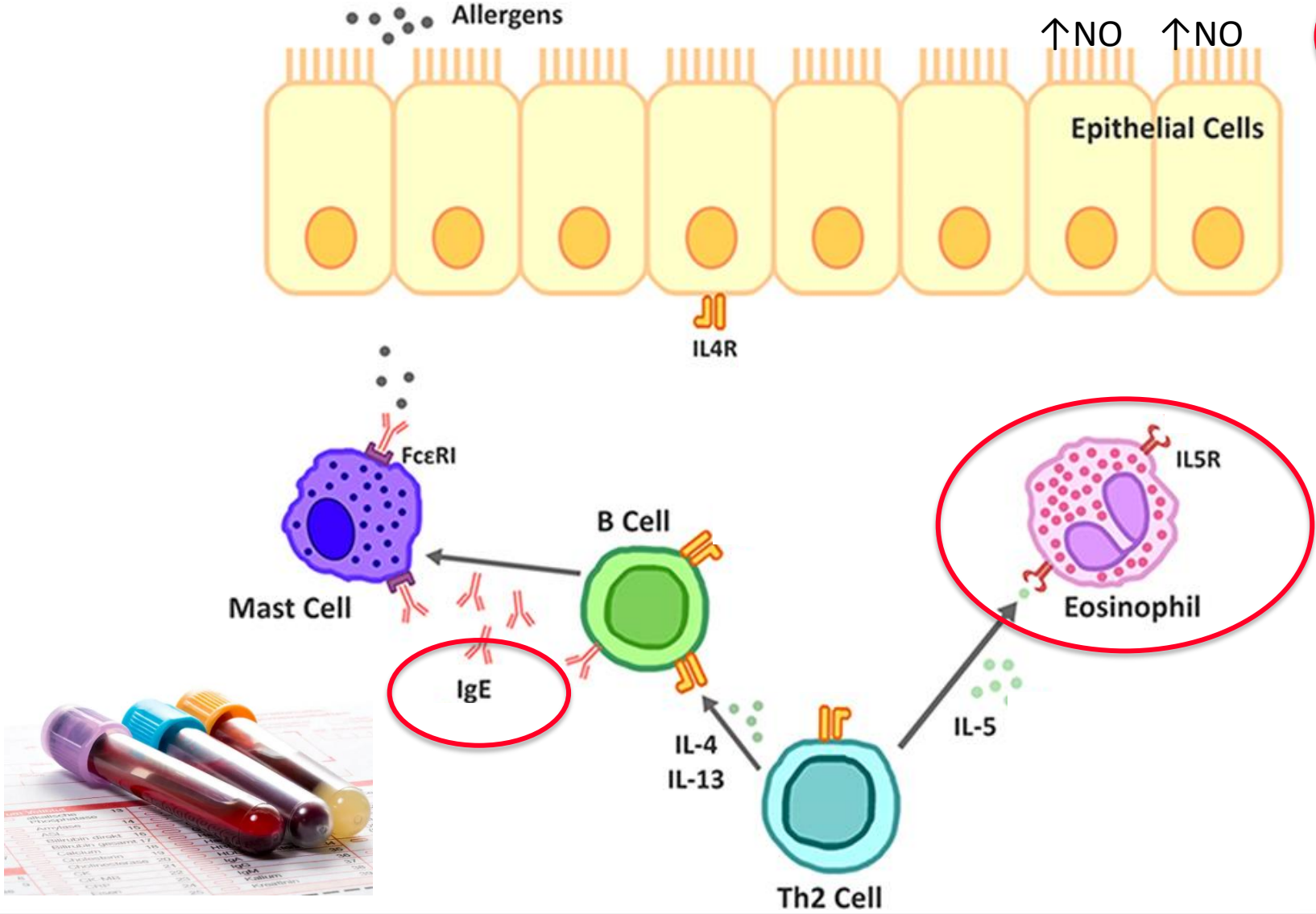
1. *WHO, Asthma Factsheet, 2020*
2. *Chung et al, ERJ, 2014*
3. *Wenzel et al, Nature Med, 2012*
4. *Fitzpatrick et al, JACIIP, 2017*

Biomarkers



Adapted from Miyokawa et al, PPA, 2020

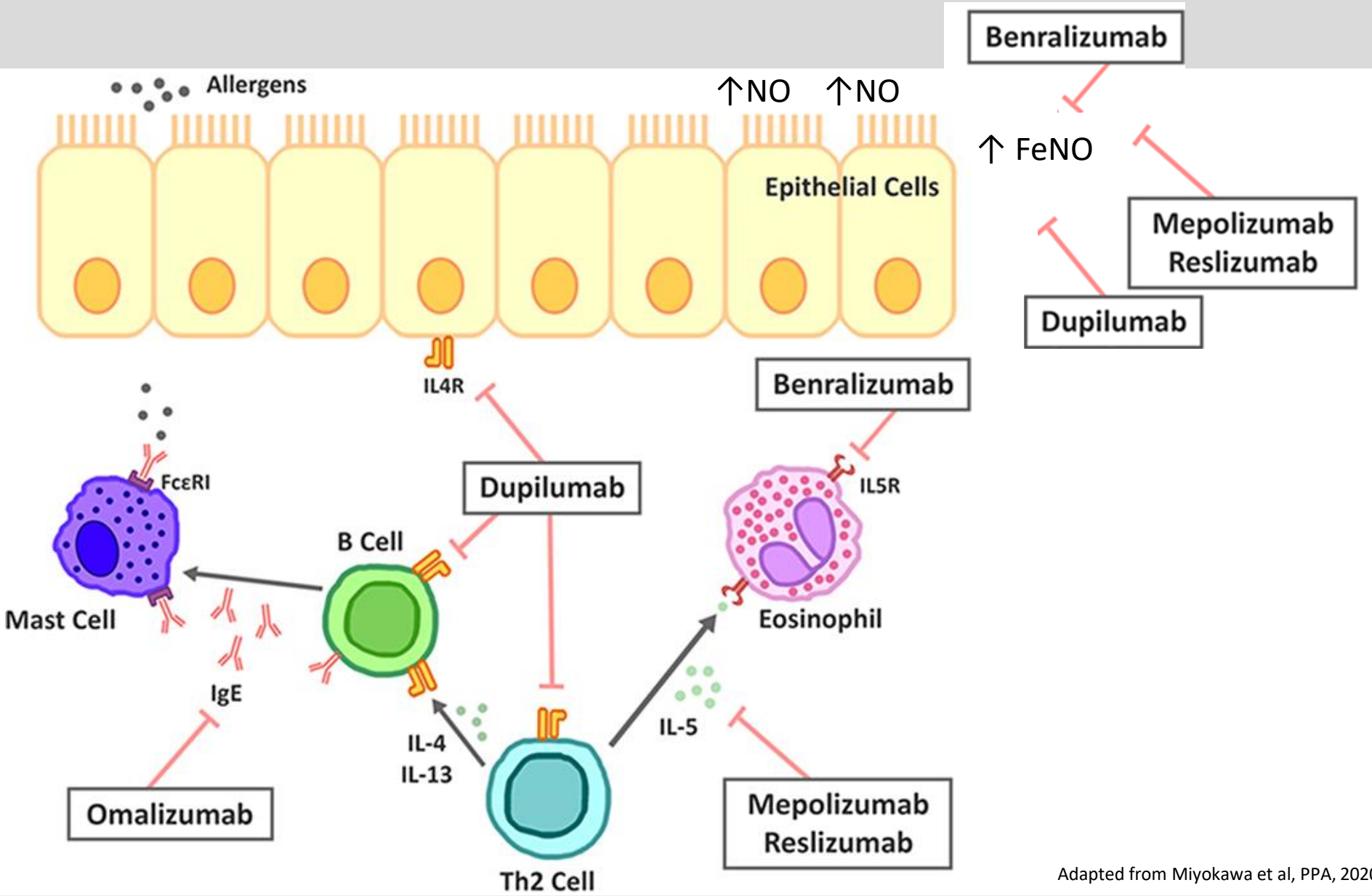
Biomarkers



↑ FeNO

Adapted from Miyokawa et al, PPA, 2020

Biomarkers



Adapted from Miyokawa et al, PPA, 2020

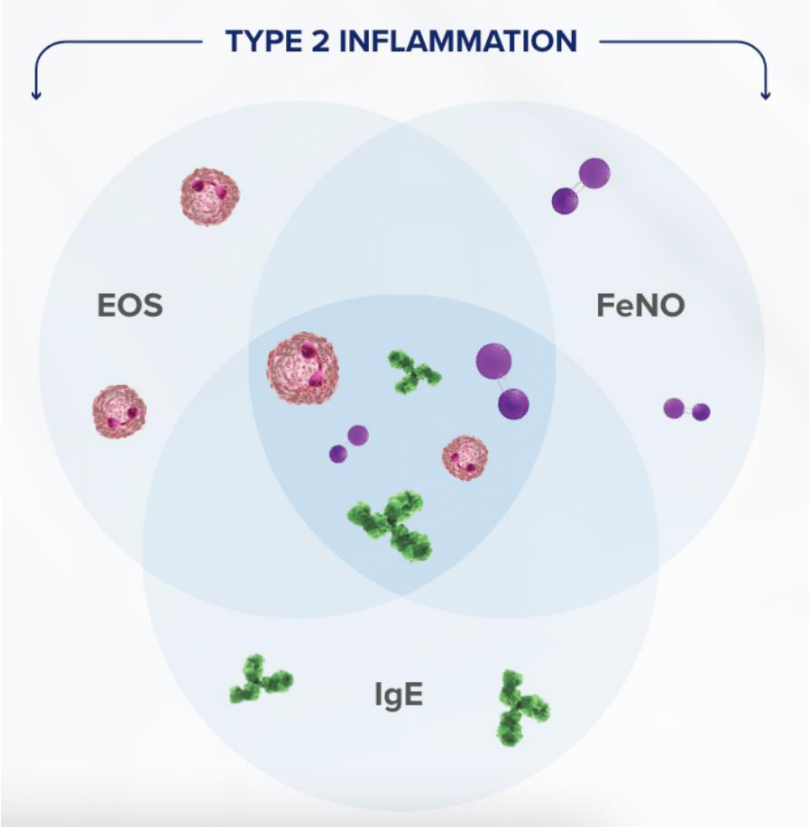
Introduction

- Most studies focus on one, or two biomarkers
- Previous cluster analyses have provided clinicopathologic insights [1,2,3]
- ?Pattern and relatability of biomarker elevation in severe asthma
- How elevation in one biomarker relates to elevation in other biomarkers

- **Why is this important?**

- **What proportion of Severe Asthma patients may respond to each set of biologics, and what/where the unmet need lies**

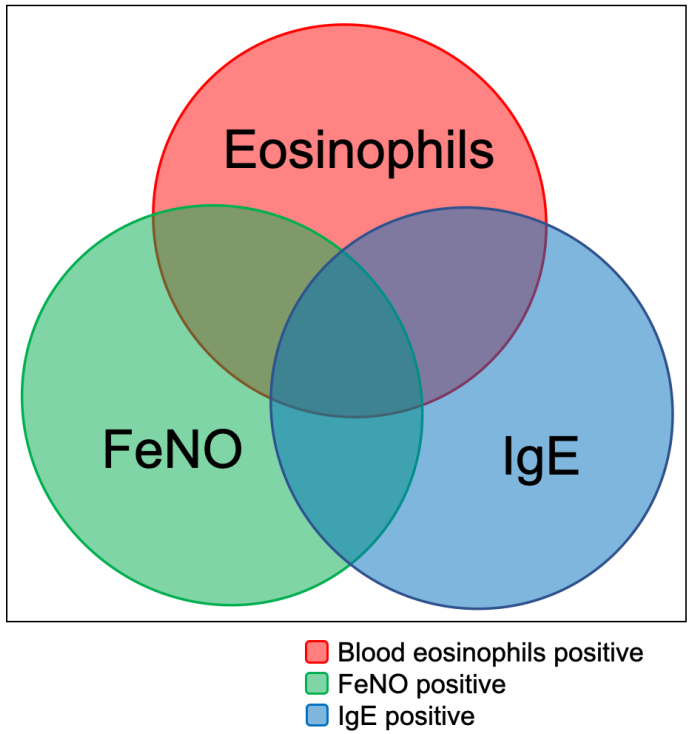
- **Different patterns of biomarker elevation may give insight into the activation of different inflammatory pathways**



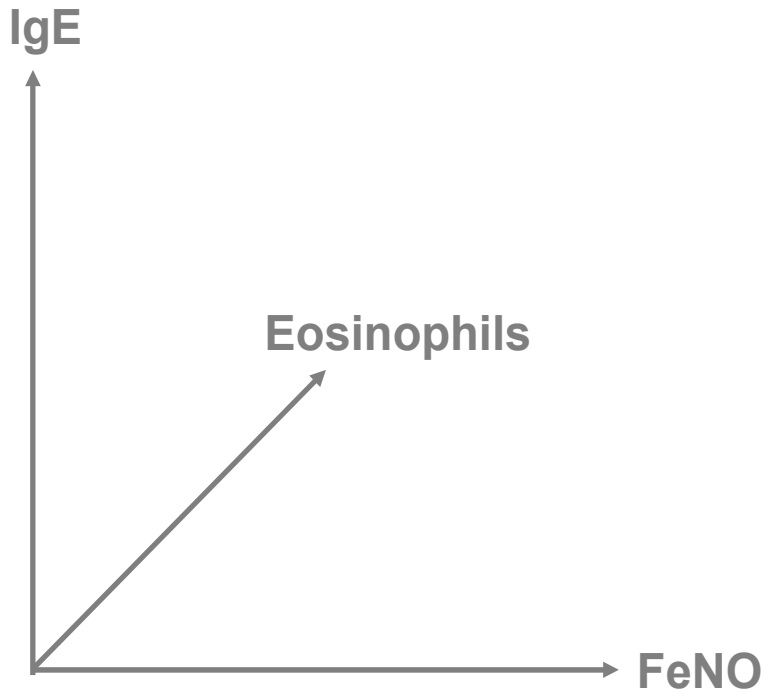
1. *Moore et al, AJRCCM, 2009*
2. *Halder et al, AJRCCM, 2007*
3. *Wu et al, AJRCCM, 2018*

Aims

1. Pre-specified thresholds for each biomarker
   - Blood eosinophils ≥ 300 cells/uL[1]
   - FeNO ≥ 25ppb[2]
   - Total IgE ≥ 75 kU/L[3]



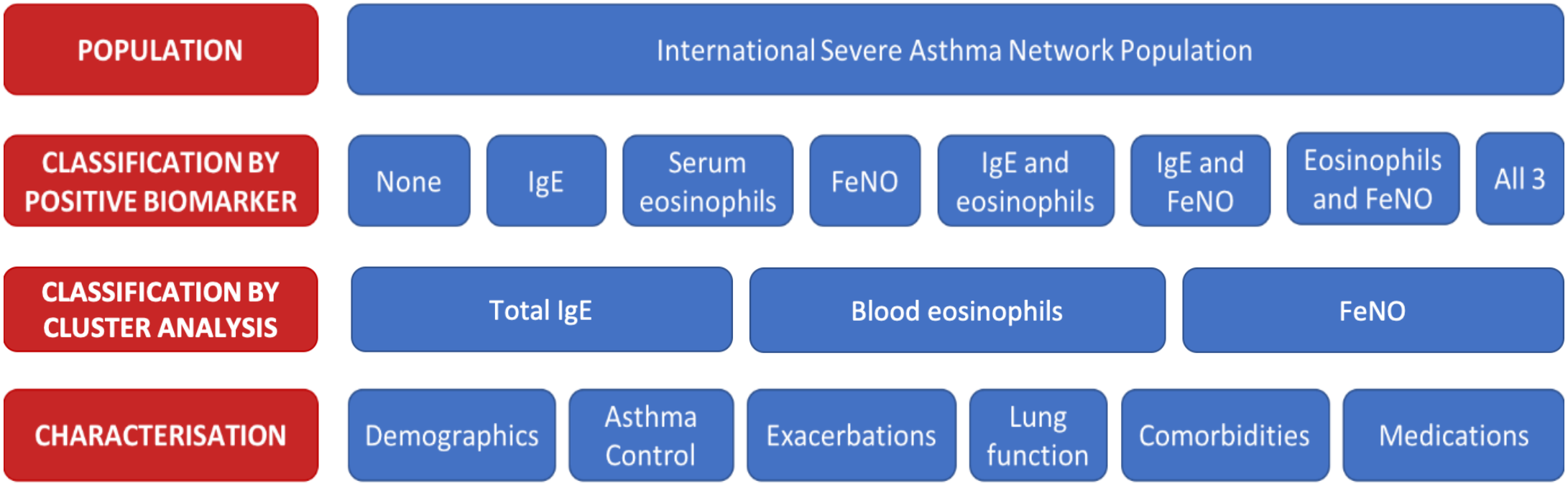
2. Cluster analysis



1. Buhl et al, ERJ, 2017
2. Dweik et al, AJRCCM, 2011
3. Bousquet et al, Res Med, 2007

Methods

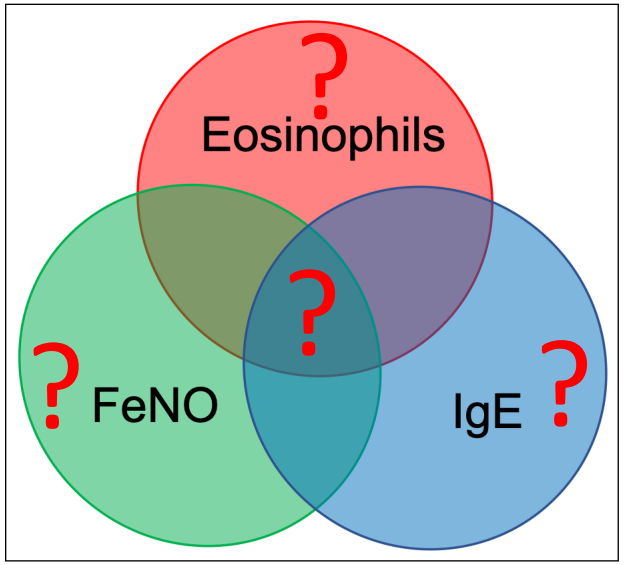
- International Severe Asthma Registry
- 10 countries: USA, Canada, Greece, Italy, Ireland, South Korea, Bulgaria, Kuwait, UK Spain
- Severe asthma: receiving GINA Step 4 treatment and remaining uncontrolled **or** GINA Step 5 treatment
- Inclusion criteria: ≥ 18 years with severe asthma AND all three biomarkers measured and available at baseline



Methods

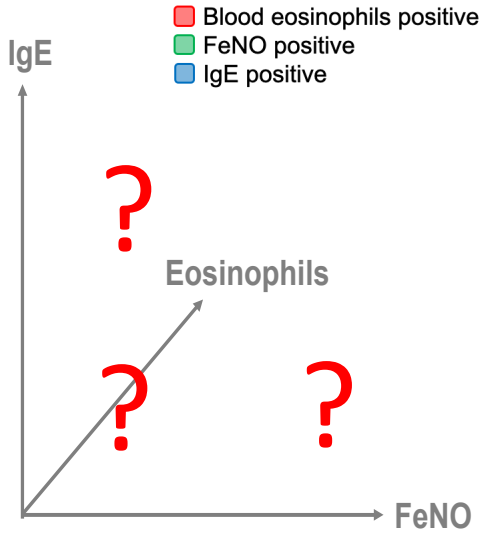
Using pre-specified thresholds for biomarker positivity:

1. Describe the proportion with positive biomarkers and their overlap
2. Point prevalence of eight biomarker groups
3. Baseline characteristics of these eight biomarker groups with comparisons:
    1. Demographics
    2. Asthma status: lung function, asthma control, exacerbations
    3. Comorbidities
4. Sensitivity analysis :
    1. Other common biomarker cut offs: Eosinophils (≥ 150), IgE (≥ 30/100/300/400/700), FeNO (≥ 50)
    2. Allergic sensitisation instead of IgE



Using biomarkers as continuous variables:

1. Hierarchical cluster analysis method with an agglomerative approach and Ward's linkage
2. K-means cluster analysis was used to test the consistency of the model using multiple different cluster numbers.



Results: Baseline Characteristics

Group	Total (1175)
Sex (% female)	64%
BMI, mean (st. dev)	30 (±7.5)
Age, mean (st. dev)	53 (±15)
Poor Asthma control: % (number)	80% (510)
Exacerbations, mean (± st. dev.)	4 (±4)
FEV_1 pre %predicted, mean (± st. dev.)	72% (±22)
Allergic rhinitis: current % group (number)	60% (488)
Chronic rhinosinusitis: current % group (number)	66% (354)
Eczema: current % group (number)	10% (104)
Nasal polyps: current % group (number)	35% (204)

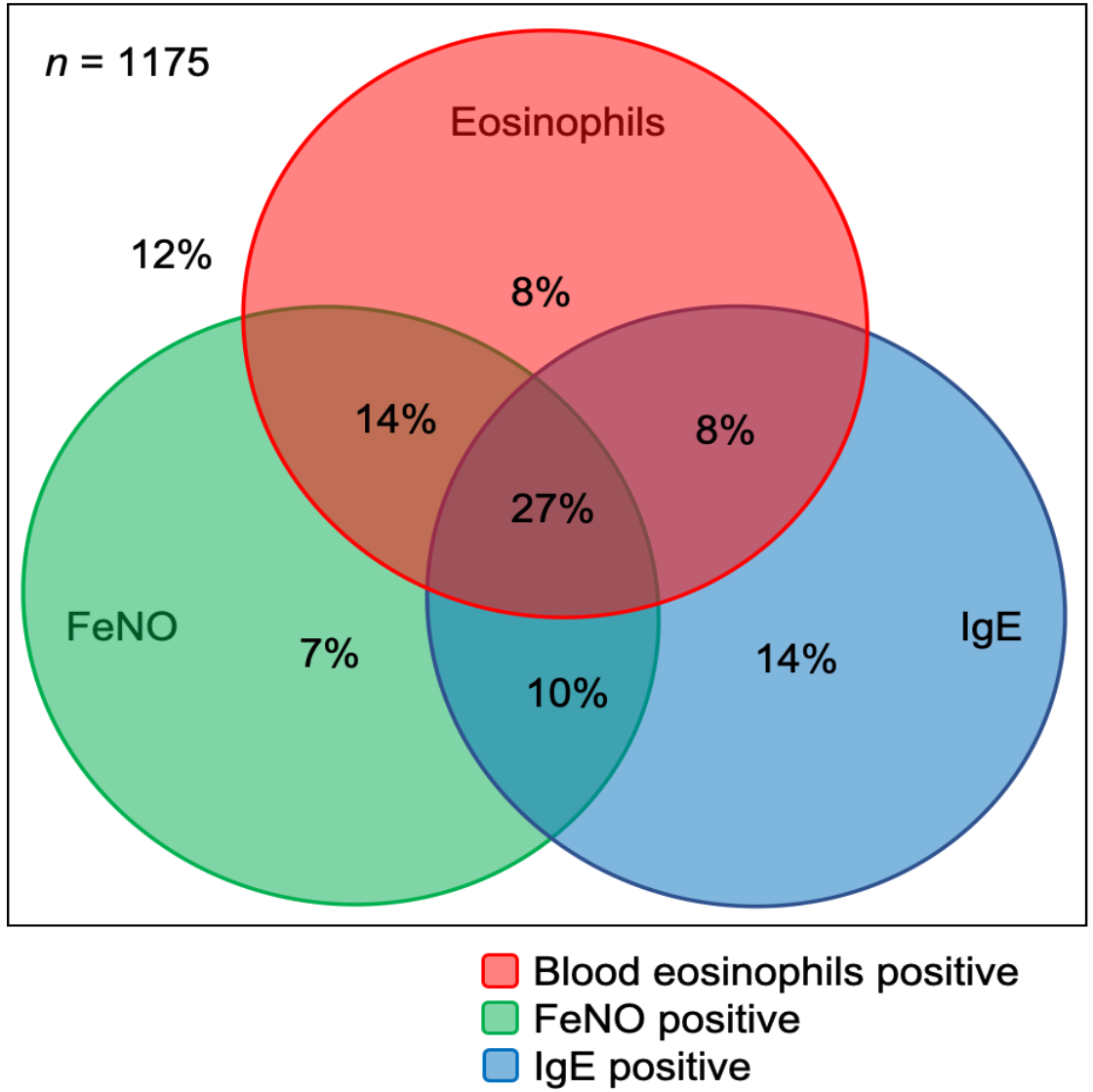
Results: Biomarker Positivity by Pre-specified Thresholds

- Eosinophil positive: 57%
- FeNO positive: 58%
- IgE positive: 59%

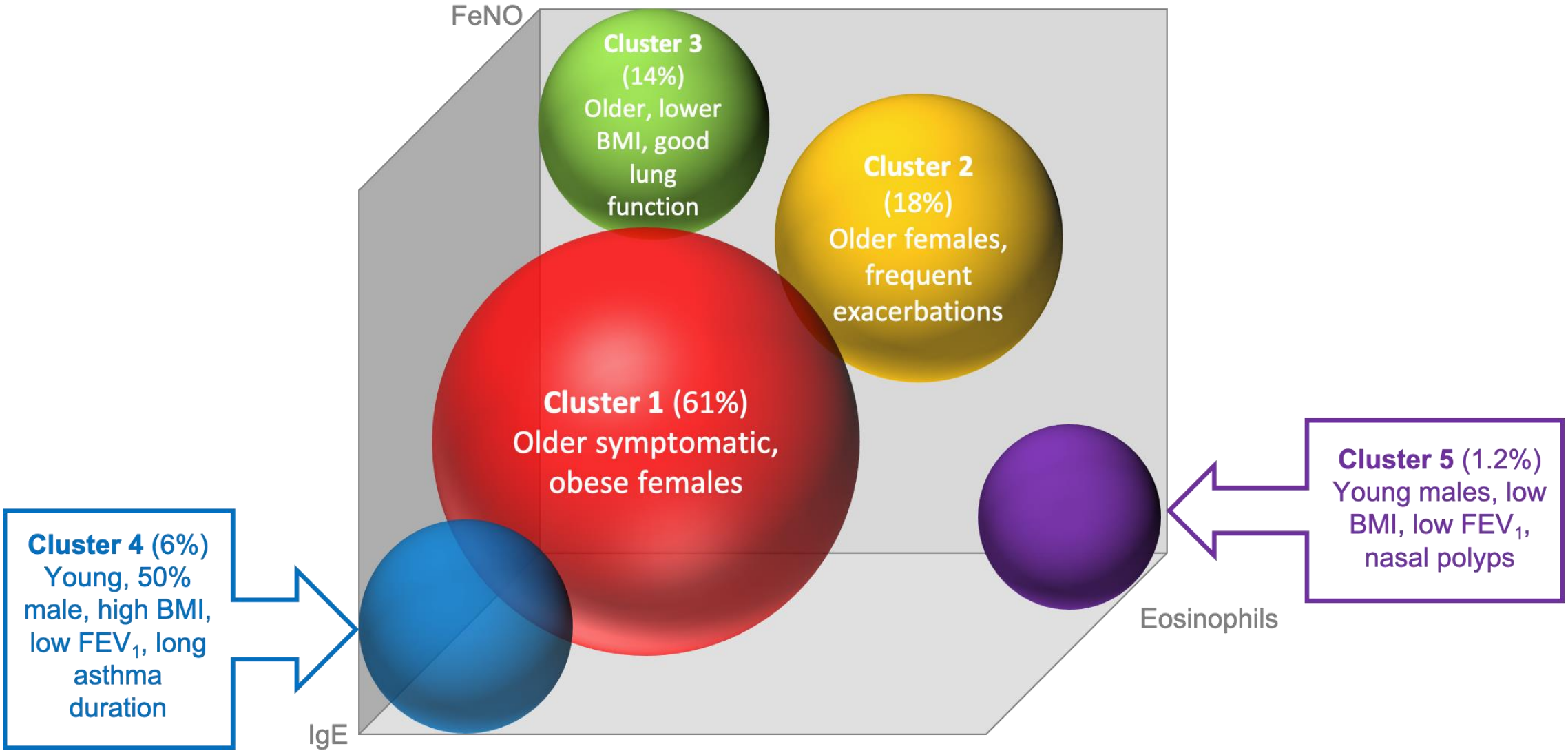
- Comparisons between biomarkers groups:
  - Triple –ve – more females (74% Vs 57%, p = 0.01)

- Sensitivity analyses

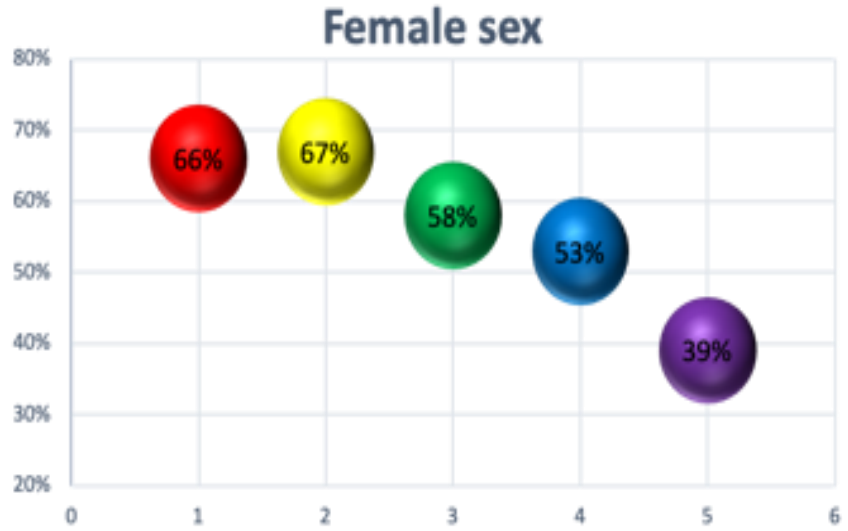
- Dichotomous cut offs highlight the heterogeneity in severe asthma

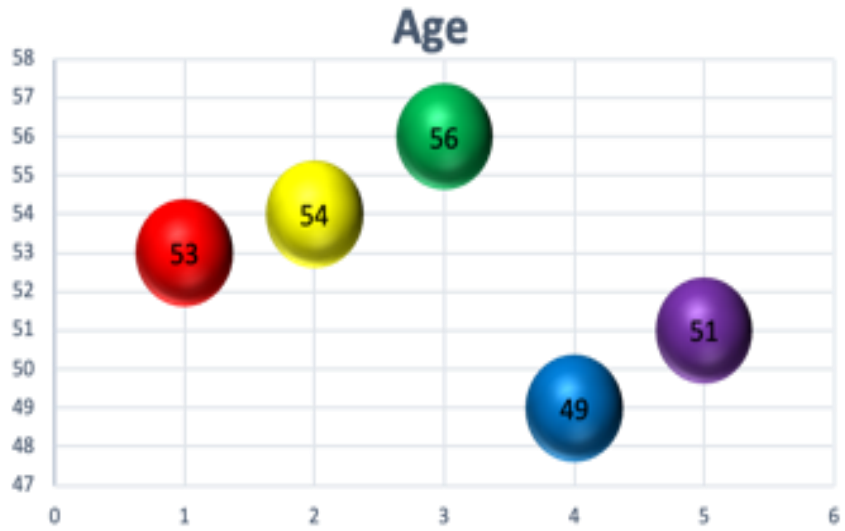


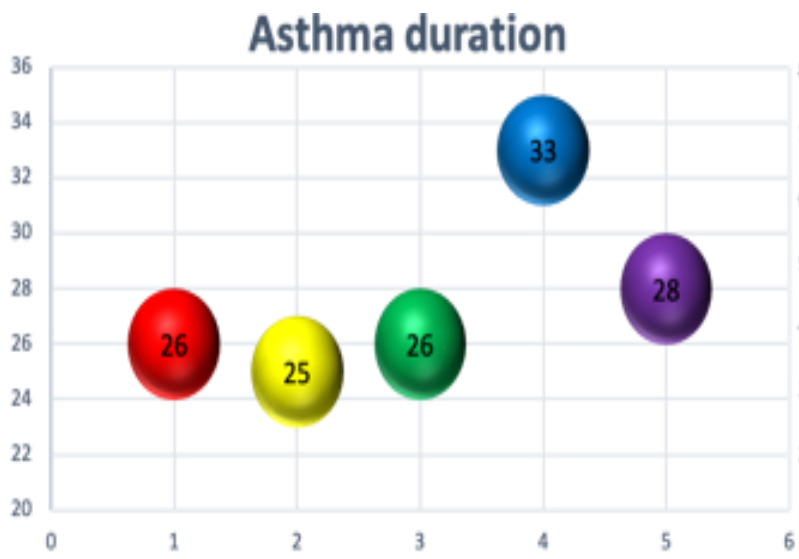
Results: Cluster Analysis

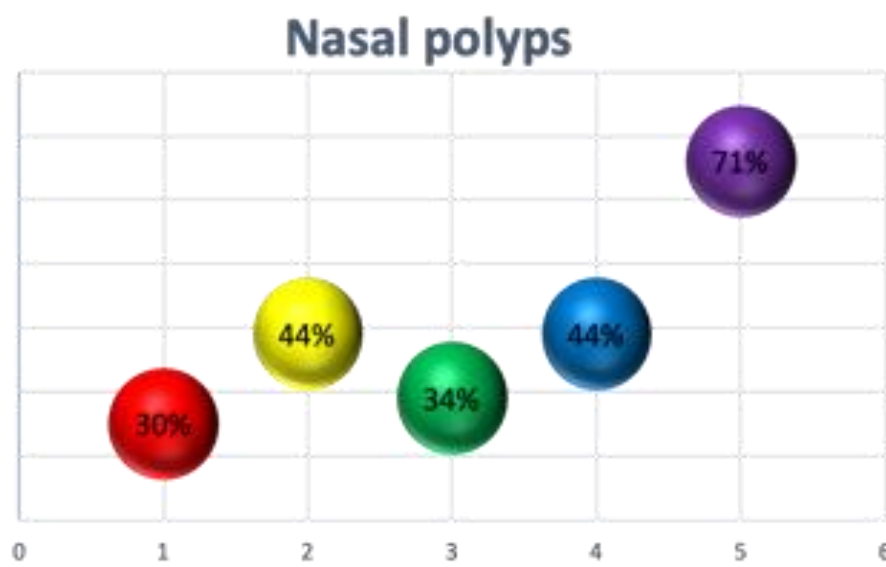


Results: Cluster Analysis Baseline Characteristics



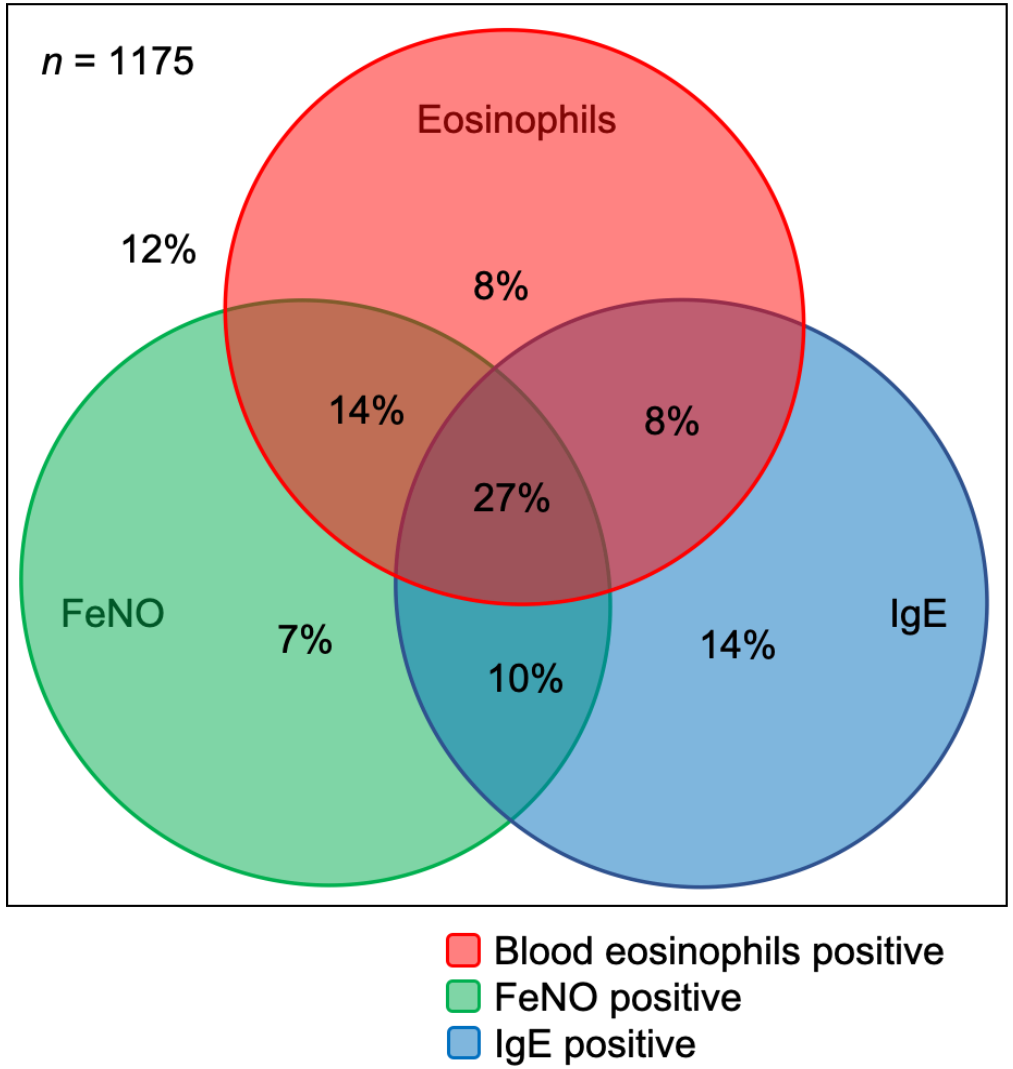






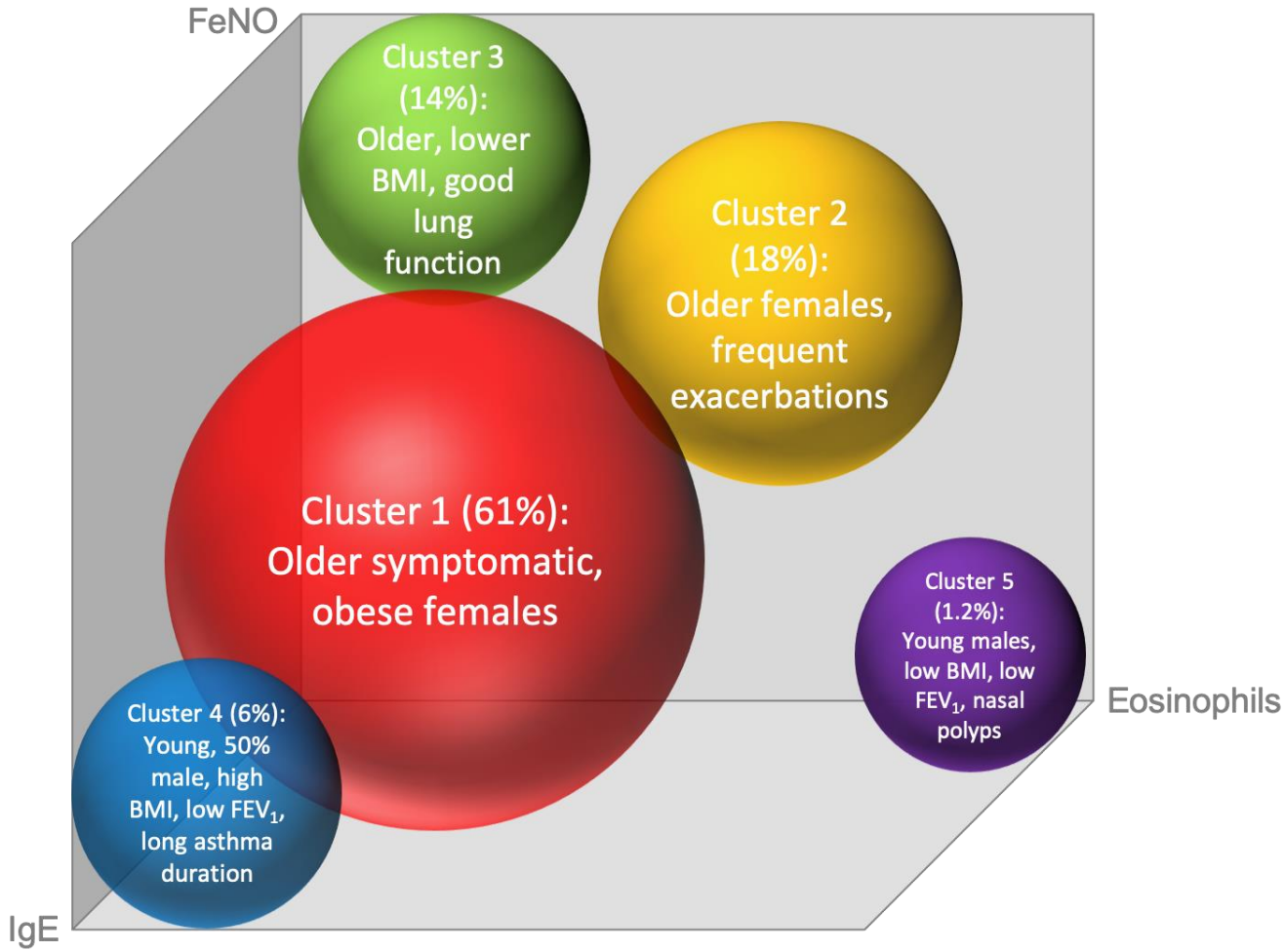
Conclusions – Dichotomous Biomarker Cutoffs

- The majority of severe asthma patients were positive for at least one biomarker
- 12% of patients were triple negative
- There is considerable overlap of inflammatory biomarker positivity
- Suggesting that a more comprehensive approach is needed to identify the best therapy for patients



Conclusions – Cluster Analysis

- We have identified and described five severe asthma clusters defined according to biomarker expression
- Each biomarker-defined cluster exhibits a unique clinical profile
- These data suggest the occurrence of discrete patterns of underlying inflammatory pathway activation
- Future directions:
  - ? Different clinical trajectory
  - ? Differential treatment responsiveness (molecular or clinical)



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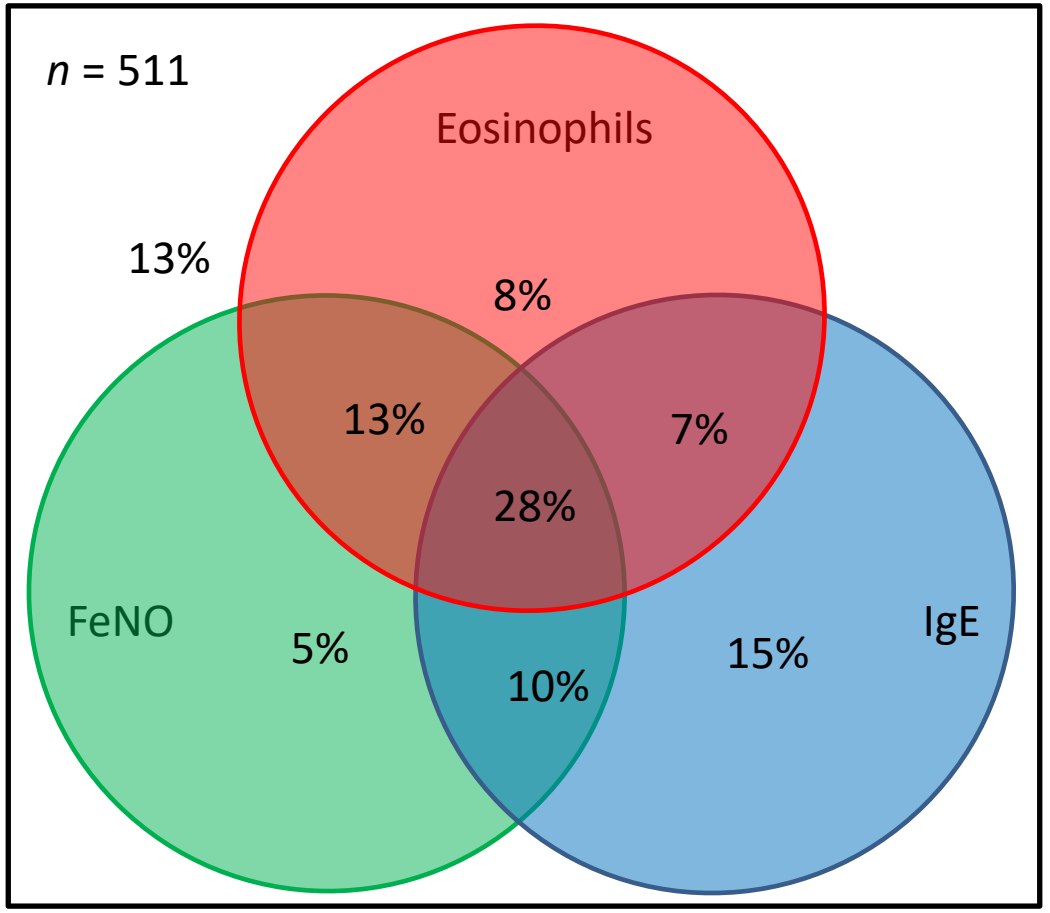
n = 511
Eosinophils
13%
8%
13%
7%
28%
FeNO
5%
10%
15%
IgE
Blood eosinophils positive
FeNO positive
IgE positive

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Total	P-value
Number	669 (61%)	200 (18%)	149 (14%)	66 (6%)	13 (1.2%)	1097	
Female sex	66%	67%	58%	53%	39%	64%	0.01
Age	53 ± 15	54 ± 14	56 ± 15*	49 ± 18*	51 ± 15	53 ± 15	0.03
BMI	31 ± 8*#	28 ± 6#	28 ± 6*	31 ± 8	27 ± 6	30 ± 8	<0.001
FEV_1 %predicted	71 ± 21	73 ± 23	75 ± 23	69 ± 18	68 ± 18	72 ± 22	NS
Blood eosinophils	240 ± 174	911 ± 372	509 ± 310	333 ± 225	4475 ± 1755	452 ± 581	<0.001
IgE	167 ± 202	187 ± 234	358 ± 402	1932 ± 1181	698 ± 824	318 ± 584	<0.001
FeNO	23 ± 17	51 ± 23	166 ± 140	38 ± 29	54 ± 44	46 ± 48	<0.001
Allergic sensitisation	78%	84%	72%	81%	60%	78%	NS
Asthma duration	26 ± 17	25 ± 17	26 ± 18	33 ± 17	28 ± 17	26 ± 17	NS
Asthma exacerbations	4.1 ± 3.9	4.5 ± 4.7	3.6 ± 3.2	3.7 ± 3.3	3.4 ± 2	4.1 ± 3.9	NS
Asthma control	84%	72%	80%	68%	71%	79%	0.003
Allergic rhinitis (current)	58%	63%	62%	65%	82%	60%	NS
Chronic rhinosinusitis (current)	66%	70%	62%	64%	75%	67%	NS
Nasal polyps (current)	30%	44%	34%	44%	71%	36%	0.01
Eczema (current)	11%	8%	7%	12%	15%	10%	NS
Baseline oral corticosteroids	47%	48%	45%	38%	39%	46%	NS