9th PCCM Annual Board Review and Advances

Impact of biologics in asthma & disparities in access.

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Disclosures

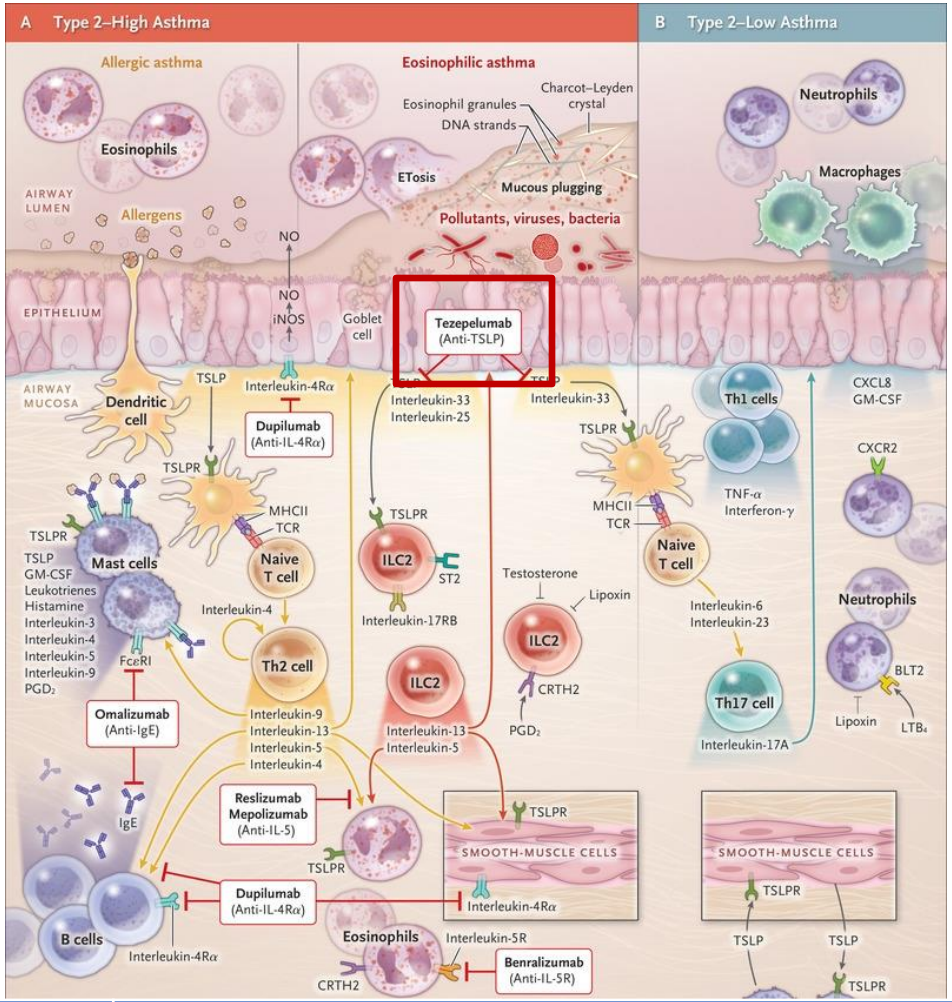
- I have no conflicts of interest to disclose

Objectives

- To highlight the impact of biologics in asthma with a focus on treatable traits.
- To evaluate specific instances in which one biologic has [might have] a comparative edge over other biologics approved for asthma.
- To examine the evidence supporting disparities in access to these targeted therapies.
- To strategize how we might improve patient use of biologics and outcomes in severe asthma.

To highlight the impact of biologics in asthma with a focus on treatable traits and specific instances in which one biologic might be favored over another.

Six biologics are now approved for asthma treatment



Cytokine	Role
TSLP	Stimulate T2 (and non-T2) inflammation

Brusselle GG, Koppelman, N Engl J Med. 2022. 2022 Jan 13;386(2):157-171.

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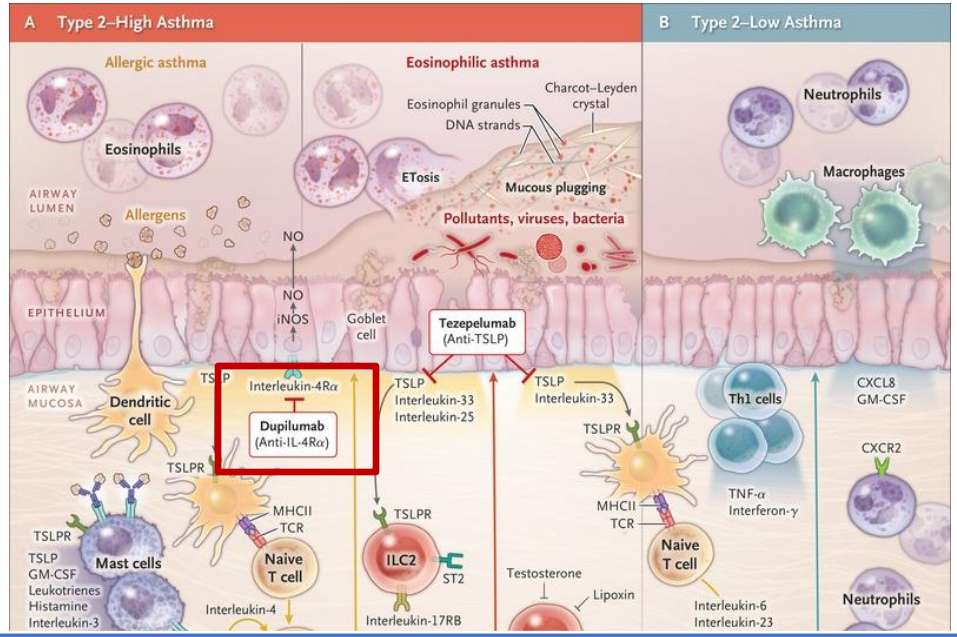

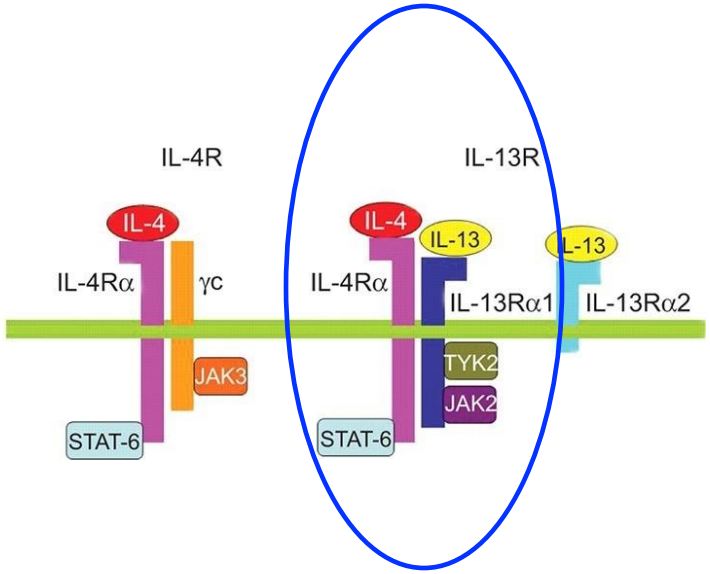

Cytokine	Role
IL4	T2 skewing Class switch: **Allergic inflammation** Airway remodeling Eosinophil recruitment
IL13	Like IL4 Airway changes: mucus hypersecretion, goblet cell metaplasia, fibrosis, airway responsiveness

Brusselle GG, Koppelman, N Engl J Med. 2022. 2022 Jan 13;386(2):157-171.

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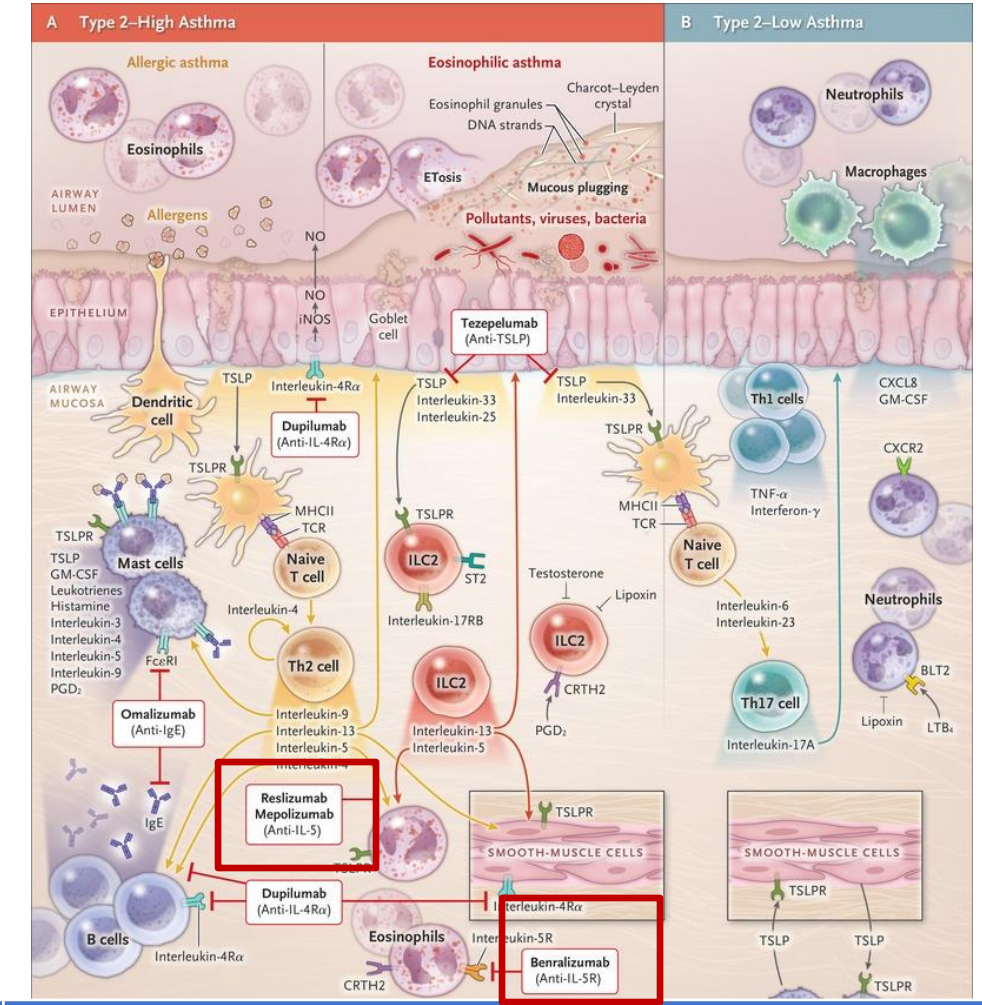

Cytokine	Role
IL5	**Eosinophil** growth, differentiation and recruitment

Brusselle GG, Koppelman, N Engl J Med. 2022. 2022 Jan 13;386(2):157-171.

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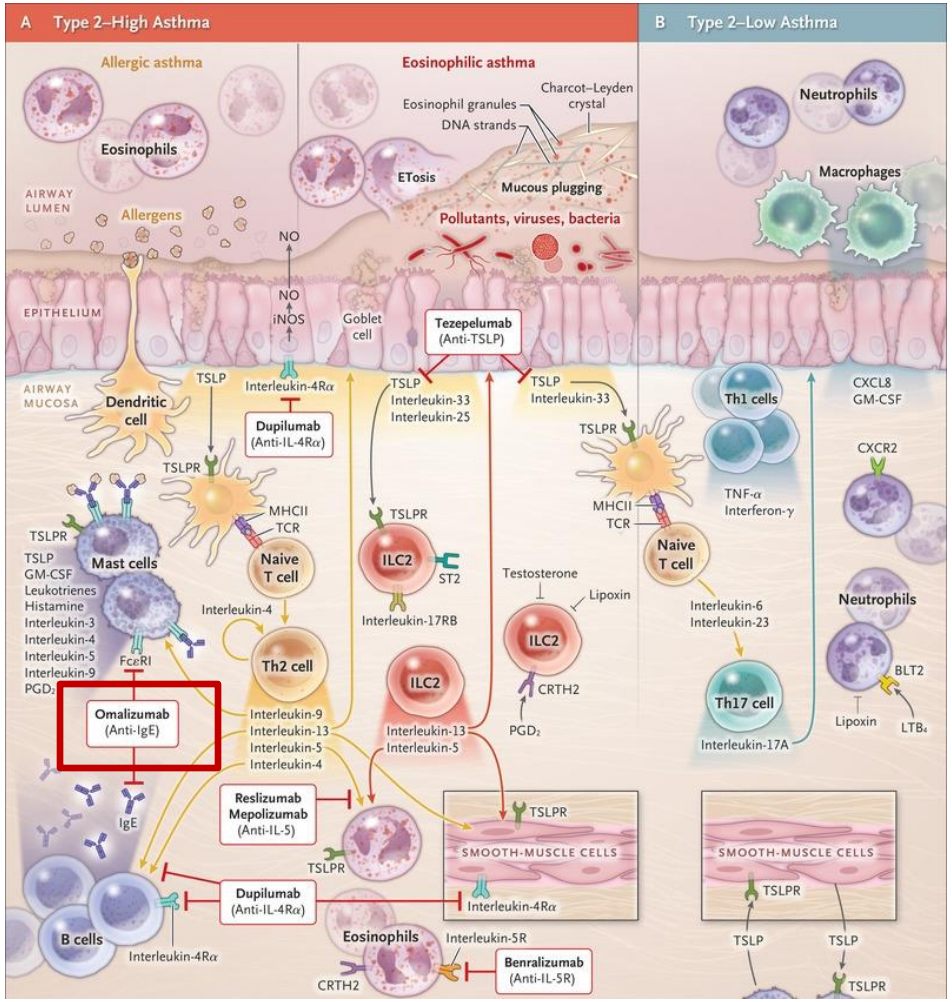


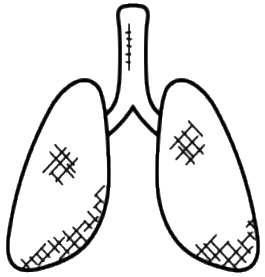
	Role
IgE	**Allergic** inflammation

Brusselle GG, Koppelman, N Engl J Med. 2022. 2022 Jan 13;386(2):157-171.

Hard to base choice on benefit from clinical trials

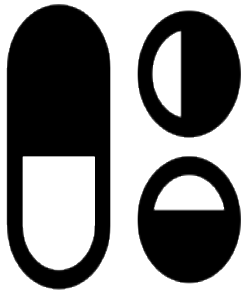
They all worked (relatively) well in the randomized trials

Reduced exacerbations
(30 - 70%)



Improved lung function (FEV1) (~90-200 milliliters, ~5-10% increase)

Improved quality of life (modest improvements)

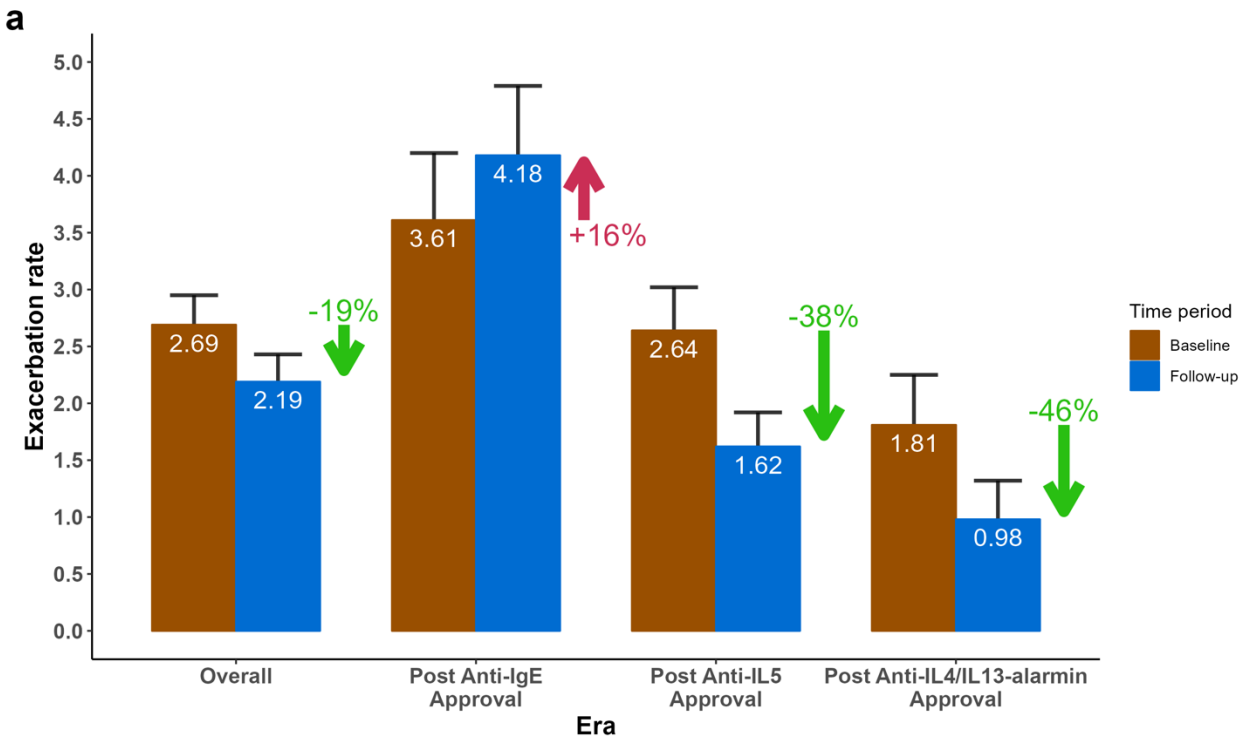


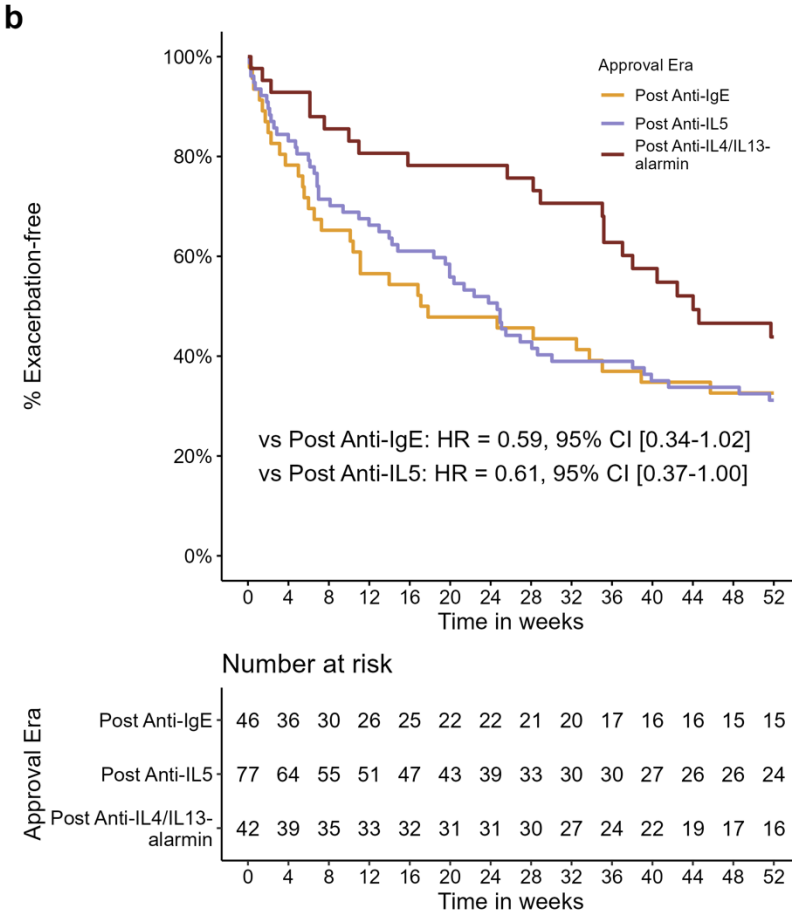
Steroid-sparing (Halving of dose to complete elimination)

MENSA, NEJM 2014
MUSCA, LancetResp 2017
SIROCCO, Lancet 2016
CALIMA, Lancet 2016
Wenzel, Castro et al, Lancet 2016
Castro, Corren et al, NEJM 2018
Akenroye et al., JACI. 2022 Nov;
Nopospon et al, JACI. 2023 Mar;
Akenroye et al. JACI Pract. 2024 Feb

All biologics are valuable; eligibility alone is not sufficient

Two individuals meeting eligibility may show vastly different response





Nopsopon, et al. Respir Med. Aug 2024. PMID: 39260678.

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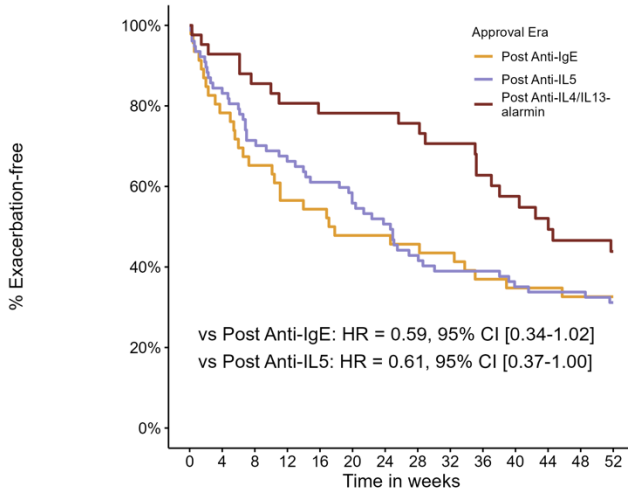
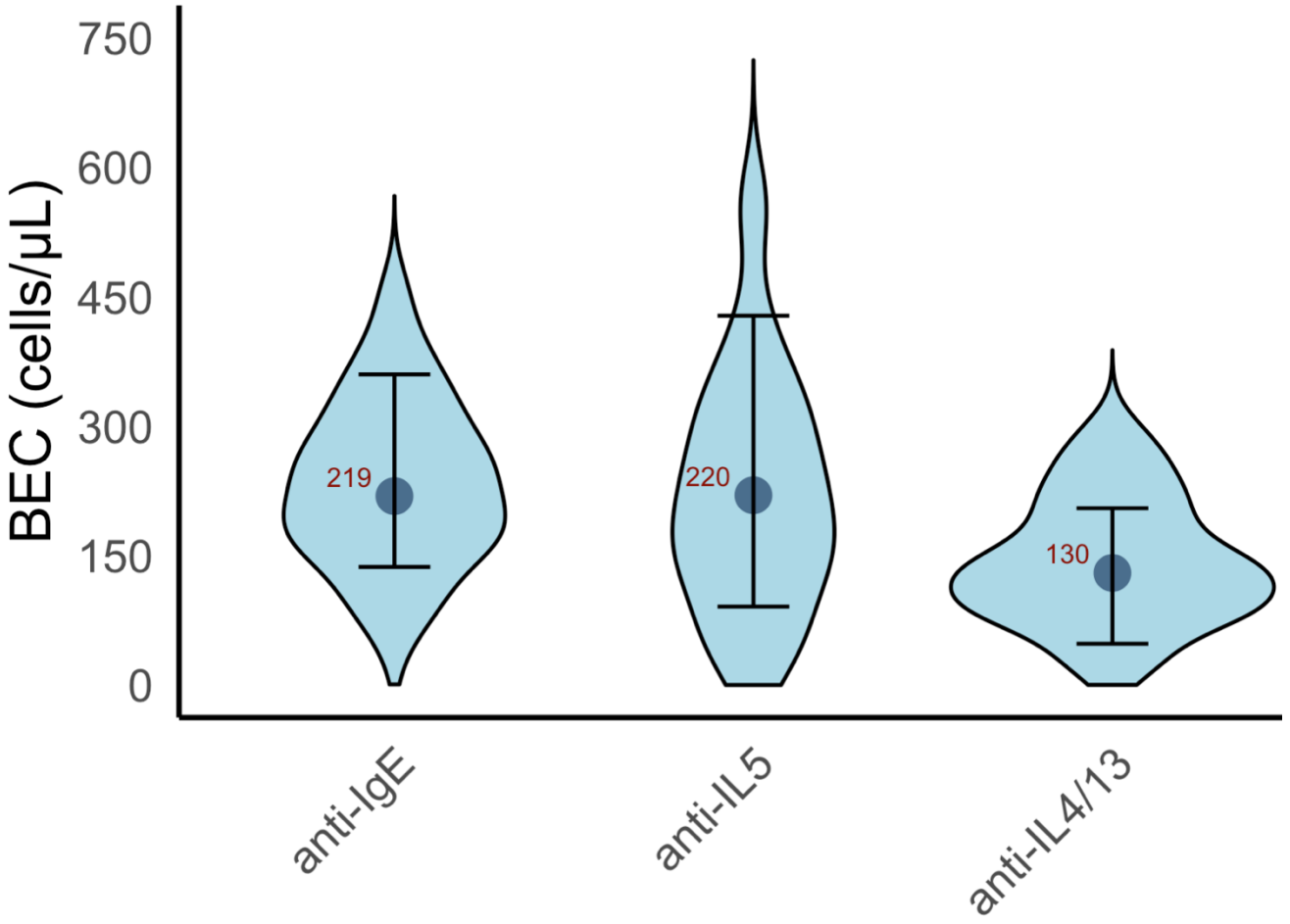
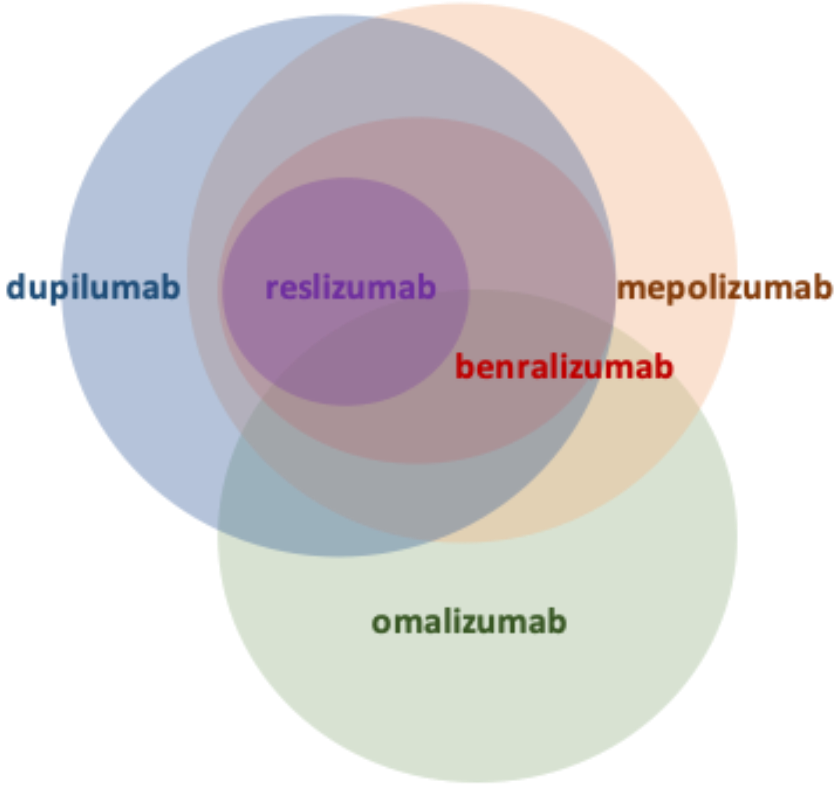
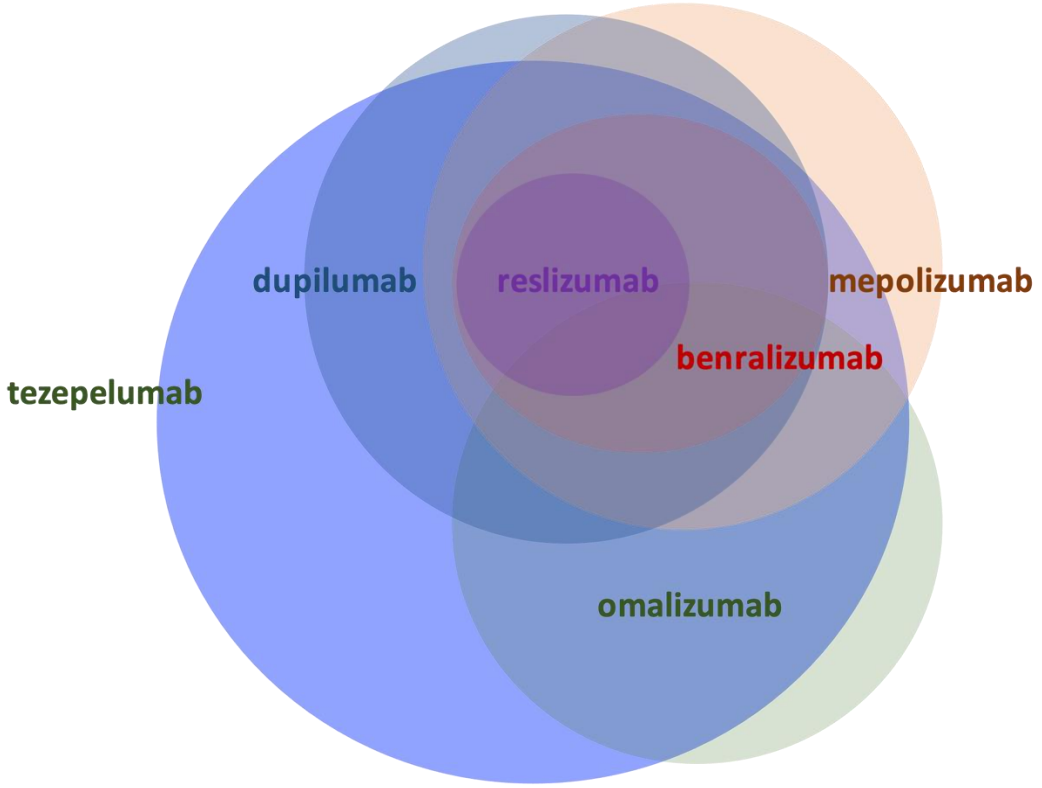




Nopsopon, et al. Respir Med. Aug 2024. PMID: 39260678.

They are all effective in the ‘right’ patient
There is a high overlap in eligibility for these therapies





Akenroye A, et al. J Allergy Clin Immunol. 2020. PMID: 31866437

Precision Medicine in Asthma

Treatable traits and targeted management approaches

- Match the right patient to the right therapy
  - One size does not fit all
- Choose the therapy that maximizes value or goals of therapy
  - Decrease exacerbations, halt declining lung function, reduce OCS dose
- Treatable "issues"
  - Modifiable traits
- Commonly occurring concurrently in patients with asthma
  - Pulmonary domain: airway eosinophilic inflammation, exacerbation-prone, chest infections-prone, bronchiectasis, hyperinflation
  - Extrapulmonary domain: Osteopenia, significant activity limitation, GERD, obesity, cachexia
    - Behavioral: smoking, medication nonadherence, anxiety, depression

McDonald, Fingleton, et al. ERJ 2019 53: 1802058
Pfeffer, Rupani, & Simoni. Front Allergy 2023; 4: 1240375

Possible cases of severe asthma in the clinic

- Case 1: 28-year-old man with allergic rhinitis (AR) and asthma triggered by dog & dust
  - IgE 230 ku/L, absolute eosinophil count (AEC): 180 cells/mcl
- Case 2: Same patient but IgE 230 ku/L, AEC: 1800 cells/mcl
- Case 3: 28-year-old woman planning to have a baby
- Case 4: 58-year-old woman with ?AR, FeNO 30 ppb, IgE 42, AEC 110 cells/mcL
- Case 5: 39-year-old obese man with poor response to omalizumab & dupilumab
  - RAST: Alternaria 0.32; others <0.10 ku/L; FeNO: 20 ppb, IgE 42; eosinophil count: 310 cells/mcL

The indications for respiratory biologics keep growing
Other indications for these therapies

The 'growing' list of FDA-approved indications for respiratory biologics [Nov 6, 2024]

Omalizumab	Mepolizumab	Benralizumab	*Reslizumab	Dupilumab	Tezepelumab
Allergic asthma (≥6 yrs.)	*Eosinophilic asthma (≥6 yrs.)	Eosinophilic asthma (≥12 yrs.)	Eosinophilic asthma (≥18 yrs.)	Eosinophilic asthma (≥6 yrs.)	Severe asthma (≥12 yrs.)
Chronic hives (≥12 yrs.)	EGPA (≥18 yrs.)	EGPA (≥18 yrs.)		OCS-dependent asthma (≥6 yrs.)	
CRSwNP (≥18 yrs.)	CRSwNP (≥18 yrs.)			CRSwNP (≥18 yrs.)	
IgE-mediated food allergy (≥1 yr.)	Hypereosinophilic Syndrome (≥12 yrs.)			Atopic dermatitis (≥6 months)	
				EoE (≥1 yr. + ≥15 kg)	
				Prurigo nodularis (≥18 yrs.)	
				COPD (≥18 yrs.)	

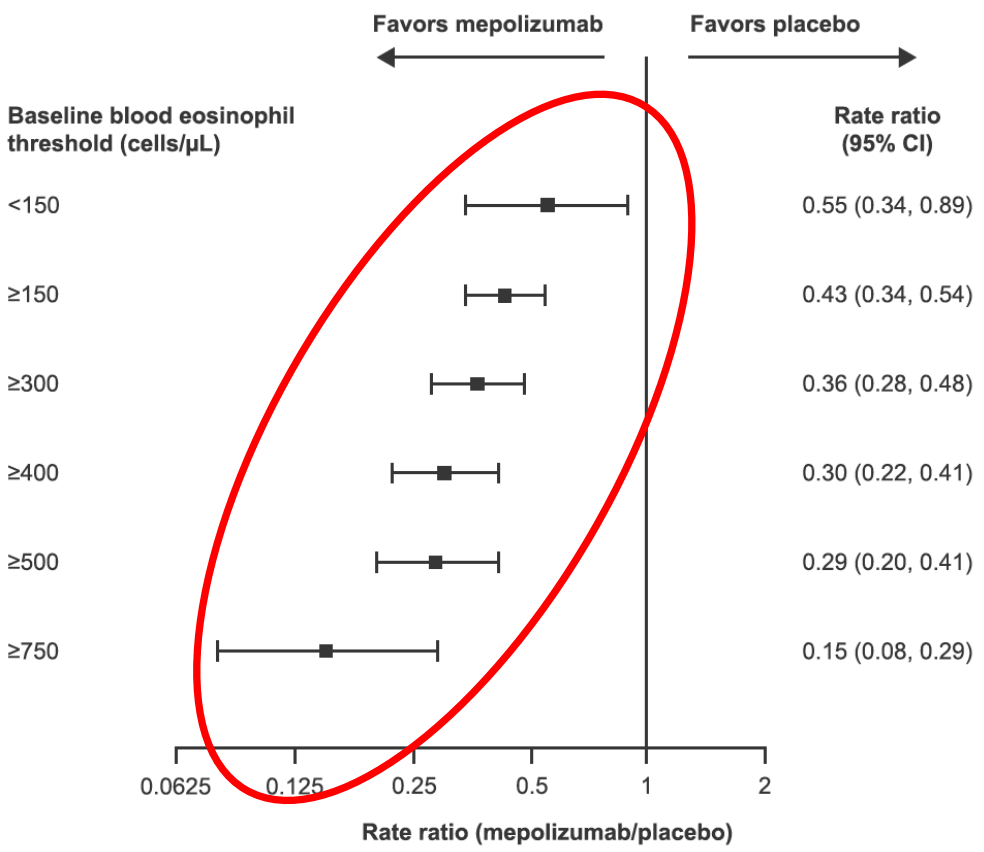
*All are administered subcutaneously except reslizumab which is an infusion. Reslizumab is also the only one dosed as mg/kg for adults. Xolair dose and dosing interval depends on weight and IgE level;
Abbreviations: COPD, chronic obstructive pulmonary disease; CRSwNP- chronic rhinosinusitis with nasal polyposis; EGPA, eosinophilic granulomatosis with polyangiitis; EoE- eosinophilic esophagitis; OCS- oral corticosteroids;

Pulmonary treatable traits
Exacerbation- or admissions-prone; eosinophilic airway inflammation

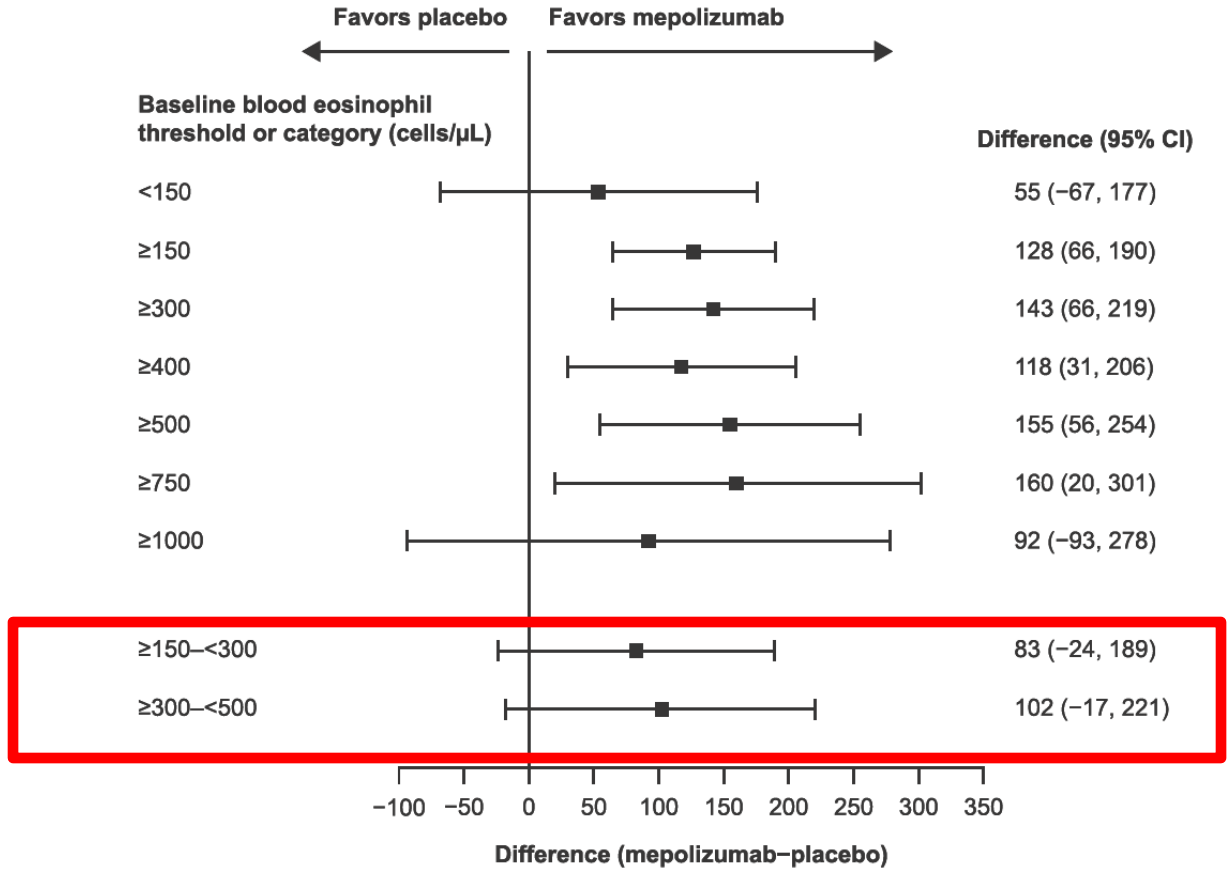
- Exacerbation rate reduction was (is) the main outcome in most asthma-related studies
  - If FDA-approved, 'significantly' improves asthma-related exacerbations.
- Asthma-related admissions is a 'rare event'
  - Sub-component of 'exacerbations'
- Five of the six currently approved biologics are approved for eosinophilic asthma
  - Anti-IL5s: mepolizumab, reslizumab, benralizumab
  - Anti-IL4 receptor alpha: dupilumab
  - Anti-TSLP: Tezepelumab ('biomarker-free')

Most of these biologics work better with higher AEC

Reduction of exacerbations



Improvement in lung function (FEV1)

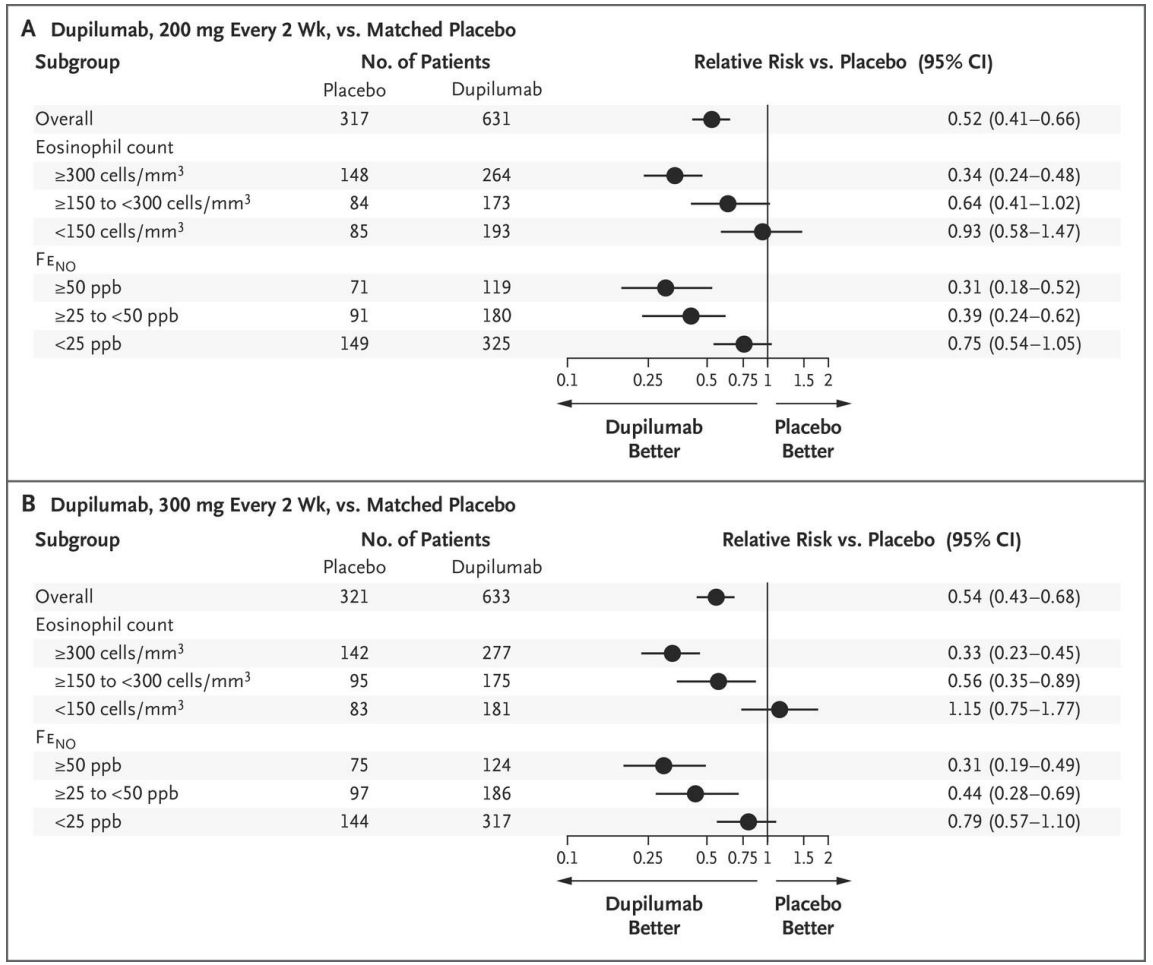


AEC: absolute blood eosinophil count

Albers, et al. I, Respir Med 159 (2019)

Most of these biologics work better with higher AEC

- Anti-IL5/IL-5R
  - Mepolizumab
  - Benralizumab
  - Reslizumab
- Anti-IL4Ra
  - Dupilumab



A Dupilumab, 200 mg Every 2 Wk, vs. Matched Placebo

Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	317	631	0.52 (0.41–0.66)
Eosinophil count			
≥300 cells/mm³	148	264	0.34 (0.24–0.48)
≥150 to <300 cells/mm³	84	173	0.64 (0.41–1.02)
<150 cells/mm³	85	193	0.93 (0.58–1.47)
FE_{NO}			
≥50 ppb	71	119	0.31 (0.18–0.52)
≥25 to <50 ppb	91	180	0.39 (0.24–0.62)
<25 ppb	149	325	0.75 (0.54–1.05)

B Dupilumab, 300 mg Every 2 Wk, vs. Matched Placebo

Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	321	633	0.54 (0.43–0.68)
Eosinophil count			
≥300 cells/mm³	142	277	0.33 (0.23–0.45)
≥150 to <300 cells/mm³	95	175	0.56 (0.35–0.89)
<150 cells/mm³	83	181	1.15 (0.75–1.77)
FE_{NO}			
≥50 ppb	75	124	0.31 (0.19–0.49)
≥25 to <50 ppb	97	186	0.44 (0.28–0.69)
<25 ppb	144	317	0.79 (0.57–1.10)

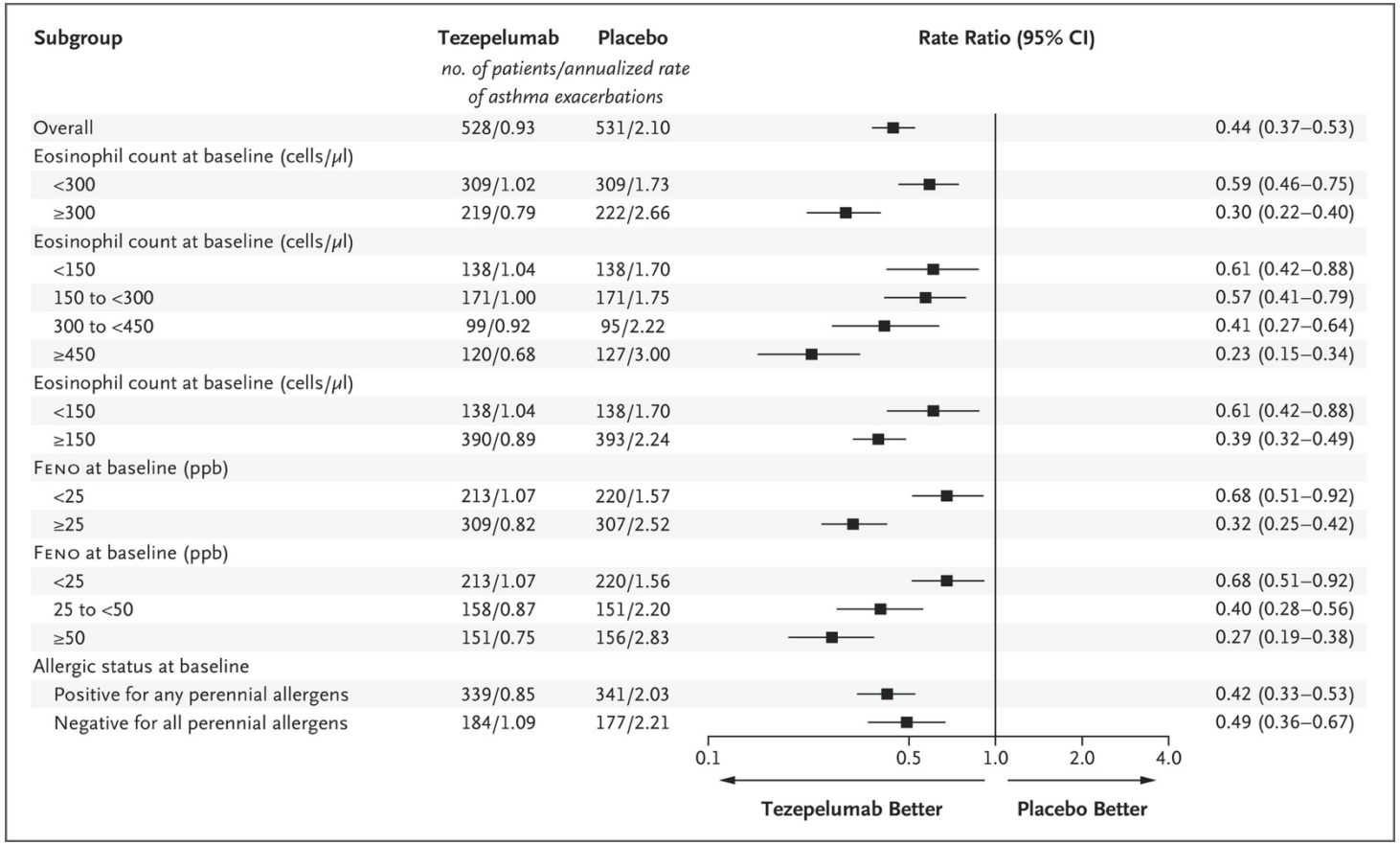
BEC: absolute blood eosinophil count

Castro, et al. N Engl J Med 2018;378:2486-2496
.

Tezepelumab works better with higher T2 biomarkers

Though approved for both T2-high and T2-low asthma

- Anti-IL5/IL-5R
  - Mepolizumab
  - Benralizumab
  - Reslizumab
- Anti-IL4Ra
  - Dupilumab
- Anti-TSLP
  - Tezepelumab



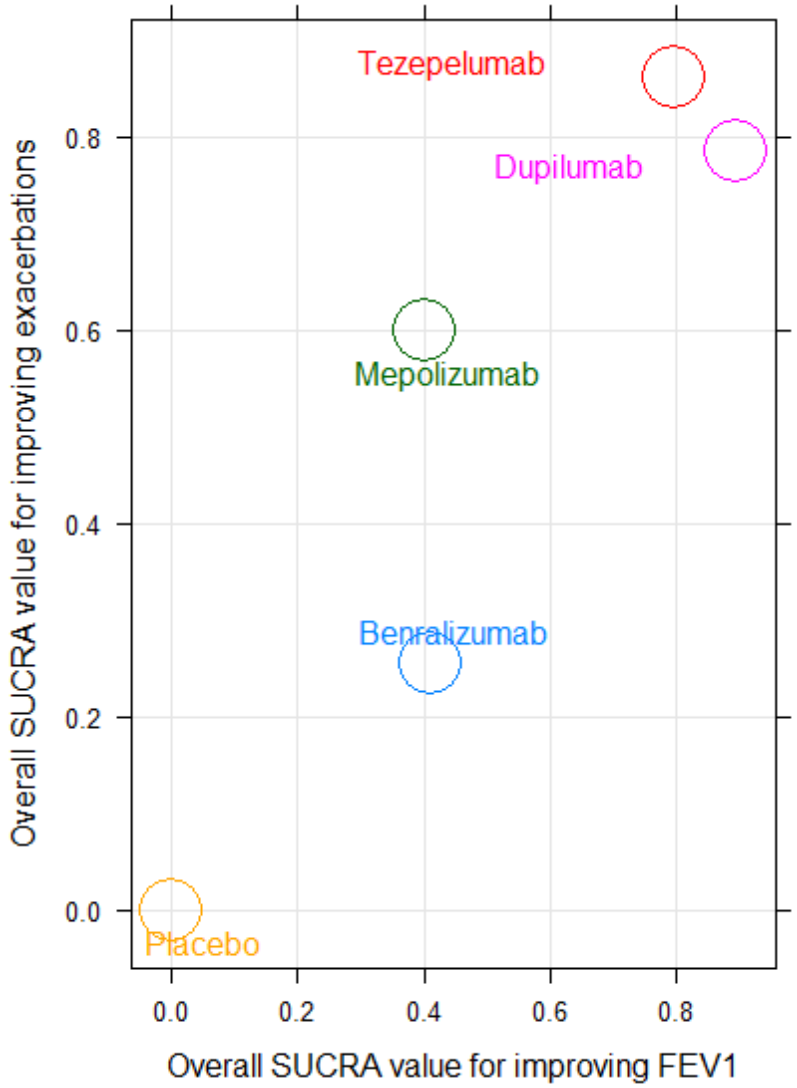
Menzies-Gow et al, N Engl J Med 2021; 384:1800-1809

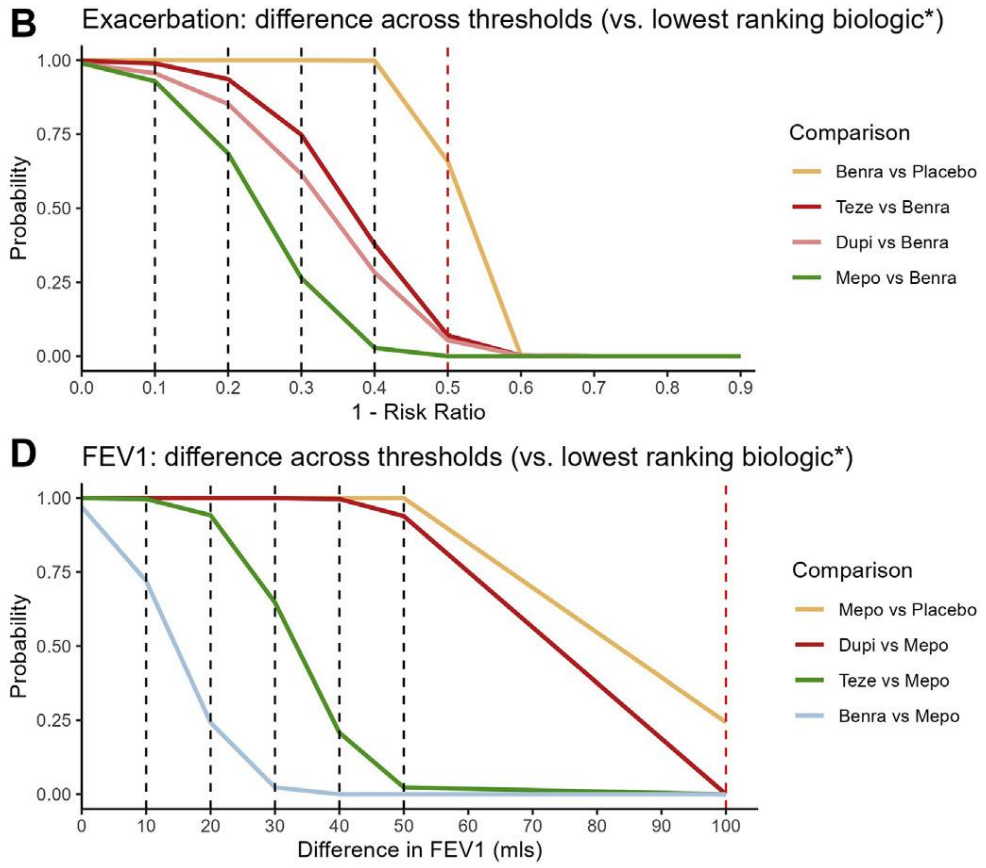
Data on comparative effectiveness are sparse

There are no head-to-head trials and most of the data are from indirect treatment meta-analyses or observational studies

Anti-IL4Rα & -TSLP outperform anti-IL-5s in eosinophilic asthma

But these differences *may* not be clinically significant

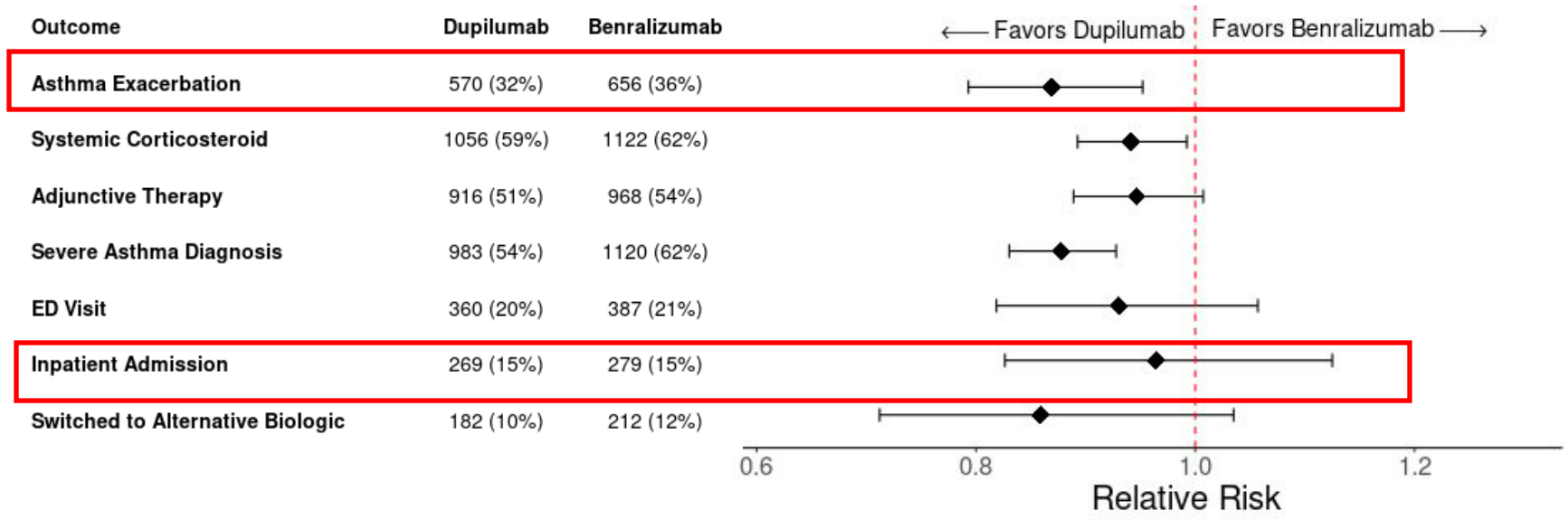




Nopospon et al, J Allergy Clin Immunol. 2023 Mar;151(3):747-755.

Differences between biologics for admissions are even smaller

Admissions-prone: In 1,805 matched dupilumab and benralizumab patients

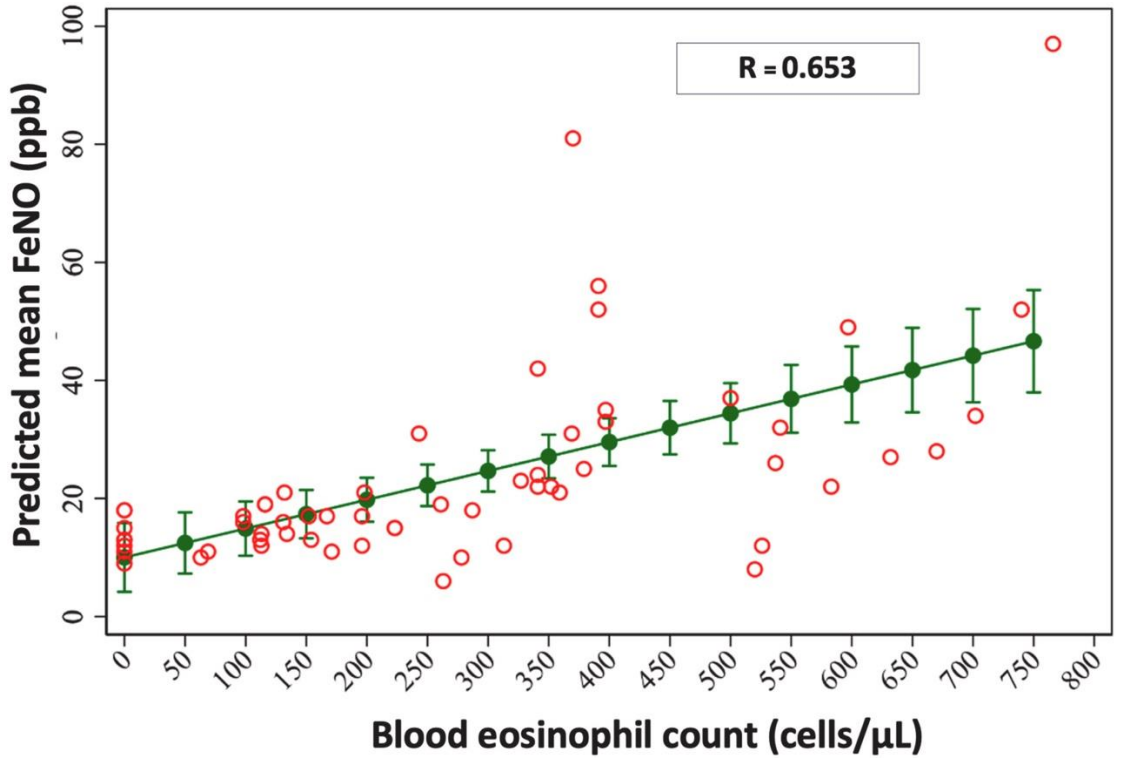


Kearney et al, Ann Am Thorac Soc. 2024 Jun; PMID 38241013
Akenroye et al, J Allergy Clin Immunol Pract. 2024 Feb. PMID: 38431251

Pulmonary treatable traits: Elevated FeNO

Higher FeNO correlates with [airway] eosinophilia and exacerbations

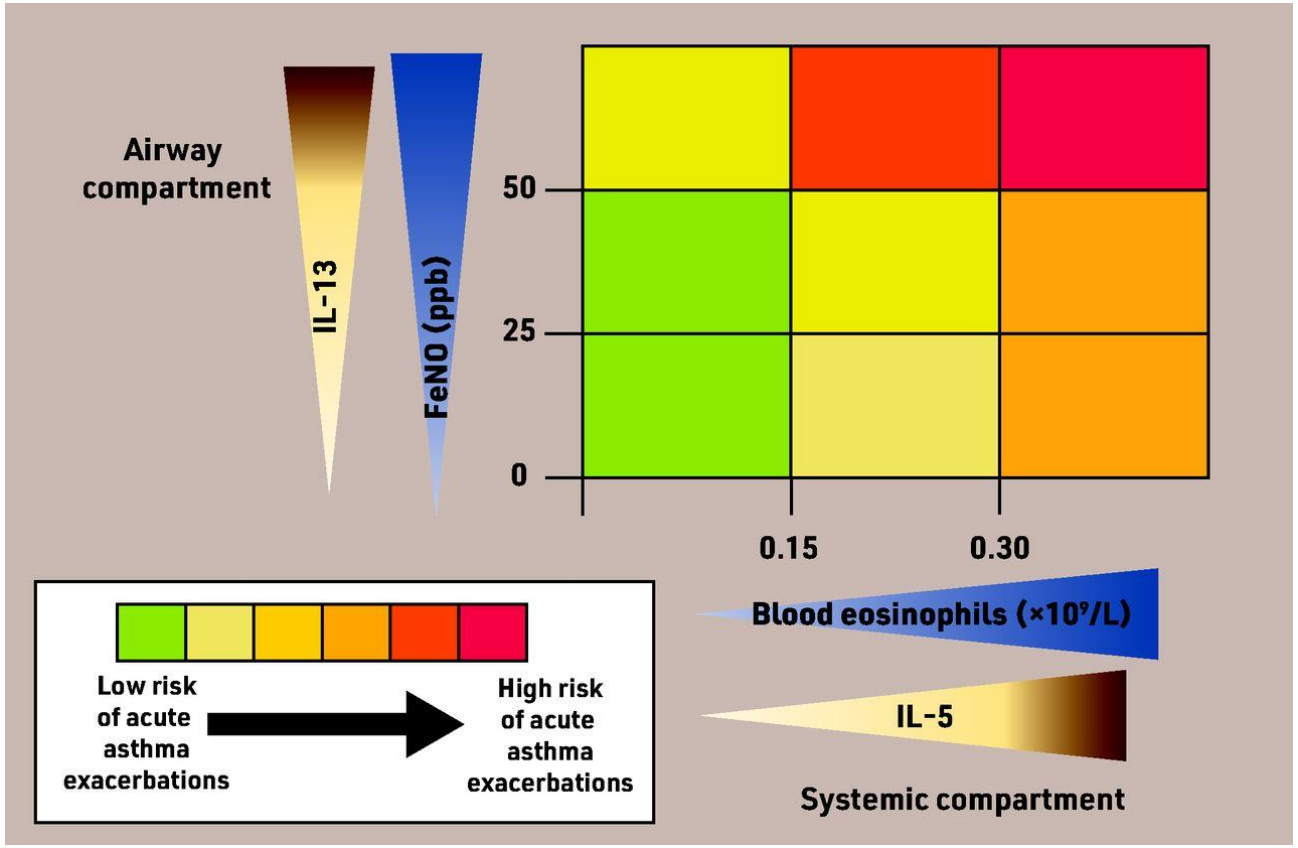
FeNO levels and assessment of airway inflammation, from the ATS guidelines[1]			
FeNO (ppb)	LOW	INTERMEDIATE	HIGH
Adults	< 25	25-50	> 50
Children	< 20	20-35	> 35
Type 2 inflammation	Unlikely	Possible	Likely



NiOX.com
Keeratichahanont et al, Respir Med, Aug 2024

FeNO: Not a great predictor of anti-IL5/5R response

FeNO (“magnet”) & eosinophils (“bomb”) might reflect airway vs peripheral blood

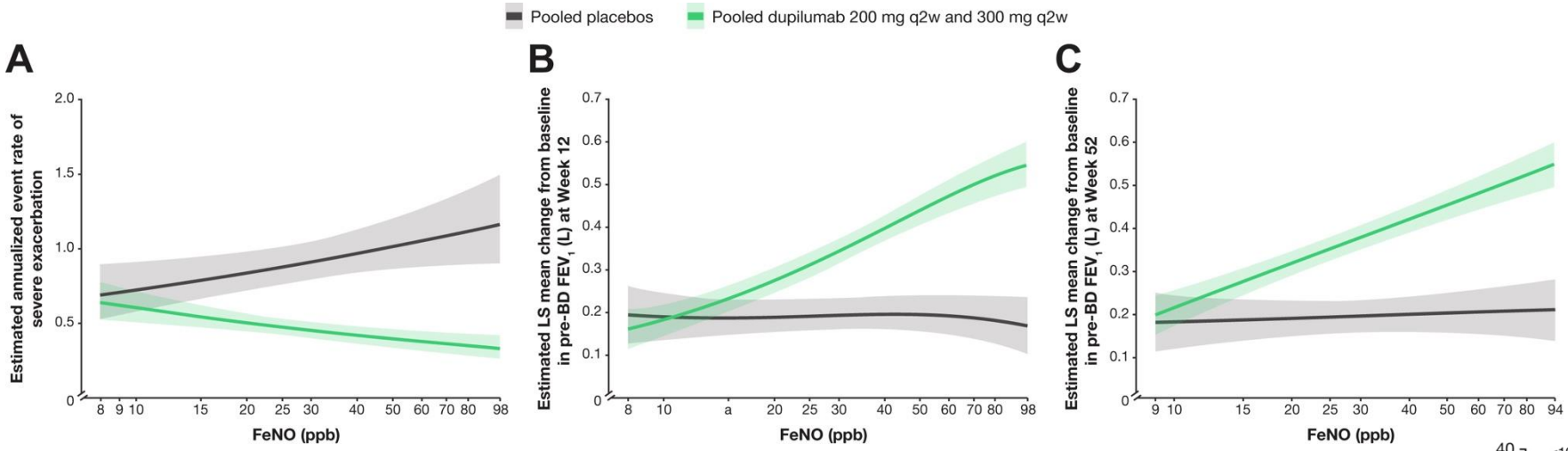


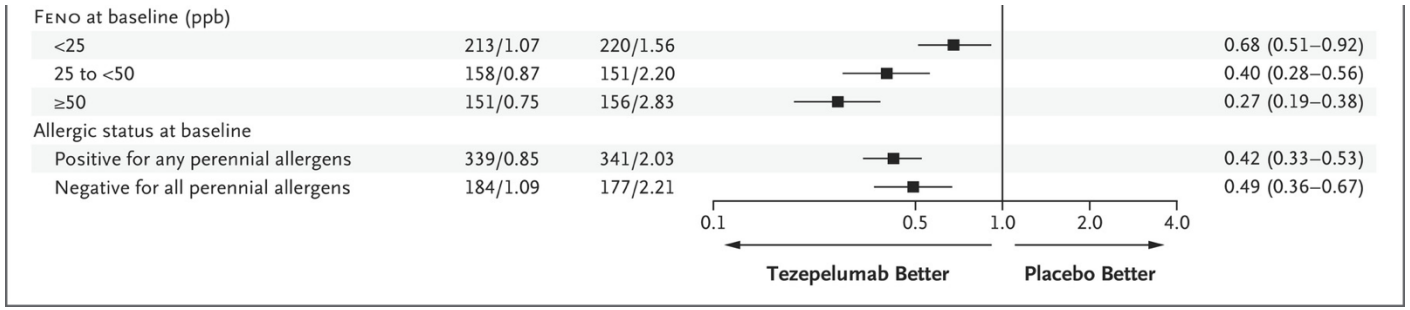
Couillard, Pavord, et al. Respirology, Volume: 27, Issue: 8, Pages: 573-577, 19 May 2022
Wang, Stonham, et al. British Journal of Gen Pract 2023

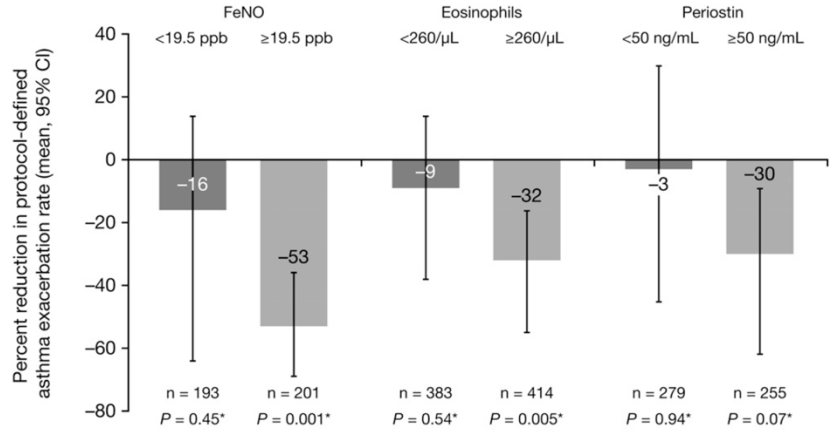
FeNO predicts response to dupilumab and tezepelumab

To a lesser extent, omalizumab. In general, not to the anti-IL5/5R agents.

Greater FeNO reduction, better lung function







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

Pavord etal, JACI-IP, Apr 2023
Hanania , Am J Respir Crit Care Med , 2013
Menzies-Gow et al, N Engl J Med 2021; 384:1800-1809

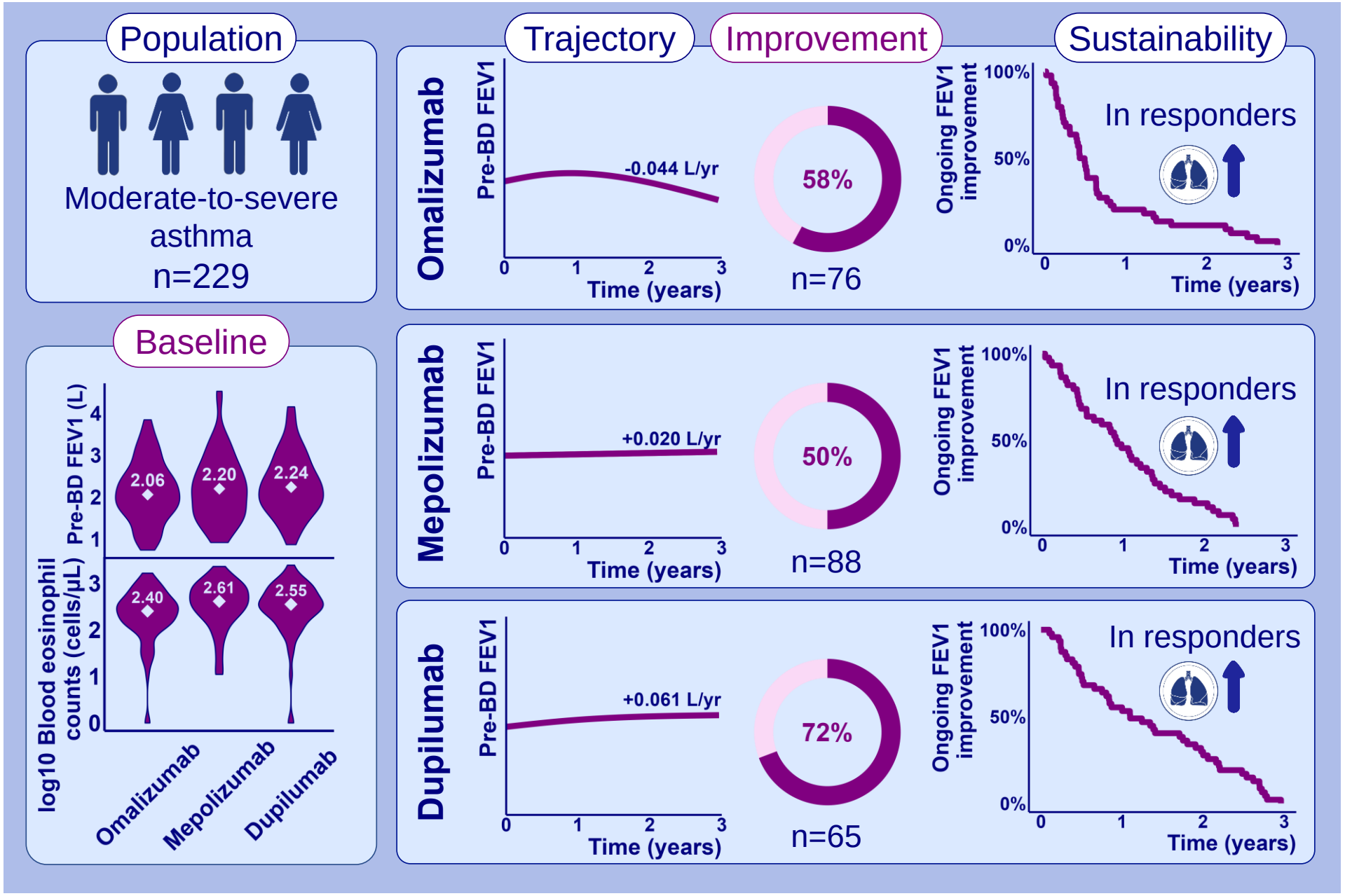
Pulmonary treatable traits

Airflow limitation from airway remodeling

- The impact of the biologics on lung function, in general, is fair to moderate compared to the impact on exacerbations.

- Benefits might stagnate vs ?wear off- not disease-modifying
  - Adherence, stopping ICS, ?anti-drug antibodies

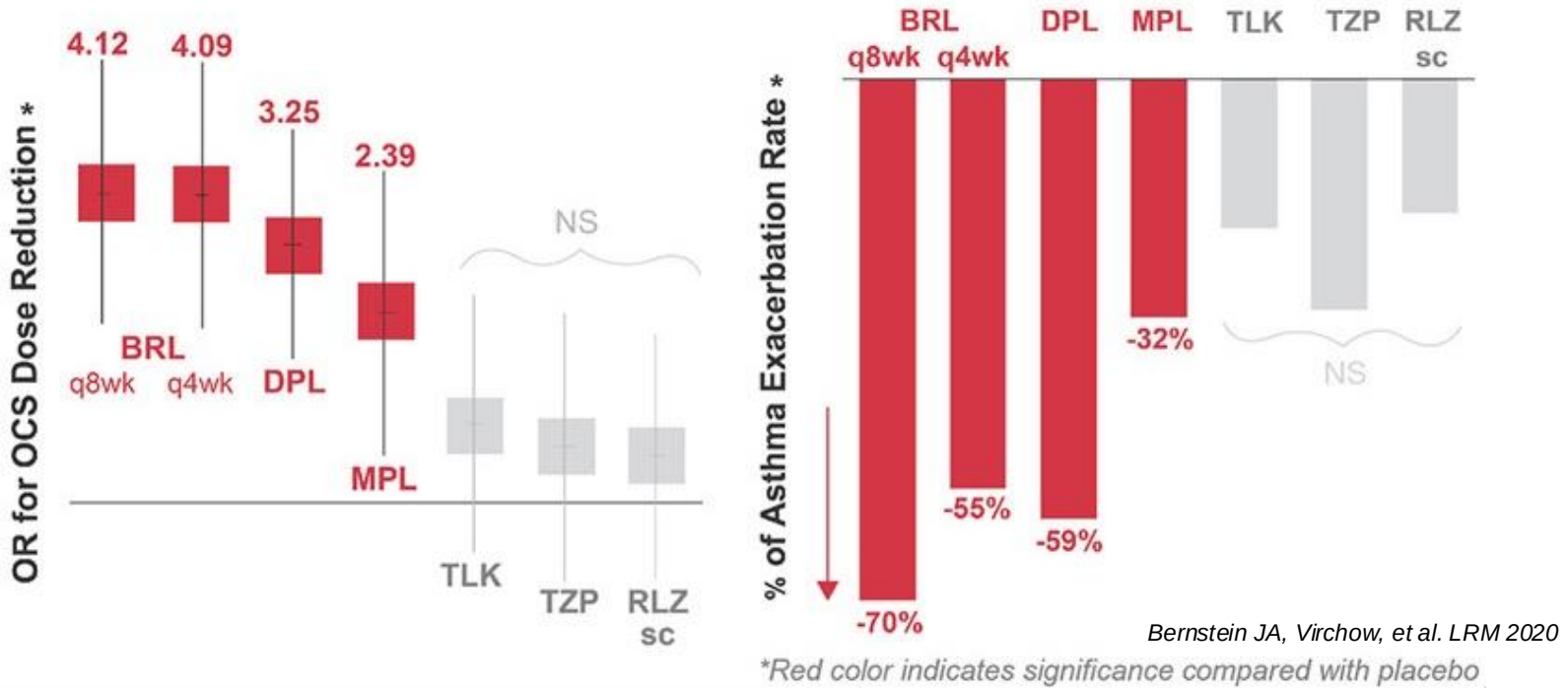
Nopsopon et al, Allergy, Jan 2024



Nopsopon et al, Allergy, Jan 2024

Extrapulmonary trait: OCS-dependence

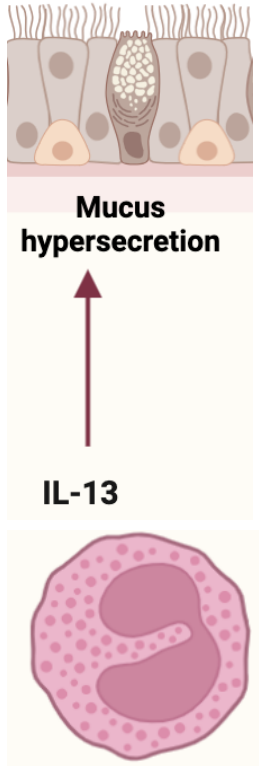
Benralizumab, mepolizumab, & dupilumab are useful in OCS-dependent disease



-When limited to those with eosinophils ≥150 cells/mcl, there was some significant benefit from tezepelumab
-The single reslizumab study used a fixed dose of 110 mg. Its usually dosed at 3 mg/kg IV [110 mg ~36.7 kg].

Pulmonary treatable traits

Mucus plugging

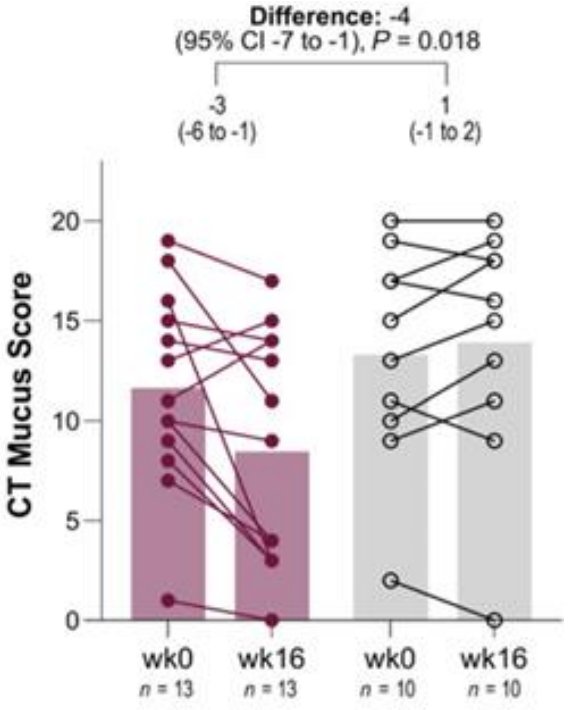


- Mucus plugs: crosslinking of oxidants from eosinophil peroxidase (EPX) and mucin cysteine thiol groups
- CT bronchopulmonary segment-based score [NHLBI Severe Asthma Research Program (SARP)] correlates with:
    - reductions in lung function
    - Sputum eosinophils (better than peripheral blood eosinophils)
    - EPX
- Sputum EPX: more sensitive than sputum eosinophils
    - Correlates better with airway eosinophilia
    - If persistent, correlates with reduced FEV_1 and exacerbations

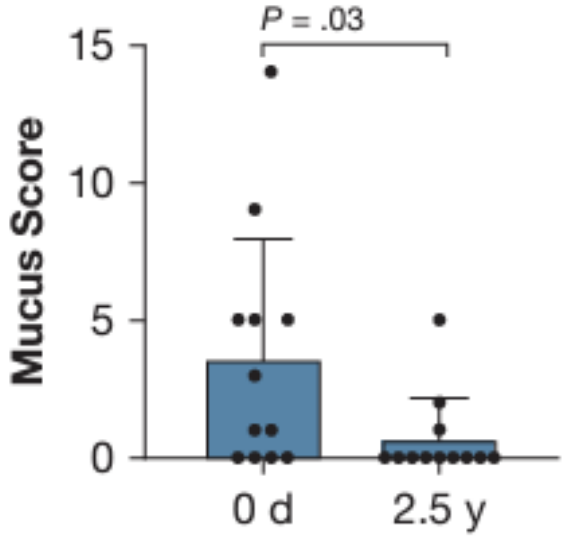
Tang, Charbit, et al. J Allergy Clin Immunol. Sep 2024
Jarjour NN & Busse W, AJRCCM Aug 2024
Dunican EM, Elicker BM, et al. J Clin Invest 2018
Garrido et al, Allergology Int. July 2024

Mucus plugging: MUCIN + EPX

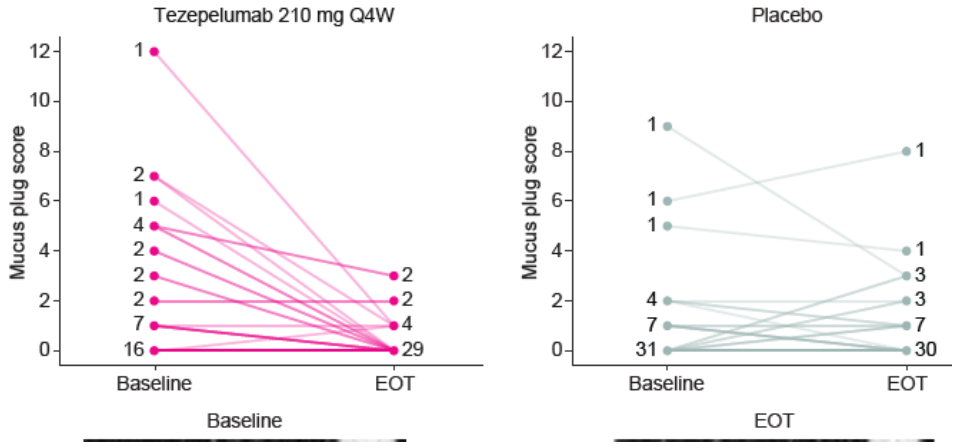
Dupilumab, tezepelumab, and/or benralizumab may be helpful



Dupilumab: -4 over 16 weeks



Benralizumab: -2 over 2.5 years



Tezepelumab: -1.8 over 28 weeks (End Of Treatment)

Svenningsen S, et al. Thorax 2019
McUntosh MJ, et al. Chest 2023
Nordenmark et al. NEJM Evid. Sept 2023
Garrido et al, Allergology Int. July 2024

Pulmonary/Extra-pulmonary treatable traits

Aspirin-exacerbated asthma; chronic rhinosinusitis with nasal polyposis

	Patient-important outcomes						Surrogate outcomes	
	HRQoL SNOT-22 (0-110)‡	Symptoms VAS (0-10 cm)	Smell UPSIT (0-40)†	Rescue OCS	Rescue polyp surgery	Adverse events	Nasal polyp size (0-8)	CT score LMK (0-24)
Standard care*	50.11	6.84	14.04	31.96%	21.05%	73.78%	5.94	18.35
Dupilumab	**-19.91** (-22.50, -17.32)	**-3.25** (-4.31, -2.18)	**10.96** (9.75, 12.17)	**-21.73** (-24.61, -18.22) RR 0.32 (0.23, 0.43)	**-16.35** (-18.13, -13.48) RR 0.22 (0.14, 0.36)	**0.13** (-8.12, 9.88) RR 1.00 (0.88, 1.13)	**-2.04** (-2.73, -1.35)	**-7.51** (-10.13, -4.89)
Omalizumab	**-16.09** (-19.88, -12.30)	**-2.09** (-3.15, -1.03)	**3.75** (2.14, 5.35)	**-12.46** (-23.65, 12.78) RR 0.61 (0.26, 1.40)	**-7.40** (-11.04, -2.43) RR 0.65 (0.48, 0.88)	**-2.60** (-15.58, 13.28) RR 0.96 (0.79, 1.18)	**-1.09** (-1.70, -0.49)	**-2.66** (-5.70, 0.37)
Mepolizumab	**-12.89** (-16.58, -9.19)	**-1.82** (-3.13, -0.50)	**6.13** (4.07, 8.19)	**-10.23** (-15.98, -2.88) RR 0.68 (0.50, 0.91)	**-12.33** (-15.56, -7.22) RR 0.41 (0.26, 0.66)	**-3.07** (-13.44, 9.07) RR 0.96 (0.82, 1.12)	**-1.06** (-1.79, -0.34)	
Benralizumab	**-7.68** (-12.09, -3.27)	**-1.15** (-2.47, 0.17)	**2.95** (1.02, 4.88)	**-9.91** (-16.30, -0.96) RR 0.69 (0.49, 0.97)	**-2.53** (-9.05, 7.16) RR 0.88 (0.57, 1.34)	**-1.48** (-13.28, 12.54) RR 0.98 (0.82, 1.17)	**-0.64** (-1.39, 0.12)	**-1.00** (-3.83, 1.83)
Reslizumab					**-18.82** (-20.93, 20.56) RR 0.11 (0.01, 1.98)	**-2.55** (-19.49, 19.18) RR 0.97 (0.74, 1.26)		
AK001						**2.54** (-27.11, 51.03) RR 1.03 (0.63, 1.69)	**-0.20** (-1.61, 1.21)	
Etokimab	**-1.30** (-8.99 to 6.40)					**188.14** (-59.76, 4879.1) RR 3.55 (0.19, 67.13)	**-0.33** (-1.58, 0.92)	
ASA Desensitization	**-10.61** (-14.51, -6.71)	**-2.74** (-3.92, -1.57)	**2.72** (-1.17, 6.61)		**-16.00** (-19.79, 0.21) RR 0.24 (0.06, 1.01)	**209.21** (8.30, 901.87) RR 3.84 (1.11, 13.22)	**-0.95** (-2.44, 0.55)	**-0.31** (-3.50, 2.88)

Classification of intervention (colour)[24]				Certainty (shading)[24, 29]
Among most beneficial	Among intermediate beneficial	Among least beneficial/not clearly different from placebo	No data (blank)	High/moderate (solid)
Among most harmful	Among intermediate harmful			Low/very low (shaded)

Oykhman, P et al, J Allergy Clin Immunol. 2022. Apr

Pulmonary: comorbid COPD; Behavioral trait: Smoking

As at 09/16/2024, none of these are approved for COPD in the US

-Dupilumab now approved for COPD in US/UK

-Benralizumab in Phase 3 (RESOLUTE). Prior study suggested some modest benefit in COPD at higher BEC cutoff (≥220 cells/mcl) and Mepolizumab [Phase 3, METREX & METREO] also some benefit in COPD eosinophilic phenotype.

-Multiple others in the pipeline, including anti-TSLPs, e.g. tezepelumab, anti-IL33 agents: itepekimab, tozorakimab

Bhatt, Rabe, et al. NEJM, May 2023
Pavord, Chanez, et al. NEJM, Oct 2017

Possible cases of severe asthma in the clinic

- Case 1: 28-year-old man with allergic rhinitis (AR) and asthma triggered by dog & dust
  - IgE 230 ku/L, absolute eosinophil count (AEC): 180 cells/mcl
- Case 2: Same patient but IgE 230 ku/L, AEC: 1800 cells/mcl
- Case 3: 28-year-old woman planning to have a baby
- Case 4: 58-year-old woman with frequent exacerbations and very poor lung function. Indeterminate AR, FeNO 30 ppb, IgE 42, AEC 110 cells/mcL
- Case 5: 39-year-old obese man with poor response to omalizumab & dupilumab
  - RAST: Alternaria 0.32; others <0.10 ku/L; FeNO: 20 ppb, IgE 42; eosinophil count: 310 cells/mcL

In conclusion…

Impact of respiratory biologics

- All biologics are valuable in the right patient
- But medications are only valuable if used!

Disparities in access & potential strategies to improve use of biologics in patients who need them.

The main take-away points:

- We might be less likely to prescribe biologics for individuals belonging to historically marginalized groups (HMG) and/or starting later.

-Affordability: Payment structure and insurance is everything [almost everything]!

- Publicly insured HMG individuals have the greatest limitations to access.

---Publicly insured non-HMG can get biologics at a higher rate than their HMG counterparts.

Insurance type influences utilization patterns of biologics

Payment structures exacerbate disparities in biologics use

- Annually, biologic therapies cost $28,000 - $45,000

- Payment assistance programs are generally for those with commercial insured

Mauger and Apter, JACI Jan 2019
Inselman et al, JACIIP Feb 2020

Insurance type influences utilization patterns of biologics

Payment structures exacerbate disparities in biologics use

- Annually, biologic therapies cost $28,000 - $45,000

- Payment assistance programs are generally for those with commercial insured

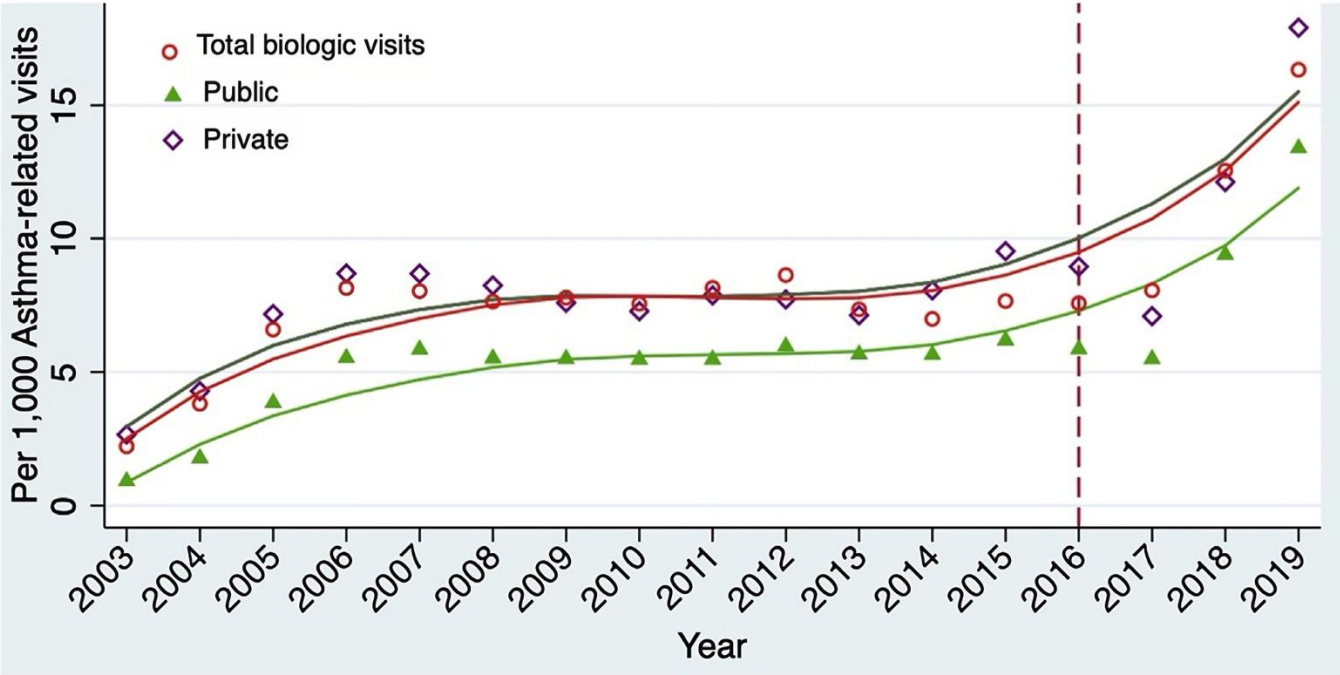
Mom reported she has a bill of $550 for the *** injections and was wondering if we could help lower the cost of the drug.

I noticed on my bill this morning that $2,800.00 was pending due to insurance issues. I will have to cancel my next injection if this is not resolved before that.

Publicly insured patients are unlikely to initiate biologic therapy

- IQVIA National Disease and Therapeutic Index
- Nationally representative all-payer survey of ambulatory care
- 2003 – 2019
- Patients ≥6 years with asthma
- Excluded: other chronic lung diseases or alternate indications

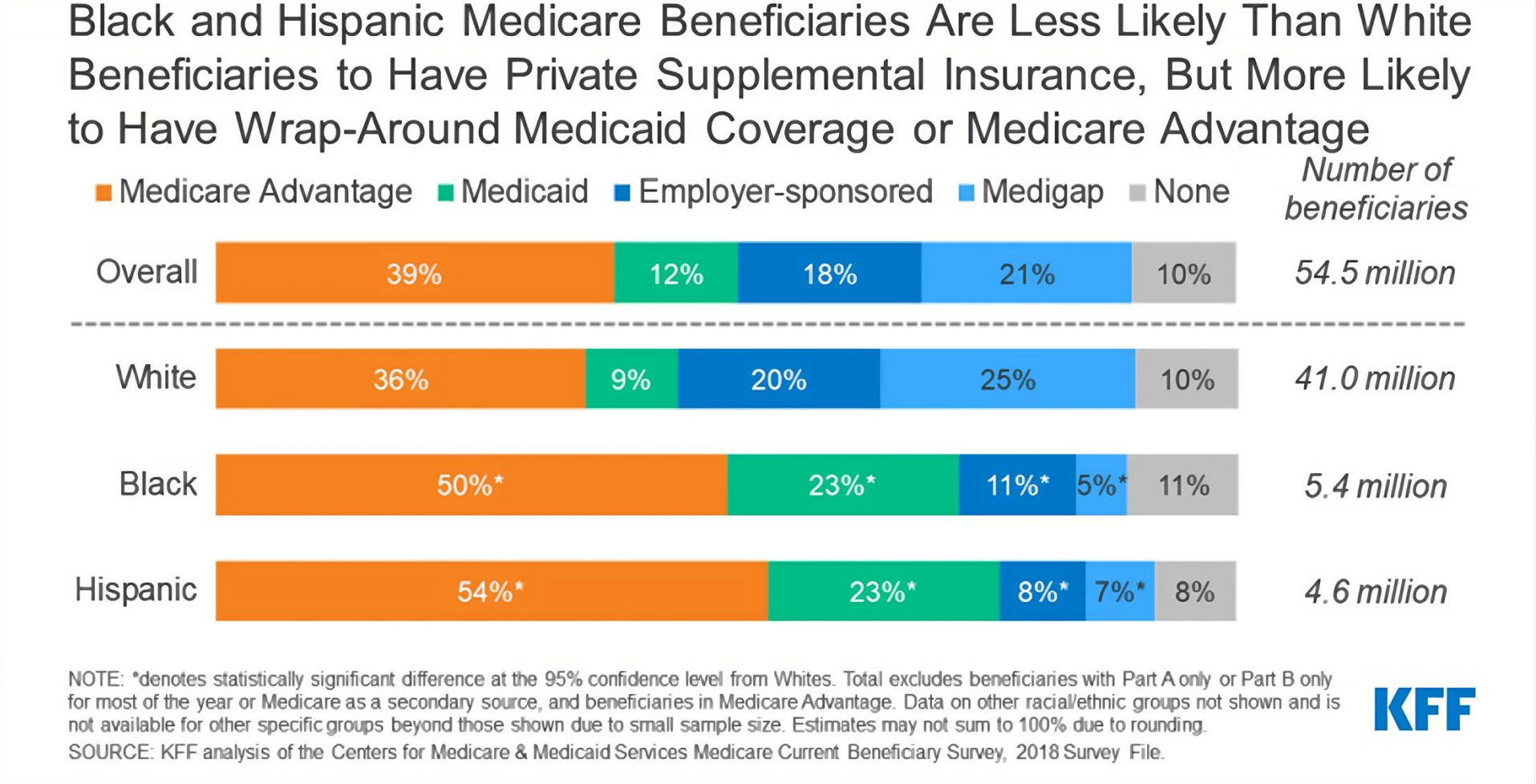
- Outcome: Prevalent use of biologics per 1,000 asthma treatment visits



Akenroye et al, JACI Nov 2021

Not all insurances are created equally

Black and Hispanic patients less likely to have supplemental insurance



Publicly insured individuals are less likely to be prescribed biologics

Does race/ethnicity modify insurance's effect on biologic use?

- Retrospective EHR cohort: adults prescribed omalizumab or mepolizumab
- Outcome: 'did not initiate therapy' within 12 months of prescription

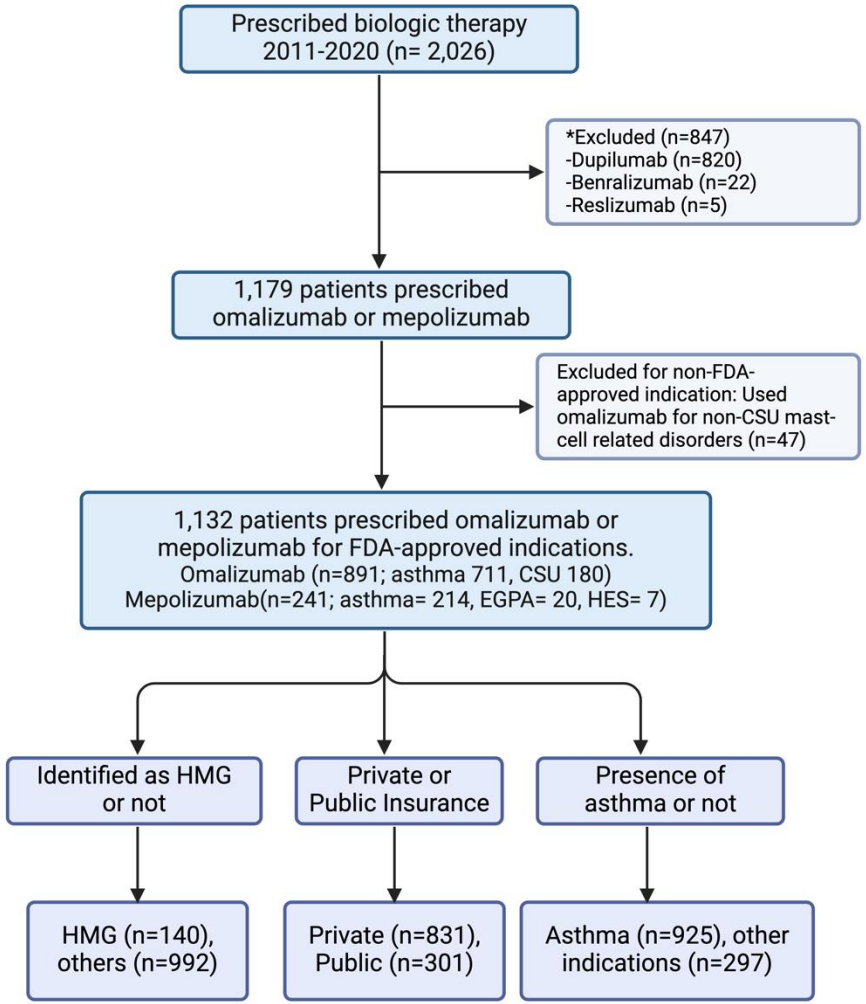
$$logit\ P(dnit = 1|insur, race) \sim \beta_0 + \beta_1 * \text{insur} + \beta_2 * \text{race} + \beta_3 * \text{insur*race}$$

- Exposure: Insurance- Public vs. Private
- Effect modifier: Belonging to an historically marginalized group (HMG) or not
  - Black, Latinx, Native/Indigenous peoples, American Indian/Alaska Native, or Other Pacific Islander
- Confounder adjustment: inverse probability treatment weighting
  - Included age, sex, initial biologic, smoking status, BMI, CCI, baseline eosinophil count, IgE level, asthma medications, and baseline exacerbation rate.

Akenroye et al, JACI Aug 2024

Publicly insured individuals are less likely to be prescribed biologics

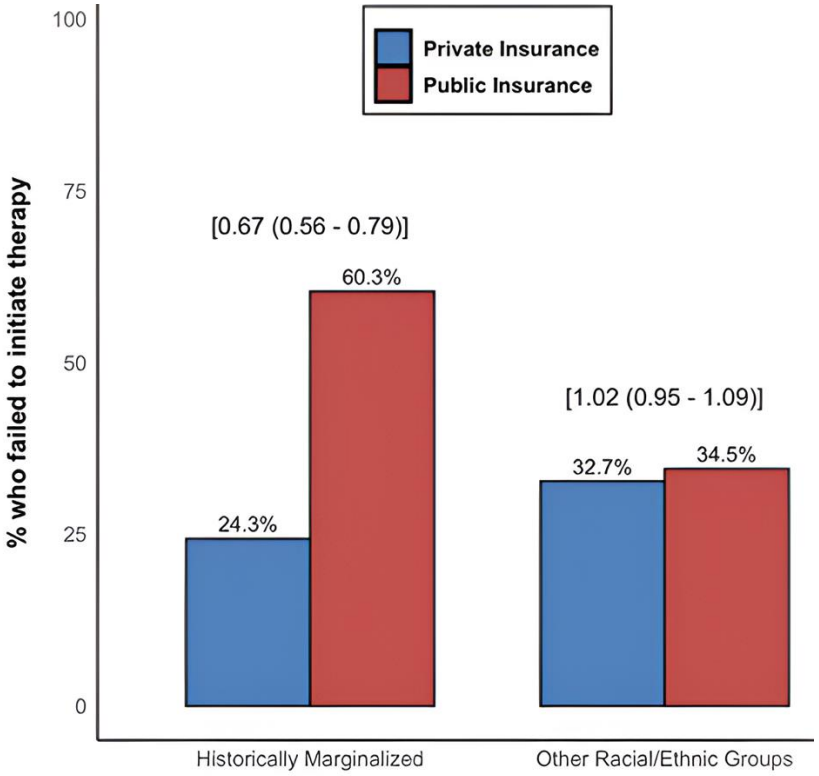
Does race/ethnicity modify insurance's effect on biologic use?



Akenroye et al, JACI Aug 2024

One-quarter of patients did not initiate the prescribed biologic

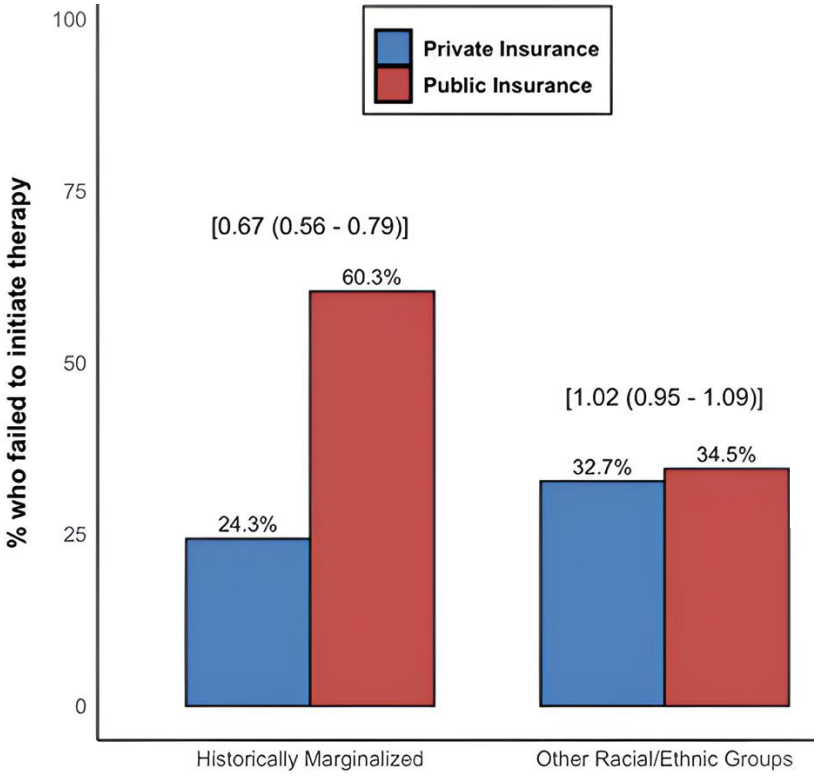
Publicly insured individuals belonging to HMG were less likely to initiate therapy



Akenroye et al, JACI Aug 2024

Publicly insured HMG individuals were less likely to initiate therapy

Though HMG were sicker at baseline [regardless of insurance type]

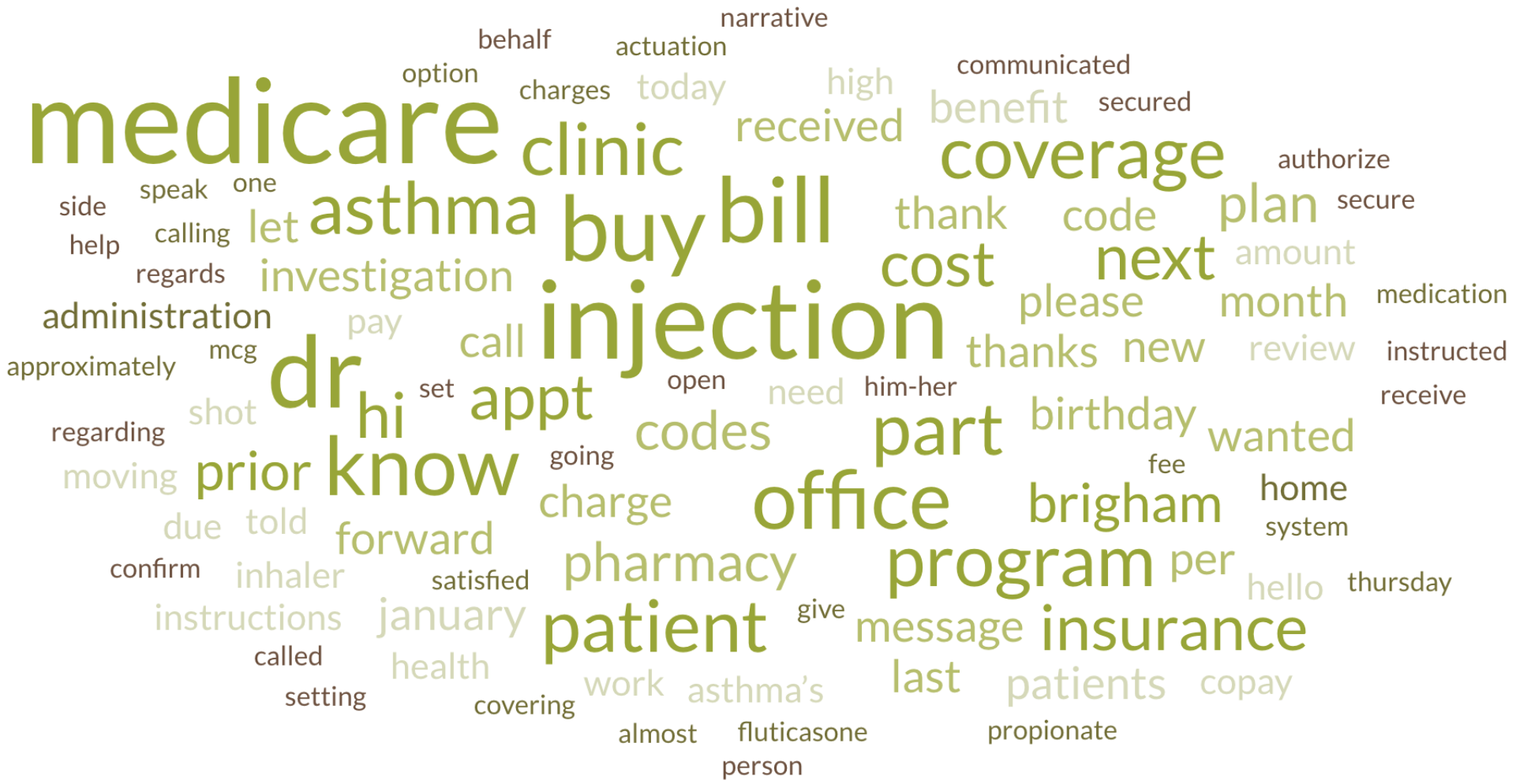


	Private	Public	*P* value
Among individuals belonging to HMGs			
Sample size, n	59	60	
Exacerbation rate in prior year	2.0 ± 2.5	2.2 ± 2.5	.70
Prebronchodilator FEV_1 (L)	2.2 ± 0.6	1.8 ± 0.5	<.001
Among individuals belonging to other racial/ethnic groups			
Sample size, n	616	190	
Exacerbation rate in prior year	1.4 ± 2.3	1.6 ± 2.4	.20
Prebronchodilator FEV_1 (L)	2.4 ± 0.8	2.1 ± 0.7	<.001
Comparing HMG vs non-HMG			
Exacerbation rate in prior year	2.0 ± 2.5 vs 1.4 ± 2.3; $P = .04$	2.2 ± 2.5 vs 1.6 ± 2.4; $P = .11$	
Prebronchodilator FEV_1 (L)	2.2 ± 0.6 vs 2.4 ± 0.8; $P = .11$	1.8 ± 0.5 vs 2.1 ± 0.7; $P = .002$	

Akenroye et al, JACI Aug 2024

Not all insurances are created equally

Underinsured might be the new uninsured



To reduce disparities in the use & access to biologics

We need to ask:

- Is it indicated?
  - Should I be prescribing a biologic today?
- Is it covered or affordable?
  - Will this be sustainable?
- If prescribed, follow-up: Did the patient initiate therapy?
- What patient or system-level factors may lead to non-initiation?
  - How can we create systems to mitigate these factors?

In conclusion…

Impact and access of respiratory biologics

- All biologics are valuable in the right patient
  - Consider treatable traits
    - Pulmonary, extrapulmonary, behavioral
- We may be starting biologics later in HMG
- Publicly insured HMG patients are the least likely to use
- System-level interventions, local improvements, advocacy
  - Prior authorization processes
  - Systems in place to trigger prescriptions, identify at risk to '*dnit*' patients.
  - Advocacy on costs, payment, etc.

Thank you!

https://druguselab.bwh.harvard.edu/

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