Asthma phenotype debate:
“Phenotyping should be done on all asthma patients”

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Outline

--Benefits from phenotyping

(blood eosinophils, FENO, bronchodilator response)

--Asthma severity assessments can change

--The fragmentation of the healthcare system

--disconnect between the ER, primary care, and specialists

--Rebuttal

Learning objectives

1. To review the data on blood eosinophils and FENO as predictive biomarkers for asthma exacerbations and as treatment response biomarkers for asthma biologics.
2. To discuss the disconnect between asthma severity assessments and asthma morbidity
3. To evaluate the impact of the healthcare system fragmentation on asthma management

Definition of a biomarker and its uses

"Characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic intervention"

The National Institutes of Health Biomarkers Definitions Working Group (2001)

- Diagnose
- Predict disease course
- Identify therapeutic eligibility
- Define populations with optimal treatment response
- Monitor treatment responses
- Monitor adverse effects from therapy

- Ideally: cheap, easy to collect and measure, non-invasive, accurate

Clin Pharmacol Ther. 2001;69(3):89-95, Pavord Clin Exp Allergy 2017

Blood eosinophils predict exacerbations

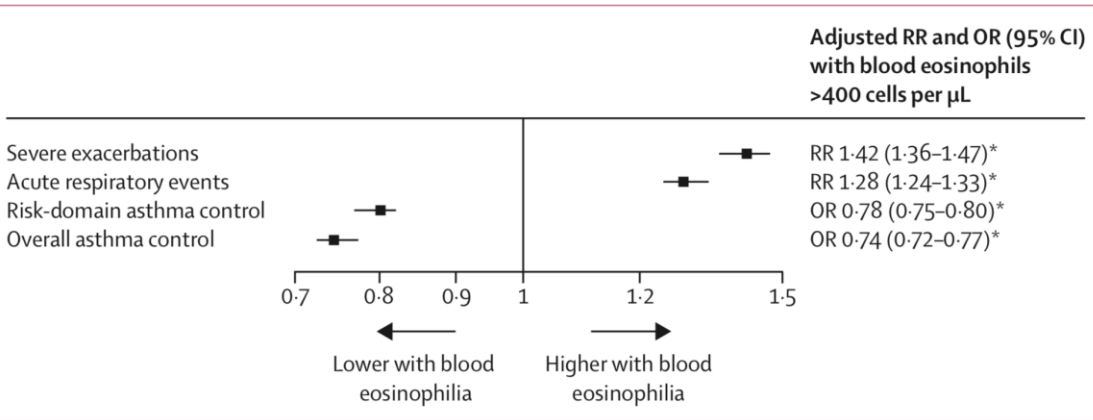


Figure 2: **Adjusted rate ratios (RRs) for severe exacerbations and acute respiratory events, and odds ratios (ORs) for asthma control, for patients with peripheral blood eosinophil count greater than 400 cells per µL (*vs* 400 cells per µL or less) during 1 outcome year**

*Adjusted for age, sex, body-mass index, smoking status, and Charlson comorbidity index score. p<0·0001 for all comparisons.

UK cohort w N=130,248 pts with asthma, blood eosinophils available and 2 years prospective follow-up data

In two UK databases, n=148, 021 pts:

- 14% were never eosinophil-hi (<300/uL)
- 41% were intermittently high (>=1 w eos>300/uL, <75% of all CBCs were >300/uL)
- 46% were persistently high (>=75% of all CBCs were >300/uL)
- **Both intermittently and persistently high groups had greater risk of exacerbations**

--Pooled data from 6 similar industry sponsored RCTs show blood eosinophils as one of the strongest predictors of exacerbations

--Insert Wessex severe asthma cohort about T2 high at least once in 10 years!

Price Lancet Resp Med. 2015; Tran J Asthma Allergy 2021; Kraft ERJ 2021

US asthma guidelines on FeNO, NAEPP Expert Panel Review 4

SECTION II

Recommendations on the Use of Fractional Exhaled Nitric Oxide Testing in the Diagnosis and Management of Asthma

Cloutier JACI 2020

US asthma guidelines on FeNO: helps with diagnosis

- **Recommendation 1:**
- Patients 5+ years of age with unclear asthma diagnosis after history and clinical findings, or in whom spirometry cannot be done, use FeNO as adjunct evaluation (conditional, moderate)

- FeNO **<25** ppb (or <20 ppb in children ages 5–12 years): suggests diseases other than asthma (e.g., COPD, vocal cord dysfunction, obesity), well-treated asthma, or non-type 2 inflammatory asthma.
- FeNO **25-50** ppb (or 20-35 ppb in kids 5–12 y/o) are inconclusive
- FeNO **>50** ppb (or >35 ppb in children ages 5–12 years): suggests elevated T2 inflammation and supports the diagnosis of asthma.

- With a pre-test probability = 60% … PPV =81%, NPV=70%
- Not bad for a point of care biomarker!

Dweik AJRCCM 2011, Cloutier JACI 2020

History, plus spirometry, plus FENO: even better

TABLE 4 Univariate logistic regression on the training cohort (n=166)

	OR (95% CI)
Wheezing intensity score	1.72 (1.26–2.40)***
Dyspnoea intensity score	1.20 (0.89–1.62)
Cough intensity score	1.10 (0.81–1.49)
Airway secretion intensity score	1.21 (0.89–1.66)
Chest tightness intensity score	1.03 (0.79–1.35)
FEV_1 (% pred)	0.95 (0.93–0.97)****
FEV_1/FVC (%)	0.90 (0.86–0.95)****
F_{ENO} (ppb)	1.02 (1.002–1.04)*

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; F_{ENO}: exhaled nitric oxide fraction. *: p<0.05; ***: p<0.001; ****: p<0.0001.

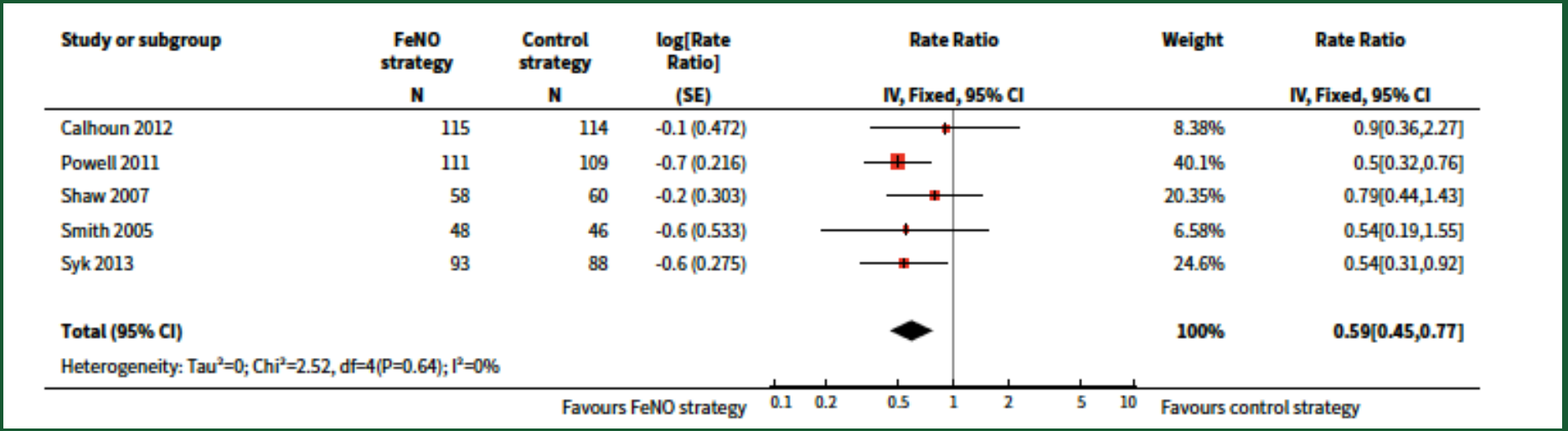
- A prospective observational study of n=303 people with breathing symptoms (i.e., wheeze, dyspnea, chest tightness, coughing, sputum production), but no asthma diagnosis

- The best response curve was a combo of wheezing, spirometry and FeNO (ROC AUC = 0.73, sensitivity = 52%, specificity = 91%, NPV = 60%, PPV = 88%).

Louis ERJ Open Research 2023

US asthma guidelines on FeNO: helps with ICS dose adjustments

- **Recommendation 2:**
- Patients 5+ years with persistent allergic asthma for whom there is uncertainty in choosing, monitoring and adjusting the dosing, **use with frequent FeNO** assessments (i.e., every 2-3 months) **to monitor and manage** the treatment strategy (conditional, low)



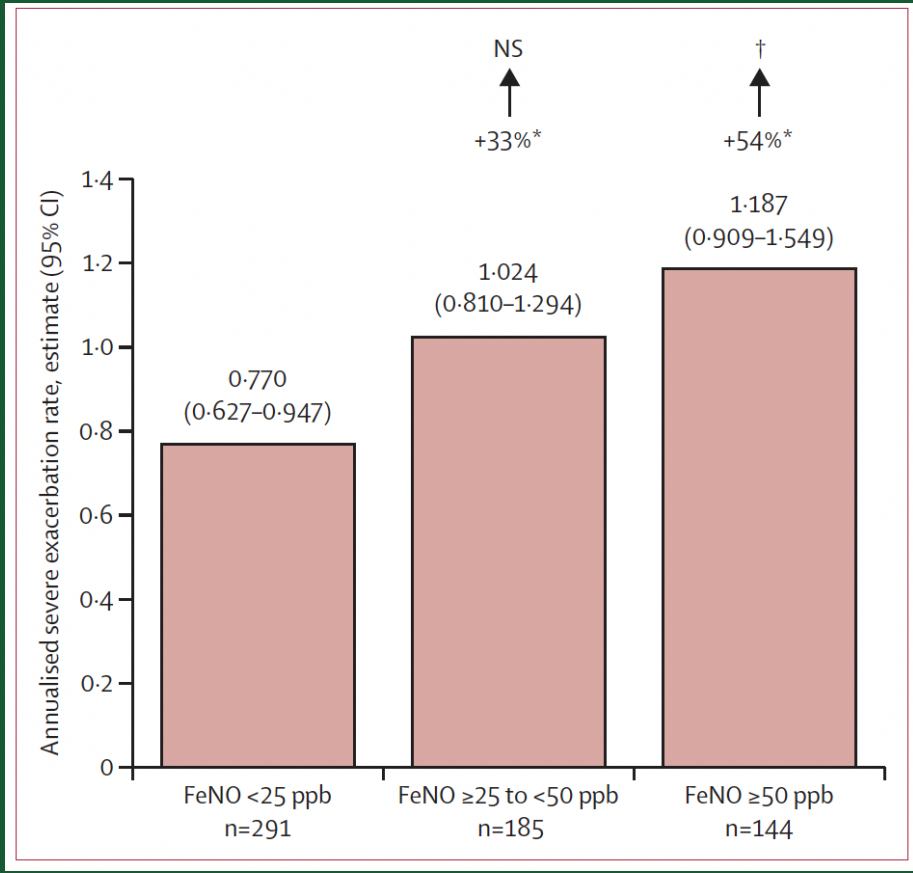
- A meta-analysis showed that FeNO-guided management significantly reduced asthma exacerbation rates vs. standard management, but similar reductions were not seen in ICS dose or asthma symptoms.

Petsky Cochrane 2016, Cloutier JACI 2020

Elevated FeNO also predicts exacerbations

- **Recommendation 3:**
- Patients 5+ years with persistent allergic asthma, do not use alone to assess asthma control, predict future exacerbations, or assess exacerbation severity (strong, low).

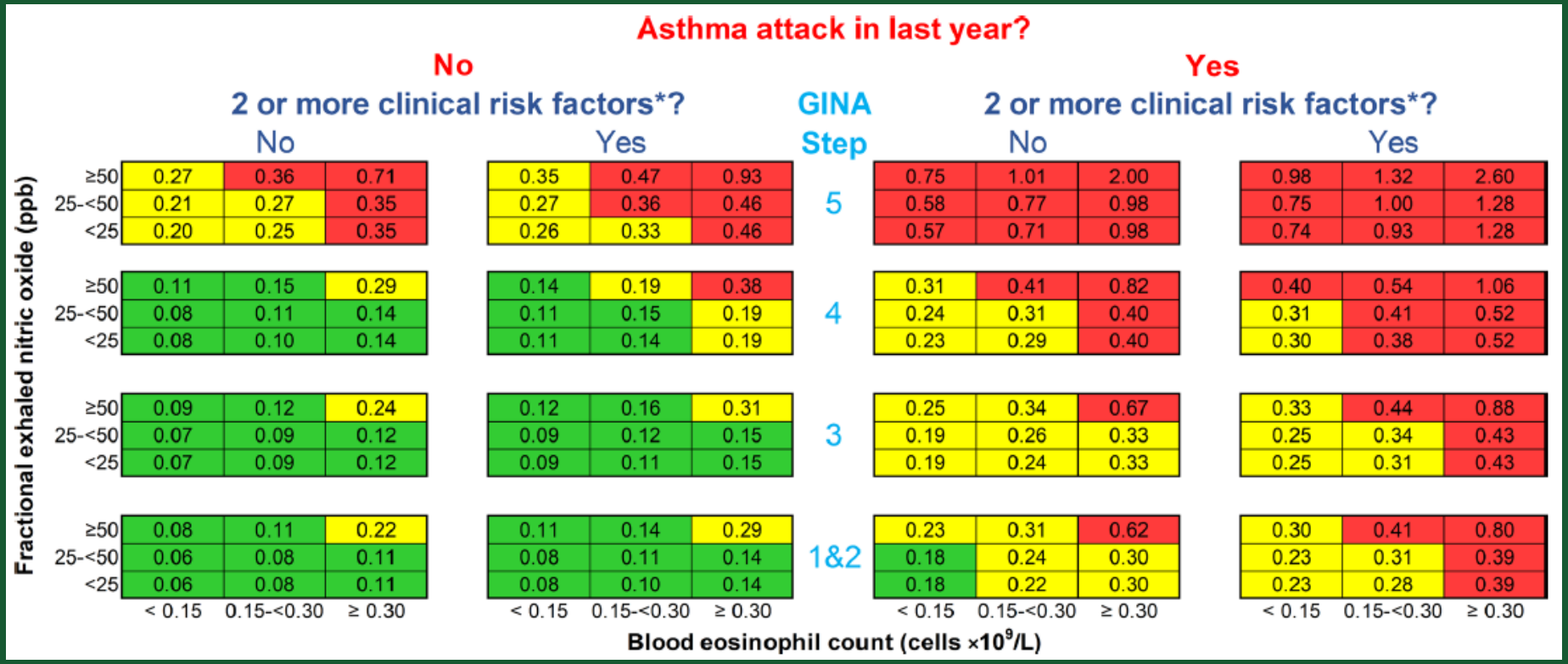
Post hoc analysis of the LIBERTY-QUEST trial; N=620 pts with moderate-severe asthma assigned to placebo



Busse Lancet Resp Med. 2021, Guida Curr Opin Allergy Immunol 2023, Cloutier JACI 2020

Blood eosinophils plus FeNO helps predict asthma exacerbations in combination with other biomarkers

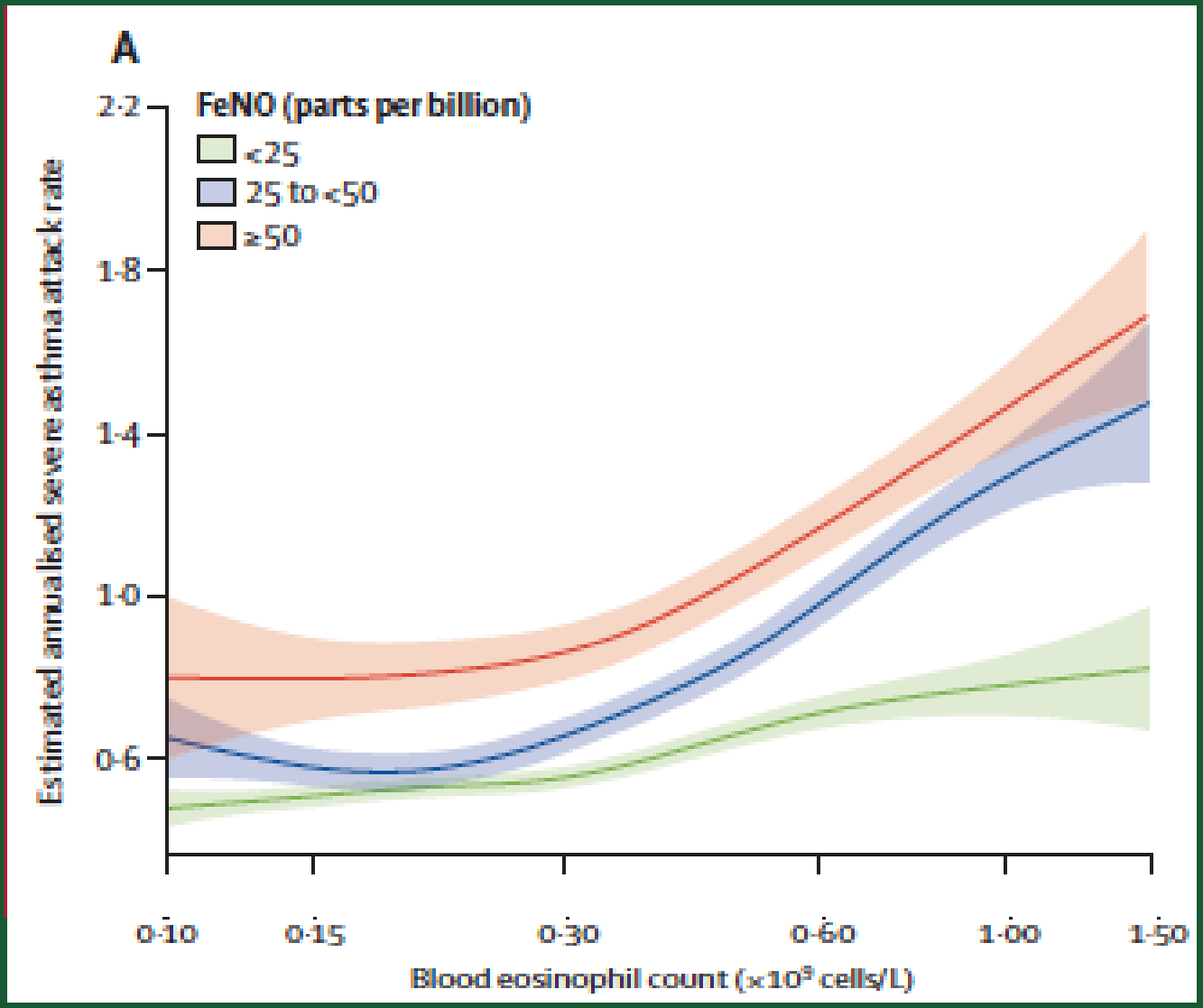
The ORACLE!



Scores were determined from pooled control arm patients with asthma (N=3,051) from Novel START, CAPTAIN, QUEST, Benralizumab Phase 2b, PATHWAY, STRATOS 1–2 and DREAM trials

Couillard Thorax 2022

Blood eosinophils plus FeNO help predict asthma exacerbations



The New ORACLE!

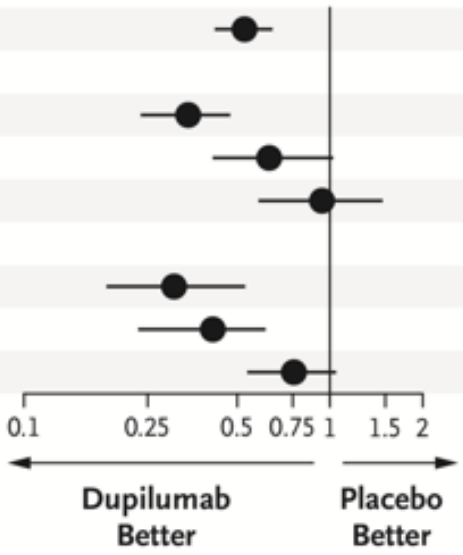
Scores were determined from pooled control arm patients with asthma (N=6,513) from 22 RCTs

Meulmeester Lancet Respir 2025, in press

FeNO and blood eosinophils predict treatment responses to several biologics

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)

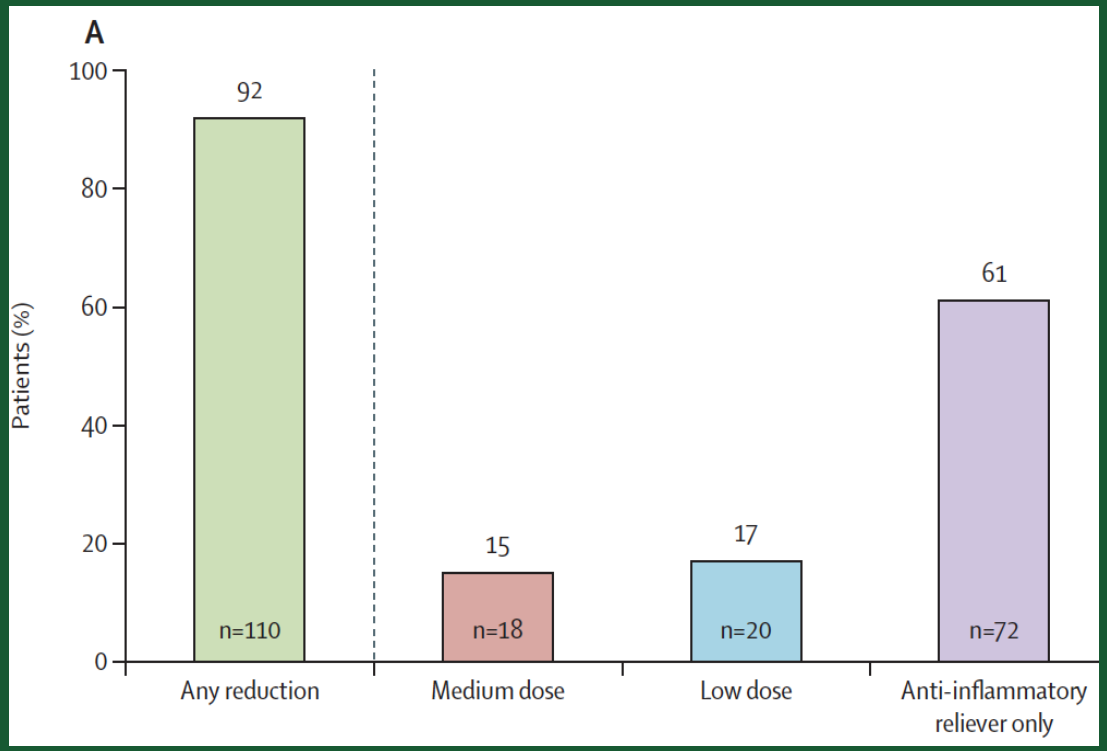


FeNO also predicts better treatment responses to tezepelumab and omalizumab

Blood eosinophils predict better treatment responses to all asthma biologics

Castro NEJM 2018

Possible additional indications for phenotyping with FENO



Phase 4, randomized, open-label, trial (SHAMAL) of adults with severe eosinophilic asthma: tapering the ICS controller therapy while on anti-IL5 pathway targeting biologic

Reduction group w similar asthma outcomes and adverse events, used <1/3 the cumulative ICS dose.

But the prn group experienced increases in FENO and worsening lung function, therefore … FENO testing might help preserve lung function in patients pursuing such a strategy

- FeNO + inhaler dose counting can **identify non-adherence** to inhaler tx (Hnin JACI IP 2024)
- Can help identify pts **who can successfully taper down** ICS therapy (Wang ERJ 2020)

Jackson Lancet 2024

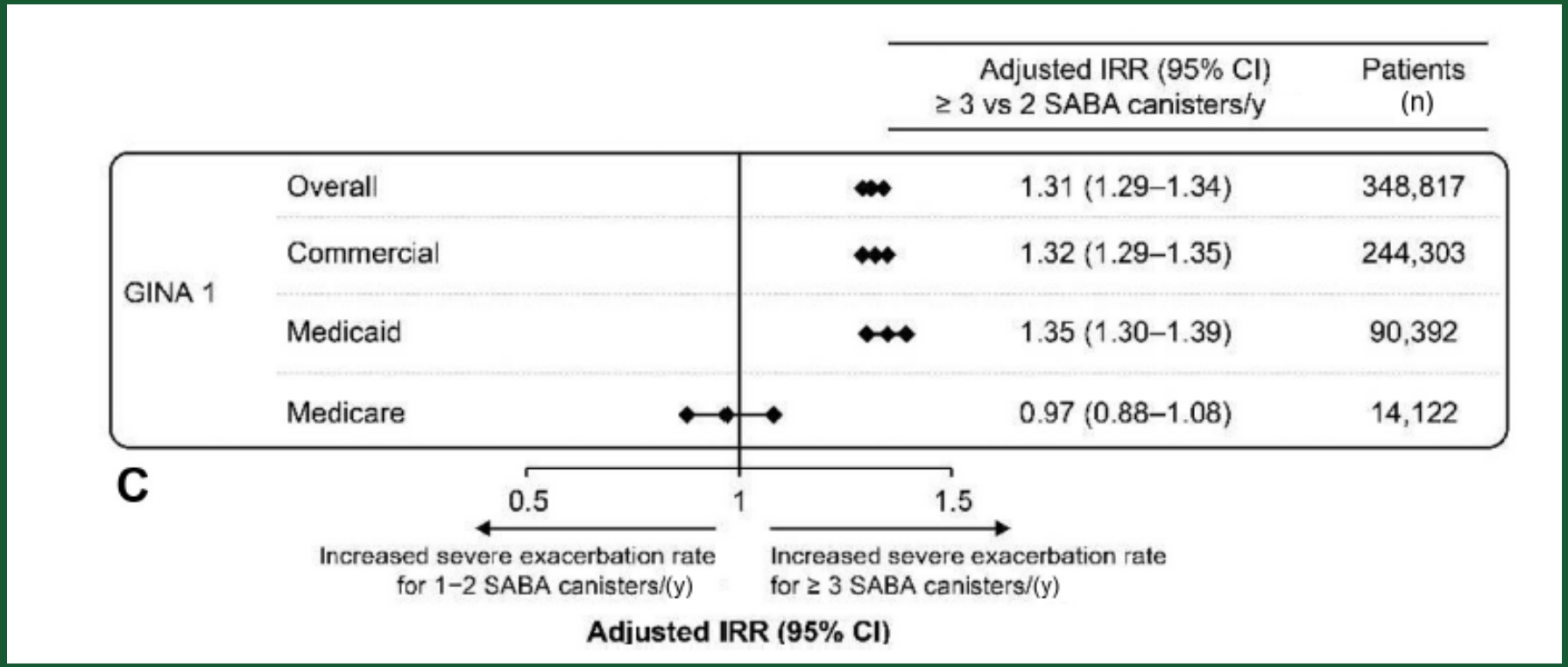
Summary #1

--Blood eosin nd elatively cheap and ca s to asthma h nd

"Exacerbations and predicting therapeutic responses to biologics are issues relevant only to moderate to severe asthma. Most patients have mild asthma. What you're arguing is mostly irrelevant!"

Severity assessments are inaccurate

- "Mild intermittent asthma" treated with SABA only (GINA 2018) is also at risk of exacerbations.



Data from the SABINA program (SABA use in asthma)

Quint JACI IP 2022

Mild asthma also exacerbates

- Classifying asthma severity by clinician prescriptions is inaccurate
- Many patients are misclassified as mild intermittent and yet are still at risk of exacerbations.

TABLE 1 Annual Exacerbation Events by Asthma Severity (GINA Steps) and Control (SABA Fills) in All Patients With Asthma Who Experienced an Event, Receiving Either Medicaid or Commercial Insurance (N = 1,005,522)

	Any severe exacerbation		Inpatient		Emergency department		Outpatient/office		OCS only	
	%	Mean[a] (SD)	%	Mean[a] (SD)	%	Mean[a] (SD)	%	Mean[a] (SD)	%	Mean[a] (SD)
Overall	52.4	1.81 (1.3)	2.5	1.15 (0.6)	3.9	1.17 (0.5)	12.8	1.26 (0.6)	51.4	1.79 (1.3)
Asthma control[b]										
1 SABA fill (well controlled)	55.1	1.60 (1.1)	1.6	1.11 (0.5)	2.3	1.05 (0.2)	10.1	1.11 (0.4)	54.5	1.59 (1.0)
2-3 SABA fills (not well controlled)	48.3	1.75 (1.2)	2.3	1.15 (0.6)	3.5	1.11 (0.4)	12.4	1.22 (0.5)	47.2	1.74 (1.2)
≥4 SABA fills (very poorly controlled)	56.3	2.19 (1.7)	4.0	1.17 (0.5)	7.1	1.29 (0.7)	17.6	1.43 (0.9)	55.1	2.17 (1.6)
GINA Step 1 (all)[c]	57.0	1.68 (1.1)	2.2	1.14 (0.6)	4.1	1.12 (0.4)	12.1	1.15 (0.4)	56.2	1.66 (1.1)
GINA Step 2 (all)	41.9	1.60 (0.9)	1.8	1.13 (0.5)	2.7	1.13 (0.4)	10.9	1.23 (0.5)	41.1	1.59 (0.9)
GINA Step 3 (all)	45.0	1.85 (1.3)	2.5	1.14 (0.5)	3.8	1.20 (0.5)	13.4	1.33 (0.7)	44.1	1.83 (1.3)
GINA Steps 4-5 (all)	55.2	2.32 (1.8)	3.9	1.18 (0.6)	4.8	1.31 (0.8)	15.9	1.45 (0.9)	53.9	2.30 (1.8)

IBM MarketScan Commercial and Medicare Supplemental databases

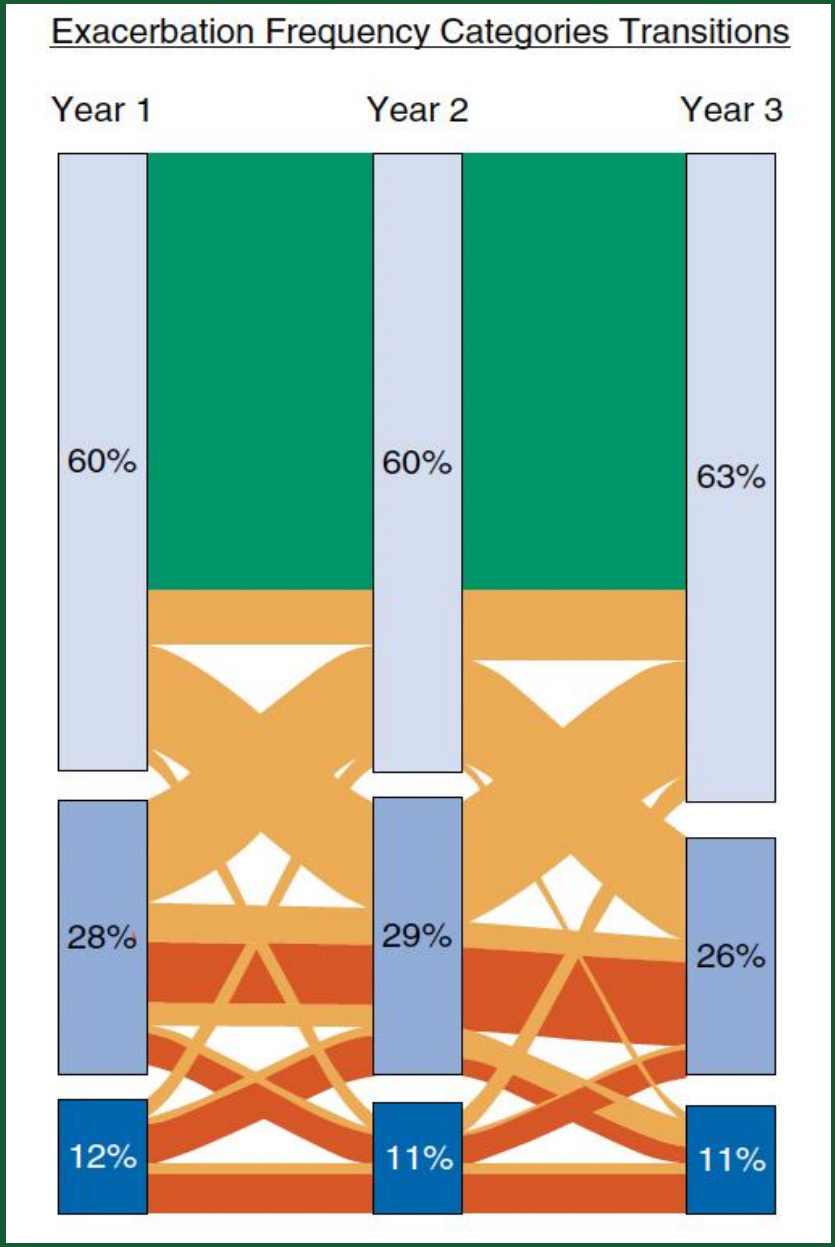
Pollack 2022

Non-severe asthma can accrue high healthcare burdens

- Insert Joe Zein figure SARP3/Ubiopred

Zein Lancet Respir 2024

Exacerbation frequency changes



NHLBI SARP3

Annual Exacerbation Frequency Categories
- Zero Exacerbations
- 1–2 Exacerbations
- >2 Exacerbations

3-year Longitudinal Exacerbation Phenotypes
- Exacerbations Resistant Asthma (ERA)
- Exacerbations Intermittent Asthma (EIA)
- Exacerbations Prone Asthma (EPA)

People change, phenotype them when you can!

Peters AJRCCM 2020

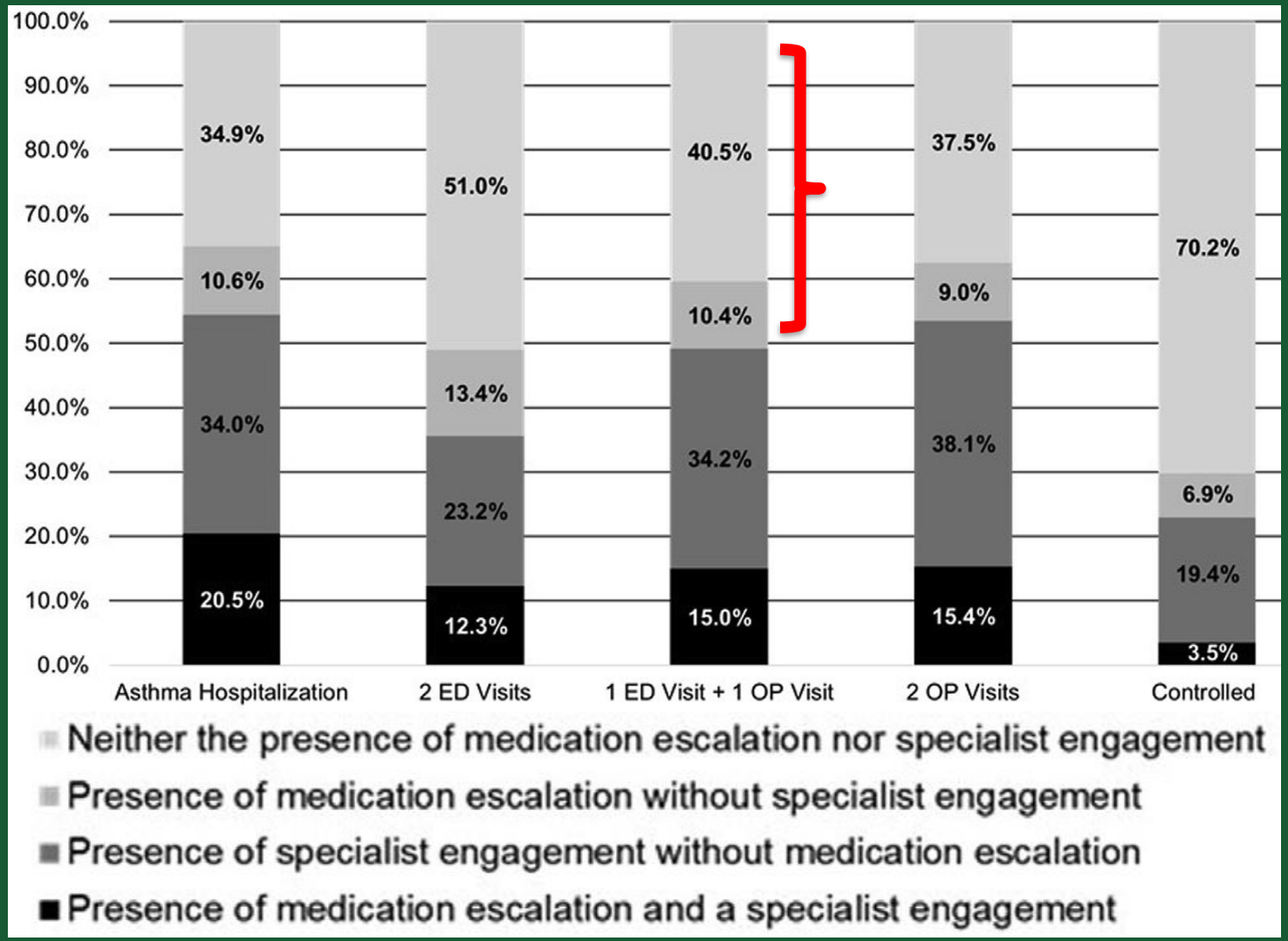
Summary #2

--Asthma sev ssess re
asthma can a g rity
can change o ie

"Why should we phenotype a relatively well controlled patient? I can treat them just as well without phenotyping them."

The fragmentation of the healthcare system

Catch them while you can! (and phenotype them!)



Retrospective analysis of two large, real-world claims databases
Inovalon
MORE2 Registry
(N=90,3868

Only half of patients with uncontrolled asthma and an exacerbation saw a specialist in the following year

Carr JACI IP 2024

The fragmentation of the healthcare system

Catch them while you can! (and phenotype them!)

Most uncontrolled asthma sees PCPs not specialists

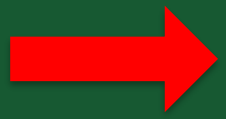
Insert Ortega figure

Ortega J Asthma 2022

Communication gaps between PCPs and specialists

N=85 attendings and residents from USF, IM, Peds and Fam medicine, cross-sectional survey-based study

- 77% referred to asthma specialists only after 2+ exacerbations
- 82% do not get labs to manage asthma
- 90% do not use blood eosinophils to manage asthma
- 42% were unfamiliar with asthma biologics
- Similar results with GSK funded IIS with N=405 with PCPs from throughout the US (AAFP)



Phenotype them whenever you can!

Patel et al. Abstract presented at ACAAI 2023, manuscript submitted to JACI IP, under review

Summary #3

--Most patients wit[illegible]ncontrolle

--Most don't do s[illegible]fter

--Primary care is [illegible] thma, don't phenotype[illegible]s, a[illegible] biologics

--Ther[illegible]m while y[illegible]

"It's just not cost effective"

Rebuttal against not phenotyping all patients w asthma

"It's not cost effective"

"It's too inaccurate"

"Guidelines don't require it"

Final summary

1. We have biomarkers available that can help us manage asthma
2. Asthma severity assessments are frequently inaccurate, biomarkers can help predict risk
3. Biomarkers can help predict risk even if asthma severity assessments of a patient change over time
4. Our healthcare system is fragmented, and we communicate poorly with PCPs who likely won't phenotype patients for us, so let's do it when we can

Any questions? Jcardet@usf.edu

Thank you!