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Association of blood eosinophils and exhaled nitric oxide with exacerbations in patients with asthma, COPD and asthma+COPD: the NOVELTY study

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ABSTRACT

Background Blood eosinophils (EOS) and fractional exhaled nitric oxide (FeNO) are potential biomarkers for disease progression and treatment response in asthma and chronic obstructive pulmonary disease (COPD). We investigated their association with exacerbations in asthma, COPD and asthma+COPD.

Methods NOVEL observational longiTudinal studY is a multicountry prospective study of patients with physician-assigned asthma, COPD and asthma+COPD. Negative binomial and logistic regression analyses were performed for baseline EOS/FeNO (separately and combined), by diagnosis, and for different exacerbation subtypes (all, antibiotics-only, oral corticosteroids (OCS)-only).

Results Higher baseline EOS was significantly associated with increased risk of all exacerbations in asthma (incidence rate ratio (IRR) 1.09, 95% CI 1.01 to 1.18, p=0.033), with a trend increase with COPD (IRR 1.09, 95% CI 1.00 to 1.19, p=0.069) but not asthma+COPD. Higher baseline FeNO was significantly associated with decreased risk of all exacerbations in COPD (IRR 0.91, 95% CI 0.84 to 0.99, p=0.025) and increased risk of OCS-only exacerbations in asthma (OR 1.16, 95% CI 1.04 to 1.29, p=0.006) and asthma+COPD (OR 1.55, 95% CI 1.22 to 1.97, p<0.001). In exacerbation risk in asthma (IRR 1.14, 95% CI 1.05 to 1.24, p=0.003), while in COPD, both higher EOS (IRR 1.12, 95% CI 1.02 to 1.24, p=0.033) and lower FeNO (IRR 0.87, 95% CI 0.78 to 0.96, p=0.009) were independently associated with exacerbation risk.

Conclusions Higher EOS predicted exacerbations in asthma and COPD, while FeNO showed heterogeneous associations, particularly for OCS-only treated exacerbations. Assessment of exacerbation subtype might improve personalised management. Interpretation is limited by physician-assigned diagnoses, potential ICS confounding and recall bias.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Asthma and chronic obstructive pulmonary disease (COPD) are prevalent pulmonary diseases. Patients with asthma and/or COPD and a type 2 high phenotype are at increased risk of exacerbations; blood eosinophils (EOS) and fractional exhaled nitric oxide (FeNO) have been proposed as biomarkers to identify this phenotype.

WHAT THIS STUDY ADDS

⇒ Using data from NOVEL observational longiTudinal studY, we found that high levels of EOS at baseline were associated with increased risk of all exacerbations in asthma and COPD over 1 year. Higher baseline FeNO levels are associated with decreased risk of all exacerbations in COPD and significantly associated with increased risk of oral corticosteroids-only treated exacerbations in asthma and asthma+COPD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ EOS may be a useful biomarker for exacerbation risk in patients with asthma and COPD; FeNO may be less suitable as a biomarker in COPD as levels are difficult to interpret. The findings indicate that assessment of exacerbation subtype might improve personalised management.

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are prevalent diseases characterised by airflow limitation.[1 2] Asthma and COPD are heterogenous airway diseases with clinical characteristics that may overlap. In some patients both diseases can be diagnosed at the same time (ie, asthma+COPD).[3] It is increasingly acknowledged that personalised clinical management of these obstructive pulmonary diseases is of high importance. To this end, reliable biomarkers are needed to identify patients at risk or who best respond to specific treatment options.

In both asthma and COPD, type 2 inflammation can be identified in subsets of patients, with a type 2 high phenotype being frequently associated with increased risk for exacerbations.[4 5] In randomised controlled trials, this phenotype has been observed

Table 1 Baseline characteristics FeNO population

FeNO population	Asthma n=4166	Asthma+COPD n=1016	COPD n=2588
Age, years, mean (SD)	52.25 (17.00)	64.78 (9.91)	66.74 (9.21)
Time since diagnosis, years, median (IQR)	n=4012 13.6 (4.9–28.7)	n=996 13.7 (5.6–33.7)	n=2532 5.3 (2.2–10.2)
Female, n (%)	2585 (62.0)	455 (44.8)	968 (37.4)
BMI, kg/m^2, mean (SD)	n=3895 27.91 (6.58)	n=967 28.69 (6.41)	n=2447 27.78 (6.41)
Current smoker	319 (7.7)	244 (24.0)	726 (28.1)
Former smoker	1266 (30.4)	652 (64.2)	1706 (65.9)
Never smoker	2581 (62.0)	120 (11.8)	156 (6.0)
Smoking pack-years, median (IQR)	0 (0–5.0)	26.2 (10.0–44.0)	37.5 (20.0–60.0)
Exacerbations during last 12 months, n (%)	n=4157	n=1015	n=2578
0	2721 (65.5)	545 (53.7)	1672 (64.9)
1	972 (23.4)	268 (26.4)	627 (24.3)
≥2	464 (11.2)	202 (19.9)	279 (10.8)
Allergic rhinitis, n (%)	1385 (33.2)	270 (26.6)	155 (6.0)
OCS use, n (%)	n=3855 117 (3.0)	n=970 30 (3.1)	n=2294 19 (0.8)
EOS count, 10^9/L, median (IQR)	n=1878 0.18 (0.11–0.29)	n=568 0.17 (0.11–0.26)	n=1317 0.16 (0.10–0.23)
FeNO, ppb, median (IQR)	22 (14–39)	17 (10–30)	16 (10–25)
FEV_1, litre (post-BD), mean (SD)	n=3623 2.58 (0.87)	n=905 1.88 (0.71)	n=2274 1.69 (0.72)
FEV_1, % predicted (post-BD), mean (SD)	n=3539 88.05 (20.13)	n=872 69.09 (20.80)	n=2223 62.11 (22.67)
FVC, % predicted (post-BD), mean (SD)	n=3516 94.83 (16.97)	n=872 90.95 (19.26)	n=2223 84.69 (20.47)
FEV_1/FVC, ratio (post-BD), mean (SD)	n=3633 74.88 (11.72)	n=904 59.62 (14.41)	n=2273 57.34 (16.13)
St. George's Respiratory Questionnaire, total score, median (IQR)	n=3042 24.4 (12.0–41.8)	n=747 36.8 (21.6–54.5)	n=1894 37.9 (24.1–56.6)
Asthma control test, total score, median (IQR)	n=3086 21 (17–24)	n=673 18 (14–22)	n=27 17 (15–22)
Physician assessed severity, n (%)	n=4165	n=1013	n=2588
Mild	1519 (36.5)	164 (16.2)	745 (28.8)
Moderate	1571 (37.7)	471 (46.5)	838 (32.4)
Severe	1075 (25.8)	378 (37.3)	1005 (38.8)

BD, bronchodilator; BMI, body mass index; COPD, chronic obstructive pulmonary disease; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; OCS, oral corticosteroids.

to show improved treatment response to inhaled corticosteroids (ICS) and biologicals such as anti-IL5 and anti-IL4.[6 7] Both blood eosinophil (EOS) counts and fractional exhaled nitric oxide (FeNO) have been proposed as biomarkers to identify this phenotype. Although the role of FeNO is less established than that of EOS in COPD, it has been suggested that the predictive value of both biomarkers may be irrespective of the type of obstructive pulmonary disease.[8 9] However, this has not yet been assessed in a real-life, observational cohort with asthma, COPD and asthma+COPD patients. In addition, it is unclear if combining information of both EOS and FeNO provides more accurate information than either biomarker alone.[8 10]

In the present study, we investigated if EOS and FeNO, individually and in combination, associate with the risk of future exacerbations in patients with asthma, COPD or asthma+COPD in a real-life setting.[11]

METHODS

NOVEL observational longiTudinal studY study design

We used available data from the NOVELTY study (NOVEL observational longiTudinal studY, NCT02760329) that included more than 12 000 patients with a physician-assigned diagnosis or clinically suspected diagnosis of asthma, COPD or asthma+COPD enrolled from active primary and specialist clinical practices in 19 countries in Europe, the Americas, Asia and Australia. A detailed description of the in- and exclusion criteria and study design can be found in the online supplemental appendix 1,2. In short, patients were included from the age of 18 years in seven countries and from the age of 12 years in the remaining countries. The NOVELTY study design has been published in detail before[11] and is briefly summarised here. Patients were diagnosed according to the treating physician, with no specific diagnostic criteria specified, and classified as mild, moderate or severe disease based on the physician's clinical judgement. Patients were excluded if they participated in a respiratory interventional trial in the 12 months before enrolment, if they were unlikely to complete 3 years of follow-up (eg, due to co-morbidity or substance abuse), or if their primary respiratory diagnosis was not asthma and/or COPD. Patient data were collected at baseline and either every 3 months or annually, depending on the measured outcome, for up to 3 years. Patients received standard medical care as determined by their physician and most study procedures were conducted according to local standard of care guidelines. The exceptions were performance of spirometry, measurement of FeNO and collection, storage and shipment of biosamples, which were performed in accordance with standardised procedures. A full list of NOVELTY Scientific Community members and NOVELTY study investigators can be found in online supplemental appendix tables S1 and S2), respectively.

Measurements

At baseline, data on demographics, smoking status, quality of life, treatments, exacerbations and lung function (ie, spirometry, FeNO) were collected. Then, patients were seen yearly for up to 3 years or until study discontinuation. Patient-Reported Outcome questionnaires, along with information about symptom control and adherence to treatment, were collected every 3 months using a web-based platform or telephone. Patients were treated as determined by their own physician. Data on treatment frequency, duration and modification (ie, dosage change, switch, discontinuation) were collected at each follow-up assessment. At each visit, physicians were asked to record the number of exacerbations of their patients during the previous 12 months. In a subset of patients, peripheral blood samples were collected, and assessment of differential cell counts was performed at baseline and at the yearly follow-up visits. Spirometry was performed according to standards of the European Respiratory Society/American Thoracic Society guidelines[12] and FeNO was measured at baseline using local hospital equipment or, when unavailable,

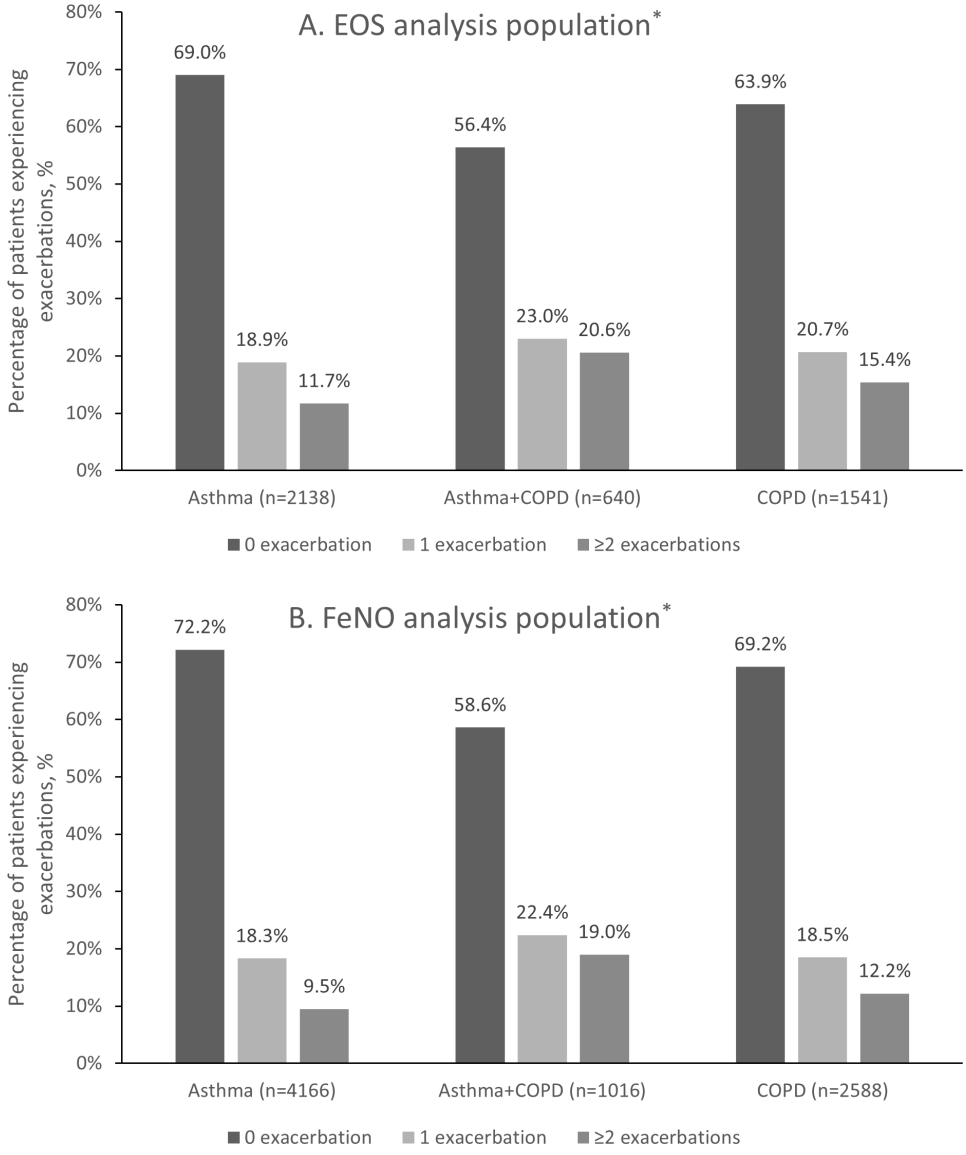

Figure 1 Exacerbations during the first year of follow-up in the NOVELTY study. (A) Number of all exacerbations in the EOS analysis. (B) Number of all exacerbations in the FeNO analysis. *Number of patients in the EOS and FeNO analysis populations differed based on available data. Data are presented as percentages (%) per diagnostic label. COPD, chronic obstructive pulmonary disease; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; NOVELTY, NOVEL observational longiTudinal studY.

the Niox Vero device provided by the study sponsor (Circassia Pharmaceuticals, Morrisville, North Carolina, USA).[13]

Exacerbations subtypes were categorised based on information reported by the patient during the subsequent study visit as follows: All exacerbations (ie, any severity; total number of exacerbations during 1-year follow-up); antibiotics-only treated exacerbations (ie, patients with all exacerbations during 1-year follow-up treated with antibiotics; 'yes' vs 'no' exacerbations at all); and oral corticosteroid (OCS)-only treated exacerbations (ie, patients with all exacerbations during 1-year follow-up treated with OCS; 'yes' vs 'no' exacerbations at all).

Statistical analysis

A detailed description of the statistical analysis methods can be found in the online supplemental appendix 2,3. In short, baseline demographics and clinical characteristics were stratified by physician-assigned diagnosis. For the current analyses, we did not perform a formal power calculation but included all patients who had baseline EOS and/or FeNO measurements collected and had exacerbation data available during the 1-year follow-up. This study was therefore a complete case analysis and assumed missing data to be at random. Patients using anti-IL5 or anti-IL4 at any time during the study were excluded. Patients who were on maintenance OCS were not excluded, as they represented only a very small proportion of patients. Data for patients from China were excluded from the present analysis due to a change in regulations on data transfer in May 2019. Blood samples that had been taken >72 hours before they were processed at the central laboratory were excluded, because longer delay was found to impact the reliability of the lab results.[14 15]

Negative binomial and logistic regression analyses for EOS and FeNO were performed for each diagnosis and for the different exacerbation outcomes. Negative binomial regression was chosen over alternative models as this was the most appropriate analysis for the outcome of exacerbations, particularly where the variance is higher than the mean, which is generally

assumed to be the case for this endpoint. EOS and FeNO were analysed as continuous variables rather than specifying cut-off values; both were log-normally distributed and were therefore log2-transformed in the models. All models were adjusted for age, sex and smoking status, which were selected a priori as potential confounders that could influence both biomarkers and exacerbation risk across disease categories. ICS use was categorised as low, medium or high dose based on the converted budesonide equivalent dosage according to Box 3–6 of the GINA guidelines.[2] For EOS models, ICS use was modelled as 'High' (Yes/No), 'Low+Medium' (Yes/No), with the reference being 'No ICS use'. For FeNO models, ICS use was modelled as 'yes' versus 'no' ICS use. This different correction for ICS use was decided on because ICS is a potent suppressor of FeNO at almost any dose, but effects EOS levels increasingly at a high dose. Accordingly, ICS use was included as a covariate in the sensitivity analyses. Finally, we were interested in whether EOS and FeNO would have a stronger association when analysed together in one model, as observed in clinical trials.[6] Therefore, we conducted a separate analysis with both EOS and FeNO in one model. SAS V.9.4 was used for all statistical analyses.

Exacerbation outcomes data are presented as n (%). Association of EOS and FeNO with exacerbations data are presented as incidence rate ratio (IRR), 95% CIs (all exacerbations) or OR, 95% CI (exacerbation subtypes). Baseline demographic data are presented as mean (SD), median (IQR) or n (%), as appropriate. Consistent with conventions in exploratory observational studies and with the American Statistical Association (ASA) guidance stating that p values represent a continuum of evidence rather than a strict threshold,[16] statistical significance was defined as $p<0.05$ and p values between 0.05 and 0.10 were reported as indicating a trend. Baseline demographic data are presented as mean (SD), median (IQR) or n (%) as appropriate.

RESULTS

Patients

In total, 4319 patients were included in the EOS analysis (asthma n=2138; COPD n=1541; asthma+COPD n=640; online supplemental appendix figure S1), 7770 patients were included in the FeNO analysis (asthma n=4166; COPD n=2588; asthma+COPD n=1016; online supplemental appendix figure S2), and 3763 patients were included in the EOS+FeNO analysis (asthma n=1878; COPD n=1317; asthma+COPD n=568). Table 1 presents the baseline characteristics of patients included in the FeNO analysis. Baseline characteristics of patients in the EOS analysis are similar and presented in online supplemental appendix table S3. Overall, patients diagnosed with asthma were younger, more often female and had the longest duration of disease. Patients diagnosed with COPD were older, had the highest number of smoking pack-years and a worse lung function as expressed by a lower forced expiratory volume in 1 s (FEV_1) %predicted and FEV_1/forced vital capacity ratio. EOS and FeNO at baseline were right skewed (online supplemental appendix figures S3 and S4) with log-normal distribution. Figure 1 and table 2 show the number of recorded exacerbations during the first year of follow-up. The proportion of patients reporting at least one exacerbation was lowest in asthma and highest in asthma+COPD.

Table 2 Exacerbations during the first year of follow-up in the NOVELTY study

EOS analysis	Asthma n=2138	Asthma+COPD n=640	COPD n=1541
Patients with exacerbation, n (%)	655 (30.6)	279 (43.6)	556 (36.1)
All exacerbations, n (%)			
0	1483 (69.4)	361 (56.4)	985 (63.9)
1	405 (18.9)	147 (23.0)	319 (20.7)
≥2	250 (11.7)	132 (20.6)	237 (15.4)
OCS-only treated exacerbations, n (%)	n=1655	n=410	n=1053
0	1483 (89.6)	361 (88.0)	985 (93.5)
1	125 (7.6)	34 (8.3)	58 (5.5)
≥2	47 (2.8)	15 (3.7)	10 (0.9)
Antibiotics-only treated exacerbations, n (%)	n=1557	n=401	n=1058
0	1483 (95.2)	361 (90.0)	985 (93.1)
1	62 (4.0)	28 (7.0)	58 (5.5)
≥2	12 (0.8)	12 (3.0)	15 (1.4)
FeNO analysis	**Asthma n=4166**	**Asthma+COPD n=1016**	**COPD n=2588**
Patients with exacerbation, n (%)	1158 (27.8)	416 (40.9)	796 (30.8)
All exacerbations, n (%)			
0	3008 (72.2)	595 (58.6)	1792 (69.2)
1	763 (18.3)	228 (22.4)	480 (18.5)
≥2	395 (9.5)	193 (19.0)	316 (12.2)
OCS-only treated exacerbations, n (%)	n=3310	n=665	n=1891
0	3008 (90.9)	595 (89.5)	1792 (94.8)
1	228 (6.9)	49 (7.4)	84 (4.4)
≥2	74 (2.2)	21 (3.2)	15 (0.8)
Antibiotics-only treated exacerbations, n (%)	n=3150	n=652	n=1912
0	3008 (95.5)	595 (91.3)	1792 (93.7)
1	119 (3.8)	43 (6.6)	95 (5.0)
≥2	23 (0.7)	14 (2.1)	25 (1.3)

Antibiotics: antibiotics-only treated exacerbations (ie, patients with all exacerbations treated with antibiotics; 'yes' vs 'no' exacerbations at all); OCS: OCS-only treated exacerbations (ie, patients with all exacerbations treated with OCS; 'yes' vs 'no' exacerbations at all).
COPD, chronic obstructive pulmonary disease; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; NOVELTY, NOVEL observational longiTudinal studY; OCS, oral corticosteroids.

Associations between EOS and FeNO with exacerbation risk

As shown in figure 2 and table 3 and online supplemental appendix figure S5, higher EOS at baseline was associated with increased risk of all exacerbations in asthma (IRR 1.09, 95% CI 1.01 to 1.18, p=0.033), whereas no association was observed for FeNO (p=0.683) (online supplemental appendix figure S6). This means that on a log2 scale, each doubling of EOS was associated with a 9% increase in the risk of having an exacerbation. In asthma+COPD, neither EOS (p=0.766) nor FeNO (p=0.877) at baseline was associated with increased risk of all exacerbations. In COPD, an association between higher baseline EOS and increased risk of all exacerbations was observed (IRR 1.09, 95% CI 1.00 to 1.19, p=0.069). Unexpectedly, for COPD, a higher baseline FeNO was associated with decreased risk of all exacerbations (IRR 0.91, 95% CI 0.84 to 0.99, p=0.025).

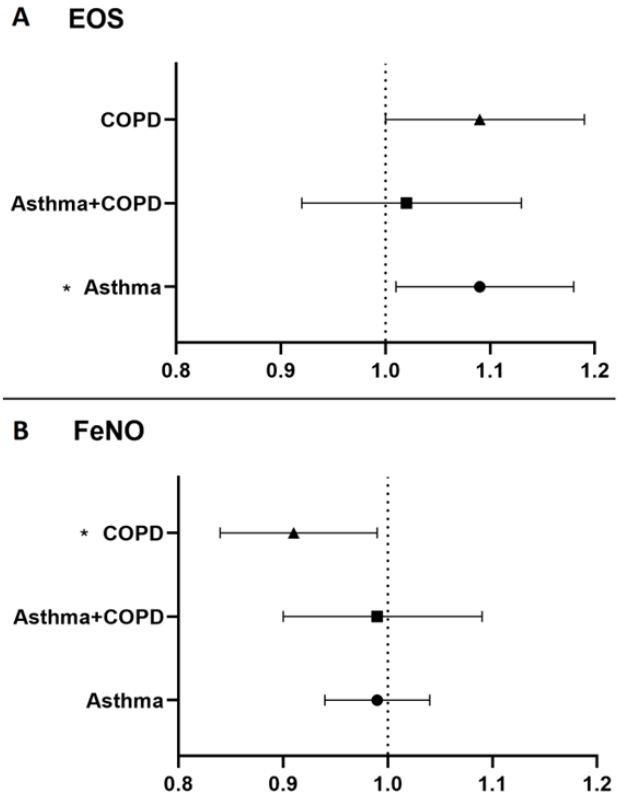

Figure 2 Association of baseline EOS and FeNO with all exacerbations. Association of baseline (A) EOS and (B) FeNO with all exacerbations during the first year of follow-up in the NOVELTY study. Data are presented as IRR, CI. All regression analyses were adjusted for age, sex and smoking status. EOS and FeNO data were log2-transformed. *p<0.05. COPD, chronic obstructive pulmonary disease; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; IRR, incidence rate ratio; NOVELTY, NOVEL observational longiTudinal studY.

Associations with exacerbation subtypes

In asthma, no associations were observed between baseline EOS and any specific exacerbation subtypes (figure 3 and table 3). Higher baseline FeNO levels were associated with increased risk of OCS-only treated exacerbations in asthma (OR 1.16, 95% CI 1.04 to 1.29, p=0.006), but with a decreased risk of antibiotics-only treated exacerbations (OR 0.75, 95% CI 0.64 to 0.89, p=0.001). In asthma+COPD, we did not find an association between baseline EOS and any of the exacerbation subtypes, whereas higher baseline FeNO levels were associated with increased risk of OCS-only (OR 1.55, 95% CI 1.22 to 1.97, p<0.001), but not antibiotics-only treated exacerbations (p=0.925). Finally, in COPD, neither baseline EOS nor baseline FeNO was associated with OCS or antibiotics-only treated exacerbations.

Regression analysis of EOS and FeNO combined in relation to exacerbation risk

The results of the analysis with both EOS and FeNO in one model are shown in table 4. In asthma, higher EOS at baseline was associated with increased risk of all exacerbations (IRR 1.14, 95% CI 1.05 to 1.24, p=0.003); however, FeNO did not contribute significantly to the model (p=0.091). Higher EOS were found to be associated with increased risk of OCS-only treated exacerbations in asthma (OR 1.18, 95% CI 1.01 to 1.39, p=0.041), whereas EOS did not independently associate with antibiotics-only treated exacerbations (p=0.947), with a trend being observed for lower FeNO (OR 0.79, 95% CI 0.61 to 1.02, p=0.071).

Neither EOS nor FeNO at baseline was associated independently to risk of all- or antibiotics-only treated exacerbations in asthma+COPD. Higher baseline FeNO, but not EOS, was independently associated with risk of exacerbations treated with OCS-only (OR 1.46, 95% CI 1.08 to 1.97, p=0.013). In COPD, both higher EOS and lower FeNO were independently associated with increased risk of all exacerbations (EOS IRR 1.12, 95% CI 1.02 to 1.24,

Table 3 Association of baseline EOS and FeNO with exacerbations during the first year of follow-up in the NOVELTY study

EOS analysis	Asthma	P value	Asthma+COPD	P value	COPD	P value
All exacerbations	n=2137		n=640		n=1540	
Log2EOS	1.09 (1.01–1.18)	0.033	1.02 (0.92–1.13)	0.766	1.09 (1.00–1.19)	0.069
OCS-only	n=1654		n=410		n=1052	
Log2EOS	1.13 (0.98–1.32)	0.102	1.27 (0.96–1.74)	0.119	1.06 (0.81–1.39)	0.669
Antibiotics-only	n=1556		n=401		n=1057	
Log2EOS	0.94 (0.79–1.14)	0.486	1.05 (0.83–1.44)	0.729	1.21 (0.93–1.58)	0.154
FeNO analysis	**Asthma**	**P value**	**Asthma+COPD**	**P value**	**COPD**	**P value**
All exacerbations	n=4166		n=1016		n=2588	
Log2FeNO	0.99 (0.93–1.04)	0.683	0.99 (0.90–1.09)	0.877	0.91 (0.84–0.99)	0.025
OCS-only	n=3310		n=665		n=1891	
Log2FeNO	1.16 (1.04–1.29)	0.006	1.55 (1.22–1.97)	<0.001	1.03 (0.83–1.29)	0.758
Antibiotics-only	n=3150		n=652		n=1912	
Log2FeNO	0.75 (0.64–0.89)	0.001	1.01 (0.77–1.32)	0.925	0.85 (0.69–1.05)	0.130

Data are presented as IRR or OR, 95% CI. All regression analyses were adjusted for age, sex and smoking status. EOS and FeNO data were log2-transformed. Antibiotics: antibiotics-only treated exacerbations (ie, patients with all exacerbations treated with antibiotics; 'yes' vs 'no' exacerbations at all); OCS: OCS-only treated exacerbations (ie, patients with all exacerbations treated with OCS; 'yes' vs 'no' exacerbations at all).
COPD, chronic obstructive pulmonary disease; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; IRR, incidence rate ratio; NOVELTY, NOVEL observational longiTudinal studY; OCS, oral corticosteroids.

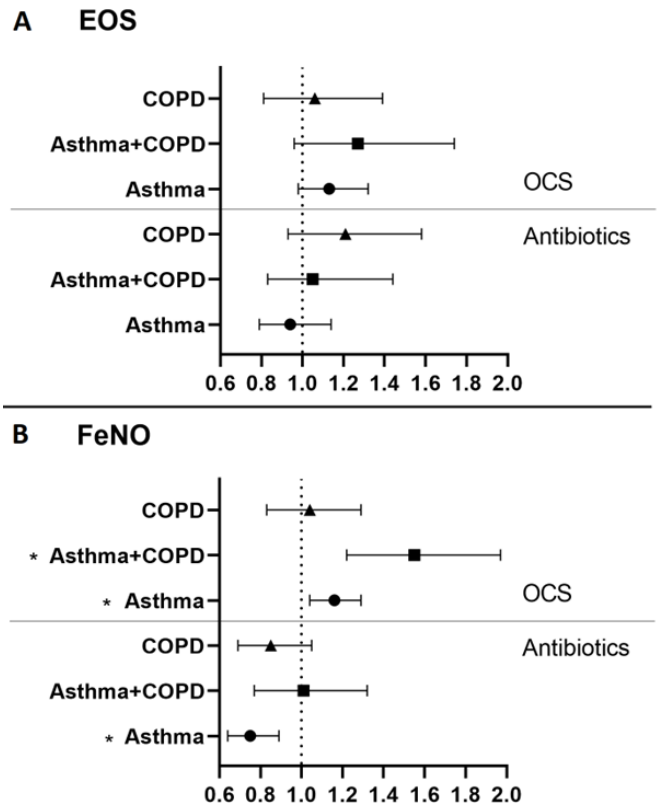

Figure 3 Association of baseline EOS and FeNO with OCS and antibiotics-only treated exacerbations. Association of baseline (A) EOS and (B) FeNO with OCS-only and antibiotics-only treated exacerbations during the first year of follow-up in the NOVELTY study. Data are presented as OR, CI. All regression analyses were adjusted for age, sex and smoking status. EOS and FeNO data were log2-transformed. Antibiotics: antibiotics-only treated exacerbations (ie, patients with all exacerbations treated with antibiotics; 'yes' versus 'no' exacerbations at all); OCS: OCS-only treated exacerbations (ie, patients with all exacerbations treated with OCS; 'yes' vs 'no' exacerbations at all). *p<0.05. COPD, chronic obstructive pulmonary disease; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; NOVELTY, NOVEL observational longiTudinal studY; OCS, oral corticosteroids.

p=0.033; FeNO IRR 0.87, 95% CI 0.78 to 0.96, p=0.009). No independent associations were observed between EOS or FeNO and risk of OCS or antibiotics-only treated exacerbations in COPD.

Effect of inhaled corticosteroids treatment

The results of the sub-analysis of the models including ICS use (ie, EOS models: High (Yes/No), Low+Medium (Yes/No), No ICS use; FeNO models: 'yes' vs 'no' ICS use; combined EOS and FeNO models: 'yes' vs 'no' ICS use) as covariate are presented in online supplemental appendix tables S4 and S5. In asthma, the association between higher EOS at baseline and all exacerbations was not significant (p=0.096, online supplemental appendix table S4). Similar to the models without ICS use as a covariate, higher FeNO was associated with increased risk of OCS-only (OR 1.15, 95% CI 1.03 to 1.29, p=0.010) and decreased risk of antibiotics-only (OR 0.74, 95% CI 0.62 to 0.88, p=0.001) treated exacerbations in asthma (online supplemental appendix table S4). Online supplemental appendix table S5 shows that in the combined EOS and FeNO model, with ICS use as a covariate, EOS at baseline is not independently associated with OCS-only treated exacerbations in asthma (p=0.093). In asthma+COPD, higher FeNO at baseline was significantly associated with increased risk of OCS-only treated exacerbations (OR 1.56, 95% CI 1.22 to 2.01, p=0.001, (online supplemental appendix table S4). In the combined EOS and FeNO models (online supplemental appendix table S5), in asthma+COPD, higher FeNO was independently associated with increased risk of OCS-only treated exacerbations (OR 1.40, 95% CI 1.02 to 1.94, p=0.037). In COPD, lower FeNO at baseline was not significantly associated with risk of all exacerbations (p=0.072) after correction for ICS use (online supplemental appendix table S4). In the combined EOS and FeNO models (online supplemental table S5), the independent association between higher EOS at baseline and increased risk of all exacerbations in COPD was not significant (p=0.070).

DISCUSSION

This is the first study exploring the role of EOS and FeNO, separately and in combination, as biomarkers to predict exacerbation risk across the spectrum of asthma, COPD and asthma+COPD in a real-life, routine clinical care setting. Our main results show that: (1) Elevated EOS levels are associated with increased risk of all exacerbations in asthma with a similar trend in COPD; (2) For FeNO, differential associations are observed for the different exacerbation types, with higher FeNO levels being associated with increased risk for OCS-only treated exacerbations both in asthma and asthma+COPD, but nil, or even inverse, associations in case of exacerbations treated with antibiotics-only and (3) In contrast to EOS, FeNO is less useful as a biomarker for exacerbation risk assessment in COPD.

The results of our study are in accordance with previous findings of elevated EOS being associated with increased exacerbation risk.[6 7] However, the associations we observed in this real-life, observational setting were weaker than expected. This may be due to lower treatment adherence and the reasonable possibility that biomarker results such as FeNO, available at the point-of-care, were discussed with patients to further improve adherence. Though it is important to note that most studies of EOS as a biomarker were clinical trials using strict inclusion and exclusion criteria, with the strongest effects being observed in those not using ICS.[17 18] In addition, these clinical trials were often enriched for exacerbations. However, there are several studies of EOS as a biomarker in real life that did find stronger associations between EOS and exacerbations in asthma and COPD compared with our study.[19 20] This could partially be explained by the fact that these studies were performed with much larger datasets as well as the fact that participation in the NOVELTY study resulted in closer monitoring of patients, which could have influenced treatment results. The longer duration of the NOVELTY study may have increased the power of the analyses; however, data collected after the first year were difficult to interpret due to the COVID-19 pandemic, which had a major impact on exacerbation incidence. Moreover, as no standardised diagnostic criteria were specified for a physician-assigned diagnosis of asthma and/or COPD,[11] there was a potential for diagnostic misclassification of patients, which may have influenced exacerbation rates. In addition, EOS and FeNO levels may potentially have influenced diagnostic labelling, which could have created a bias in this real-life study.

High FeNO levels (≥20 ppb) have previously been associated with an increased risk of COPD exacerbations in clinically stable outpatients with up to 12 months of follow-up.[21] However, the

Table 4 Association of both baseline EOS and FeNO with exacerbations in one model

	Asthma n=1878	P value	Asthma+COPD n=568	P value	COPD n=1317	P value
All exacerbations						
Log2EOS	1.14 (1.05–1.24)	0.003	1.06 (0.95–1.20)	0.310	1.12 (1.02–1.24)	0.033
Log2FeNO	0.93 (0.85–1.01)	0.091	0.94 (0.83–1.06)	0.294	0.87 (0.78–0.96)	0.009
	Asthma n=1447	**P value**	**Asthma+COPD n=364**	**P value**	**COPD n=902**	**P value**
OCS-only						
Log2EOS	1.18 (1.01–1.39)	0.041	1.29 (0.94–1.81)	0.135	1.21 (0.89–1.66)	0.230
Log2FeNO	0.92 (0.78–1.07)	0.285	1.46 (1.08–1.97)	0.013	1.13 (0.83–1.52)	0.437
	Asthma n=1349	**P value**	**Asthma+COPD n=359**	**P value**	**COPD n=910**	**P value**
Antibiotics-only						
Log2EOS	1.01 (0.82–1.28)	0.947	1.02 (0.79–1.41)	0.908	1.30 (0.97–1.76)	0.086
Log2FeNO	0.79 (0.61–1.02)	0.071	1.14 (0.83–1.57)	0.408	0.84 (0.62–1.12)	0.244

Data are presented as IRR or OR, 95% CI. All regression analyses were adjusted for age, sex, and smoking status. EOS and FeNO data were log2-transformed. Antibiotics: antibiotics-only treated exacerbations (ie, patients with all exacerbations treated with antibiotics; 'yes' vs 'no' exacerbations at all); OCS: OCS-only treated exacerbations (ie, patients with all exacerbations treated with OCS; 'yes' vs 'no' exacerbations at all).
COPD, chronic obstructive pulmonary disease; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; IRR, incidence rate ratio; OCS, oral corticosteroids.

association between smoking and decreased FeNO levels has long been noted[22 23] and this may have been a confounding factor that could explain the association between elevated FeNO levels and decreased risk of COPD exacerbations that was observed in this study; without appropriate sensitivity analyses to rule out residual confounding, this association should be interpreted with extreme caution.

Our finding of a differential association according to the type of exacerbation, with higher FeNO predicting OCS-only, but not antibiotics-only treated exacerbations in asthma and asthma+COPD, is of interest. Unfortunately, the reason for physicians to decide their choice of exacerbation treatment was not recorded in NOVELTY and no additional assessments were performed at the time of exacerbations. Although the exact underlying mechanisms of the different exacerbation types therefore remain unknown, we still found a clearly different signal thereby for the first time showing the importance of taking the subtype of the exacerbation into account. Our findings may have important implications both for daily clinical practice as well as for future studies, demonstrating that a thorough assessment to determine the exacerbation subtype may improve their personalised treatment.

We did not find the combination of EOS and FeNO to provide more accurate information on the level of type 2 inflammation, compared with the use of either biomarker alone. Overall, the associations with EOS are slightly stronger and the associations with FeNO are slightly weaker in the models with both EOS and FeNO. Since we considered the use of ICS to be a possible confounder in this respect, we performed additional analyses adjusting for this factor. Although the use of ICS, particularly when high-dosed, was strongly associated with increased exacerbation risk in all three disease categories, it did not greatly affect the association between EOS, FeNO or both combined and exacerbation risk. Taken together, our findings suggest that ICS use and the combination of EOS and FeNO in one model do not provide complementary information to more accurately assess the severity of type-2 inflammation in relation to exacerbation risk in asthma, COPD and asthma+COPD.

The strength of our study was the inclusion of well-characterised patients with physician-diagnosed asthma, COPD and asthma+COPD, or in a real-life setting. While the lack of diagnostic criteria given to assist physicians in the diagnosis of asthma and/or COPD could be perceived as a limitation, this was an intentional part of the study design to allow for future investigation of regional differences in the features and management of asthma and/or COPD. Indeed, previous studies on the NOVELTY study population found that conventional diagnostic categories in asthma and COPD are oversimplified and generalise complex and heterogeneous conditions.[24] Another limitation of our study was that, although the real-world NOVELTY study was non-interventional, with a non-random patient sample and no standardised criteria for diagnosis, treatment decisions may have been made in response to biomarker measurements as physicians had access to patient data on type 2 inflammation. As FeNO is a known predictor of ICS response, even in patients without an asthma diagnosis,[25] physicians would be more likely to prescribe ICS, which would lead to better disease control and fewer exacerbations, potentially leading to an underestimation of the risk of exacerbations in this study. As it was difficult to interpret borderline findings, the categorisation of a non-statistically significant trend (p=0.05–0.1) was included to describe some of the results in this manuscript, notably the association of higher baseline EOS with increased risk of all exacerbations in COPD, and higher baseline FeNO with increased risk of antibiotics-only treated exacerbations in asthma. However, it is important to note that this does not indicate clinically relevant outcomes and confounders (such as prior exacerbation burden, chronic bronchitis phenotype, comorbidities, adherence and seasonal variation) are not included in these analyses. It is also worth noting that as exacerbation subtypes were categorised based on medical records and patient-reported information, a possible recall bias cannot fully be excluded. Furthermore, defining exacerbations on the basis of treatment could also be considered a limitation as prescribing patterns differ widely across countries and may not reflect true biological differences in exacerbation phenotype, potentially leading to misclassification. Although this study was

a complete case analysis and could therefore potentially result in decreased statistical power, the decision to use this strategy was based on the need to preserve data integrity. Additionally, the use of a different analysis strategy may have increased power to determine statistical significance for these data. While we attempted to adjust for it as well as possible, we were unable to control treatment compliance (as it was not rigorously monitored) and inhalation technique (as this was a real-life study). Furthermore, we were unable to adjust for changes in prescribed treatment due to the short 1-year follow-up and uncertainty as to whether changes were systematically recorded. Finally, EOS variability may also have influenced results, as several intrinsic and extrinsic factors have been shown to affect EOS variability in asthma, including smoking, nasal polyps and the current season.[26]

In conclusion, in this routine care setting cohort, we show that EOS is associated with exacerbation risk in asthma and COPD. FeNO is less suitable as a biomarker in COPD as FeNO levels were difficult to interpret, possibly due to smoking. We show, for the first time, that it is important to take the type of exacerbation into account as we found FeNO to be associated with increased risk of exacerbations treated with OCS-only, but not antibiotics-only in both asthma and asthma+COPD. This finding is of importance for future studies and daily clinical practice as it indicates that assessment of exacerbation subtype might improve personalised treatment management.

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Details of the ethical approval for the 14 sites in Argentina are as follows (site name, ethics committee or institutional review board, approval number or reference): Fundación CIDEA, Comité de Ética en Farmacología Clínica de la Fundación CIDEA, not available (NA); Clínica de Alergia e Inmunología, Universidad Austral–Facultad de Ciencias Biomédicas–Comité Institucional de Evaluación, 17-002; Centro de Educación Médica e Investigaciones Clínicas (CEMIC), Comité de Ética en Investigación, NA; Centro de Medicina Respiratoria, Comité Independiente de Ética para Ensayos en Farmacología Clínica (Zieher), NA; Clínica Monte Grande, Comité de Ética de Investigaciones Clínicas, NA; Investigación en Enfermedades Alérgicas y Respiratorias (InAER), Comité de Ética en Investigación de InAER, NA; CENT (Centro de Estudios Neumonológicos), Comité de Ética en Investigación del Instituto de Investigaciones Clínicas, NA; IADIN (Instituto Argentino de Investigación Neurológica), Comité Independiente de Ética en Investigación Biomédica, NA; Instituto de Investigaciones Respiratorias, Comité Independiente de Ética para Ensayos en Farmacología Clínica (Zieher), NA; Centro Modelo de Cardiología SRL, Comité Independiente de Ética para Ensayos en Farmacología Clínica (Zieher), NA; CICBA Centro de Investigación, Comité de Ética en Investigación de InAER, NA; Hospital San Roque, Comité Institucional de Ética de la Investigación en Salud del niño y del adulto, NA; CEPROSS, Comité Independiente de Ética para Ensayos en Farmacología Clínica (Zieher), NA; and Hospital Italiano de Buenos Aires, Comité de Ética de Protocolos de Investigación del Hospital Italiano de Buenos Aires, NA. Details of the ethical approval for the 23 sites in Australia are as follows (site name, ethics committee or institutional review board, approval number or reference): Woolcock Institute of Medical Research, Monash Health Human Research Ethics Committee, HREC/16/MonH/325 2016.250; Concord Repatriation Hospital, Monash Health Human Research Ethics Committee, HREC/16/MonH/325 2016.250; Dr G.P. Katsoulotos, Bellberry Human Research Ethics Committee, 2016-09-679-AD-A-9; Peninsula Health Frankston Hospital, Monash Health Human Research Ethics Committee, HREC/16/MonH/325 2016.250; Western Respiratory Trial Specialists, Bellberry Human Research Ethics Committee, 2016-09-679-AD-A-9; Institute for Respiratory Health, Bellberry Human Research Ethics Committee, 2016-09-679-AD-A-9; Royal Melbourne Hospital, Monash Health Human Research Ethics Committee, HREC/16/MonH/325 2016.250; Australian Respiratory and Sleep Medicine Institute, Bellberry Human Research Ethics Committee, 2016-09-679-AD-A-9; Nepean Lung and Sleep, Bellberry Human Research Ethics Committee, 2016-09-679-AD-A-9; Redcliffe Hospital, Monash Health Human Research Ethics Committee, HREC/16/MonH/325 2016.250; Prince of Wales Hospital, Monash Health Human Research Ethics Committee, HREC/16/MonH/325 2016.250; Cairns Base Hospital, Monash Health Human Research Ethics Committee, HREC/16/MonH/325 2016.250; Reliance GP Super Clinic, Bellberry Human Research Ethics Committee, 2016-09-679-AD-A-9; Mater Health Services, Monash Health Human Research Ethics Committee, HREC/16/MonH/325 2016.250; The Queen Elizabeth Hospital, Monash Health Human Research Ethics Committee, HREC/16/MonH/325 2016.250; Coffs Harbour GP Super Clinic, Bellberry Human Research Ethics Committee, 2016-09-679-AD-A-9; Macquarie Respiratory and Sleep, Macquarie University Human Research Ethics Committee, 5201922599841; Paratus Clinical Blacktown Clinic, Bellberry Human Research Ethics Committee, 2016-09-679-AD-A-9; Paratus Clinical Wyong Clinic, Bellberry Human Research Ethics Committee, 2016-09-679-AD-A-9; Wamberal Surgery, Bellberry Human Research Ethics Committee, 2016-09-679-AD-A-9; John Hunter Hospital, Monash Health Human Research Ethics Committee, HREC/16/MonH/325 2016.250; Liverpool Hospital, Monash Health Human Research Ethics Committee, HREC/16/MonH/325 2016.250; and Chandlers Hill Surgery, Bellberry Human Research Ethics Committee, 2016-09-679-AD-A-9. Details of the ethical approval for the 5 sites in Brazil are as follows (site name, ethics committee or institutional review board, approval number or reference): Lung Day Hospital, Universidade Regional de Blumenau (FURB), 2.190.229; CLARE Clínica de Pneumologia/SS, Hospital Estadual Geral de Goiânia Dr. Alberto Rassi, 2.263.174; Irmandade da Santa Casa de Misericórdia de São Paulo, Santa Casa de Misericórdia de São Paulo, 1.886.473; Universidade Federal do Rio de Janeiro Hospital, Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro, 2.239.707; and Eurolatino Pesquisas Clínicas Ltda, Faculdade una de Uberlândia, 2.291.666. Details of the ethical approval for the 19 sites in Canada are as follows (site name, ethics committee or institutional review board, approval number or reference): Dr Bertley Office, Institutional Review Board services, PRO00023121; McMaster University–Saint Joseph's Healthcare, Hamilton Integrated Research Ethics Board (REB), 20029363; Grey Nuns Hospital, Health REB, Pro00071603; Taunton Health Centre, Quorum, 31645CDN/1; Recherche Clinique Sigma, Inc, Quorum, 31645CDN/6; Trial Management Group, Quorum, 31645CDN/7; Keele Medical, Quorum, 31645CDN/8; Lawson Health Research Institute, Western University Health Science REB, NA; Practice Dr. David Kanawaty, Quorum, 31645CDN/9; Les Services Médicaux Dr Bonavuth Pek, Quorum, 31645CDN/5; Cheema Research, Quorum, 31645CDN/10; University of Alberta–Research Transition Facility, University of Alberta–Health REB, PRO00069914; Gordon And Leslie Diamond Health Care Center, The Lung Centre, University of British Columbia–Clinical REB, H17-00055-A006; Dr Robert Luton, Quorum, 31645CDN/2; C and L Research, Quorum, 31645CDN/3; Burlington Lung Clinic, Quorum, 31645CDN/12; G.A. Research Associates, Quorum, 31645CDN/11; Windsor Regional Hospital, Quorum,

31645CDN/13; and Alta Clinical Research, Health Research Ethics Board of Alberta, HREBA.CTC16-0115. Details of the ethical approval for the 7 sites in Colombia are as follows (site name, ethics committee or institutional review board, approval number or reference): Hospital Universitario San Ignacio, Comité de Investigaciones y Ética Institucional de la Facultad de Medicina de la Universidad Javeriana, FM-CIE-0074-17; Instituto Neumológico del Oriente, Comité de Ética en Investigación Biomédica del Instituto Neumológico del Oriente, 55-15-12-2016; Asociación Ips Médicos Internistas de Caldas, Comité Regional de Ética en Investigación del Eje Cafetero, 14-02-02-2017; Centro Especializado en Enfermedades Pulmonares, Comité Institucional de Ética en Investigación de la Universidad El Bosque, 007-2017; Healthy Medical Center, Comité de Ética Healthy Medical Center (new EC), CEI-045-2019; Inversiones Clínica del Meta S.A., Comité de Ética de la Investigación–Riesgo de Fractura SA, 004-05 23-05-2017; and IPS Universitaria, Universidad de Antioquia, Comité de Ética en Investigación IPS Universitaria, 106-25-01-2017. Details of the ethical approval for the 4 sites in Denmark are as follows (site name, ethics committee or institutional review board, approval number or reference): Practice Dr Carsten Kjellerup, De Videnskabsetiske Komiteer Region Hovedstaden, H-16044407; Sygehus Lillebælt Vejle, Lungemedicinsk afd., De Videnskabsetiske Komiteer Region Hovedstaden, H-16044407; Lunge Medicinsk Afdeling, De Videnskabsetiske Komiteer Region Hovedstaden, H-16044407; and Aarhus Universitetshospital, De Videnskabsetiske Komiteer Region Hovedstaden, H-16044407. Details of the ethical approval for the 28 sites in France are as follows (site name, ethics committee or institutional review board, approval number or reference): Cabinet medical, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; Hôpital de la Croix-Rousse, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; Centre Hospitalier Universitaire (CHU) de la Cavale Blanche, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; Centre Hospitalier de Pau, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; Cabinet Pulmonology, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; Centre Hospitalier Intercommunal de Creteil, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; Hôpital Cochin, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; Montpellier Hospital, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; Bordeaux University Hospital, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; Centre Hospitalier de Bigorre, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; Nouvel Hôpital Civil, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; Hôpital d'Instruction des Armées Clermont-Tonnerre, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; Centre Hospitalier du Mans, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; Cabinet médical ARNASA, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; Centre Hospitalier du Pays d'Aix, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; Cabinet Medical Mabire, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; CHU de Lille, Hôpital Jeanne de Flandre, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; CHU de Limoges–Hôpital du Cluzeau, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; Cabinet Médical Delsart, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; L'Hôpital Nord-Ouest, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; Centre Hospitalier De Mulhouse, Hôpital Emile Muller, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; Groupe Hospitalier du Havre, Hôpital Jacques Monod, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; Hôpital Necker-Enfants malades, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; Centre Hospitalier Régional Universitaire Hôpital Jean Minjoz Besançon, Hôpital Jean Minjoz, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; CHU Dijon Bourgogne, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; CHU Estaing, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; CHU d'Orléans–La Source, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79; and Hôpital Charles- Nicolle, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, 2016/79. Details of the ethical approval for the 23 sites in Germany are as follows (site name, ethics committee or institutional review board, approval number or reference): Praxis Dr Feimer, Ethikkommission der Ärztekammer des Saarlandes, Bu 223/16; Thoraxklinik-Heidelberg gGmbH, Ethik-Kommission der Landesärztekammer Baden-Württemberg, B-F-2016-094#A2; Office of Dr. med. Christoph Stolpe, Ethikkommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität, 2016-673-b-S; IFG Institut für Gesundheitsförderung GmbH (No patients; Prot. AMD 2 not submitted; site closed early), AS 6(bB)/2017; Praxis Dr. med. Gesine Groth, Ethik-Kommission der Ärztekammer Hamburg, MC-412/16; Praxis Dr. med. Trauth, Ethik-Kommission bei der Landesärztekammer Hessen, MC 278/2016; Elbpneumologie, Ethik-Kommission der Ärztekammer Hamburg, MC-412/16; Gemeinschaftspraxis Reinfeld, Drs Kanniess/Präcklein, Ethikkommission bei der Ärztekammer Schleswig–Holstein, 003/17 m; Zentrum Pneumologie; Onko. and Schlafm. am Diakonieklinikum, Ethikkommission der Ärztekammer des Saarlandes, Bu 223/16; Studienzentrum Hoheisel, Sächsische Landesärztekammer–Ethikkommission, EK-BR-2/17-4; Pneumologische Praxis Dr. Thomas Ulrich, Ethikkommission der Ärztekammer Sachsen-Anhalt, 77/16; Hamburger Institut für Therapieforschung, Ethik-Kommission der Ärztekammer Hamburg, MC-412/16; Saarland University Hospital, Ethikkommission der Ärztekammer des Saarlandes, Bu 223/16; Praxis Dr. med. Grimm-Sachs, Ethik-Kommission der Landesärztekammer Baden-Württemberg, B-F-2016-094#A2; Praxis Dr. Winkelmann, Ethikkommission der Ärztekammer des Saarlandes, Bu 223/16; Practice/Centrum Dr. Christian Schlenska, Ethikkommission der Ärztekammer Niedersachsen, Ar/005/2017; Praxis Dr. J. Reinhardt, Sächsische Landesärztekammer–Ethikkommission, EK-BR-2/17-4; Pneumologische Schwerpunktpraxis Lübeck, Ethikkommission bei der Ärztekammer Schleswig-Holstein, 003/17 m; Praxis Dr. med Zeisler, Ethik-Kommission der Ärztekammer Nordrhein, 2016466; Praxis Dr. Lienert, Ethikkommission der Ärztekammer des Saarlandes, Bu 223/16; Practice for Pneumology Clinical Studies Pankow, Ethikkommission der Ärztekammer des Saarlandes, Bu 223/16; MVZ Protestant Lung Clinic Berlin Kreuzberg, Ethikkommission der Ärztekammer des Saarlandes, Bu 223/16; and Lungenpraxis Schleswig, Ethikkommission bei der Ärztekammer Schleswig-Holstein, 003/17 m. Details of the ethical approval for the 24 sites in Italy are as follows (site name, ethics committee or institutional review board, approval number or reference): Ospedale Livorno, Comitato Etico Regione Toscana, NA; Azienda Sanitaria Locale Salerno, Comitato Etico Campania Sud, n 0050079; Fondazione Salvatore Maugeri, Istituto Scientifico di Riabilitazione, Comitato Etico IRCCS Maugeri, NA; Azienda Ospedaliero Universitaria (AOU) Ospedali Riuniti, Comitato Etico INRCA, Codice INRCA: 17007B; Ospedale SS. Annunziata, Comitato Etico delle Province di Chieti e Pescara, NA; A.O. San Gerardo di Monza, Comitato Etico della Provincia Monza e Brianza, NA; Clinica Pneumologica e Tisiologica, Università di Genova, Comitato Etico Regionale della Liguria, NA; IRCCS San Raffaele Pisana, Comitato Etico dell'IRCCS San Raffaele Pisana, NA; L'Istituto di Biomedicina e Immunologia Molecolare, Comitato Etico Palermo 1, NA; AOU Ospedali Riuniti, Comitato Etico Ospedali Riuniti di Foggia, NA; AOU Policlinico Tor Vergata, Comitato Etico Indipendente Fondazione PTV Policlinico Tor Vergata, NA; Casa di Cura Musumeci, Comitato Etico di Catania 2, NA; Arcispedale Sant'Anna, AOU di Ferrara, Comitato Etico di Area Vasta Emilia Centro, EM178-2019 AOUFe/160895 EM2; AOU Careggi, Comitato Etico di Area Vasta Centro, NA; OU Policlinico Vittorio Emanuele Catania, Comitato Etico di Catania 1, 78/2019/EMPO; Università Cattolica del Sacro Cuore, Comitato Etico Segreteria Tecnico Scientifica Fondazione Policlinico Universitario A. Gemelli Università Cattolica del Sacro Cuore, NA; Azienda Ospedaliero-Universitaria San Luigi, Comitato Etico AOU San Luigi Gonzaga, 52/2017-protocol number 17314; AOU Policlinico di Modena, Comitato Etico dell'Area Vasta Emilia Nord, Prot AOU 001452/19; Presidio Ospedaliero di Pordenone, Comitato Etico Unico Regionale Aviano, NA; Università degli Studi di Napoli Federico II, Comitato Etico Università degli Studi della Campania Luigi Vanvitelli, 246/2019; Università degli Studi di Sassari, Comitato Etico Indipendente AOU di Cagliari, NA; ASP Distretto Messina Sud, Comitato Etico Interaziendale Provincia di Messina, NA; ASST Mantova, Comitato Etico Val Padana, NA; and Policlinico Gemelli, Comitato Etico Segreteria Tecnico Scientifica Fondazione Policlinico Universitario Agostino Gemelli Università Cattolica del Sacro Cuore, NA. Details of the ethical approval for the 24 sites in Japan are as follows (site name, ethics committee or institutional review board, approval number or reference): Yokohama City University Hospital, Ethical Committee, B180406005; Shizuoka General Hospital, Clinical Trial Ethics Committee, SGHIRB#2016080; Kurume University Hospital, Kurume University Ethics Committee on Life, NA; Kishiwada City Hospital, Clinical Trial Ethics Committee, 51; Fukushima Medical University Hospital, Fukushima Medical University Ethics Committee, Ippan29009; Kobe City Medical Center General Hospital, Research Ethics Review Committee, h190302; Fujita Health University Banbuntane Houtokukai Hospital, Human Genome Analysis Ethical Committee, HG19-032; Omuta Hospital, National Hospital Organization Omuta Hospital Ethics Committee, 1-1; Yamagata University Hospital, Yamagata University Ethics Committee, Dai394Go; Shizuoka Hospital, Shizuoka Hospital Ethical Committee, 18-82; Dokkyo Medical University Hospital, Ethical Committee, 28157; Toyama University Hospital, Ethical Committee, 30-5; Itami City Hospital, Municipal Itami Hospital Ethics Committee, 509(225-3); Tokyo Center Clinic, Maebashi Hirosegawa Clinic Independent Ethics Committee, NA; Ishikawa Prefectural Central Hospital, Ethical Committee, 1268; Matsue Medical Center, Matsue Medical Center Ethics Committee, NA; Tokyo National Hospital, Tokyo National Hospital Independent Ethics Committee, 28-26-Hea; Kyushu Central Hospital, Kyushu Central Hospital Ethics Committee, 182; JRC Ishinomaki Hospital, JRC Ishinomaki Hospital Ethics Committee, 16-46; Mito Medical Center, Mito Medical Center Contract Research Review Committee, NA; Fukuoka University Hospital, Fukuoka University Hospital Ethics Committee, NA; Kitakyushu Municipal Medical Center, Kitakyushu City Hospital Organization Clinical trial/clinical research review committee, 201905008; Jinyu Clinic, Maebashi Hirokawa Clinic IRB, NA; and Kanazawa Medical Center, Ethical Committee, H30-095. Details of the ethical approval for the 8 sites in Mexico are as follows (site name, ethics committee or institutional review board, approval number or reference): Hospital Universitario Dr. José Eleuterio González, Comité de Ética en Investigación del Hospital Universitario 'Dr. José Eleuterio González', NA; Centro de Investigación Medico Biológica y Terapia Avanzada, Comité de Ética en Investigación del Centro Hospitalario Vicor, S.A. de C.V., 0893; Instituto Jalisciense de Metabolismo, S.C., Comité de Ética en Investigación del Centro Hospitalario Vicor, S.A. de C.V., 0891; Clinical Trials Mexico, S.A. de C.V., Comité de Ética en Investigación de la Escuela de Medicina del Instituto Tecnológico y de Estudios Superiores de Monterrey, NA; Centro de Diagnóstico Pulmonar Avanzado S.A de Cv.,

Comité de Ética en Investigación de la Clínica Bajío, CLINBA S.C., 2017 539; Centro Respiratorio de México, S.C., Comité de Ética en Investigación de la Clínica Bajío, CLINBA S.C., 2017 579; Christus Muguerza Hospital UPAEP, Comité de Ética en Investigación de la Clínica de Enfermedades Crónicas y de Procedimientos Especiales, S.C., CEI_003_0117IC_035c; and Hospital Angeles Villahermosa, Comité de Ética en Investigación del Centro Hospitalario Vicor, S.A. de C.V., 946. Details of the ethical approval for the 11 sites in The Netherlands are as follows (site name, ethics committee or institutional review board, approval number or reference): Gelre Ziekenhuis Zutphen, Medisch Ethische Toetsingscommissie (METc) University Medical Center (UMC) Groningen, METc 2017/282; Universitair Medisch Centrum Groningen, METc UMC Groningen, METc 2017/282; St. Antonius Ziekenhuis, METc UMC Groningen, METc 2017/282; Franciscus Gasthuis, METc UMC Groningen, METc 2017/282; Noordwest Ziekenhuisgroep, METc UMC Groningen, METc 2017/282; Canisius Wilhelmina Ziekenhuis, METc UMC Groningen, METc 2017/282; Amphia Ziekenhuis, METc UMC Groningen, METc 2017/282; Centrum voor Integrale Revalidatie Orgaanfalen, METc UMC Groningen, METc 2017/282; Medisch Centrum Twente, METc UMC Groningen, METc 2017/282; Rijnstate Arnhem, METc UMC Groningen, METc 2017/282; and Máxima Medisch Centrum, METc UMC Groningen, METc 2017/282. Details of the ethical approval for the 6 sites in Norway are as follows (site name, ethics committee or institutional review board, approval number or reference): Trollåsen legesenter, Regionale komiteer for medisinsk og helsefaglig forskningsetikk (REK) Sør-Øst C, 2016/2298; Glittreklinikken, REK Sør-Øst C, 2016/2298; Kalbakken Klinikken, REK Sør-Øst C, 2016/2298; Akershus universitetssykehus HF, REK Sør-Øst C, 2016/2298; Hallset legesenter, REK Sør-Øst C, 2016/2298; and Tananger legesenter, REK Sør-Øst C, 2016/2298. Details of the ethical approval for the 18 sites in The Republic of Korea are as follows (site name, ethics committee or institutional review board, approval number or reference): The Catholic University of Korea, Yeouido St. Mary's Hospital, IRB of The Catholic University of Korea, Yeouido St. Mary's Hospital, SIRB-00239-006; Hanyang University Hospital, Hanyang University Hospital IRB, HYUH 2016-10-031-001; Asan Medical Center, Asan Medical Center IRB, S2016-1497-0001; Soon Chun Hyang University, Seoul Hospital, Soon Chun Hyang University Hospital Bucheon IRB, SCHBC 2016 11 001 0 01; Chonbuk National University Hospital, Chonbuk National University Hospital IRB, CUH 2016 11 003 002; Yeungnam University Hospital, Yeungnam University Hospital IRB, YUMC 2016-10-057-002; Ajou University Hospital, Ajou University Hospital IRB, AJIRB-BMR-OBS-16-419; Ewha Womans University Mokdong Hospital, Ewha Womans University Mokdong Hospital IRB, EUMC 2016-11-017; Korea University Guro Hospital, Korea University Guro Hospital IRB, KUGH16341-001; Kangbuk Samsung Hospital, Kangbuk Samsung Hospital IRB, KBSMC 2016 11 001 001; The Catholic University of Korea, Seoul St. Mary's Hospital, IRB of The Catholic University of Korea, Seoul St. Mary's Hospital, KIRB-00617-002; SamSung Hospital Center, Samsung Medical Center IRB, SMC 2016 10 101 003; Hallym University Sacred Heart Hospital, Hallym University Sacred Heart Hospital IRB, 2016 S060; Kangwon National University Hospital, Kangwon National University Hospital IRB, 2016 11 003 001; Seoul National University Hospital, Seoul National University College of Medicine/Seoul National University Hospital IRB, H-1610-137-804; Seoul National University Bundang Hospital, Seoul National University Bundang Hospital IRB, B-1708/412-309; Gachon University Gil Medical Center, Gachon University Gil Medical Center IRB, GAIRB2017-254; and Chonnam National University Hospital, Chonnam National University IRB, CNUH-2017-197. Details of the ethical approval for the 34 sites in Spain are as follows (site name, ethics committee or institutional review board, approval number or reference): Hospital Universitario (H.U.) San Cecilio, Comité de Ética de la Investigación (CEIm) Granada, NA; H. U. Infanta Leonor, CEIm Hospital Universitario Gregorio Marañón, NA; H. Lucus Augusti, Servicio Gallego de Salud (SERGAS), NA; H. U. Central de Asturias, CEIm Asturias, NA; H.U. Virgen de la Arrixaca, Instituto Murciano de Investigación Biosanitaria (IMIB) Virgen de la Arritxaca, NA; Hospital General Universitario (H.G.U.) Los Arcos del Mar Menor, IMIB HGU Los Arcos del Mar Menor, NA; H. U. Río Hortega, CEIm Área de Salud de Valladolid Oeste, NA; H. U. Infanta Cristina, CEIm Badajoz, NA; H. U. Miguel Servet, Comité de Ética de la Investigación de la Comunidad Autónoma de Aragón (CEICA), NA; H. U. Santa Lucía, IMIB-H Santa Lucía, NA; H. U. Alcázar de San Juan, CEIm Gerencia de Atención Integrada de Alcázar de San Juan (Ciudad Real), NA; H. Quirónsalud Barcelona, CEIm Grupo Hospitalario Quirónsalud-Catalunya, NA; H. U. Quirónsalud Madrid, Comité de Ética de la Investigación de la Fundación Jiménez Díaz, NA; Institut Clínic Respiratorio, CEIm Hospital Clínic de Barcelona, NA; Gómez Ulla Hospital, CEIm del Hospital Central de la Defensa Gómez Ulla, NA; H. Ruber Juan Bravo, Comité de Ética de la Investigación de la Fundación Jiménez Díaz, NA; Hospital Universitari Germans Trias i Pujol, CEIm Hospital Universitari Germans Trias i Pujol, NA; H. U. Ntra. Sra. Virgen de la Candelaria, CEIm del Hospital Universitario Virgen de la Candelaria, NA; Complejo Hospitalario de Navarra, CEIm de la Comunidad Foral de Navarra, NA; H.U. Príncipe de Asturias, CEIm Hospital Universitario Príncipe de Asturias, NA; H. U. de Ceuta, Área Sanitaria de Ceuta, NA; H. U. Son Espases, CEIm de les Illes Balears, NA; Hospital Povisa, SERGAS, NA; H. U. de Burgos, CEIm Área de Salud de Burgos y Soria, NA; Hospital Quirónsalud Campo de Gibraltar, CEIm Provincial de Cádiz, NA; H. General de la Defensa, CEIm Comité de Ética de la Investigación de la Comunidad de Autónoma de Aragón (CEICA), NA; H. Xeral Álvaro Cunqueiro, SERGAS, NA; CAP Centelles, CEI de la Fundació Unió Catalana d'Hospitals, NA; Hospital Civil, CEIm Provincial de Málaga, NA; Centro de Salud Torrelaguna, Comisión Central de Investigación Gerencia Asistencial de Atención Primaria, NA; Hospital Universitario Rey Juan Carlos, Comité de Ética de la Investigación de la Fundación Jiménez Díaz, NA; Hospital de La Princesa, CEIm Hospital Universitario de La Princesa, NA; Hospital de Cruces, CEIm de Euskadi, NA; and H.U. Virgen de la Victoria, CEIm Provincial de Málaga, NA. Details of the ethical approval for the 7 sites in Sweden are as follows (site name, ethics committee or institutional review board, approval number or reference): Uppsala Universitet–Akademiska Sjukhuset, Etikprövningsmyndigheten, Box 2110, 75002 Uppsala, Sweden, Dnr: 2019-0234; Medicinkliniken, Etikprövningsmyndigheten, Box 2110, 75002 Uppsala, Sweden, Dnr: 2019-0234; PTC CTC/Centrum för klinisk prövning, Etikprövningsmyndigheten, Box 2110, 75002 Uppsala, Sweden, Dnr: 2019-0234; ProbarE i Lund, Etikprövningsmyndigheten, Box 2110, 75002 Uppsala, Sweden, Dnr: 2019-0234; KTA Prim, Etikprövningsmyndigheten, Box 2110, 75002 Uppsala, Sweden, Dnr: 2019-0234; CTC Uppsala Office, Etikprövningsmyndigheten, Box 2110, 75002 Uppsala, Sweden, Dnr: 2019-0234; and Ekeby Hälsocenter, Etikprövningsmyndigheten, Box 2110, 75002 Uppsala, Sweden, Dnr: 2019-0234. Details of the ethical approval for the 23 sites in the UK are as follows (site name, ethics committee or institutional review board, approval number or reference): Nottingham University Hospitals NHS Trust-Nottingham City, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; Wishaw General Hospital, East Midlands, Leicester Central Research Ethics Committee, 16/EM/0439; Prince Philip Hospital, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; Birmingham Heartlands Hospital, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; Priory Medical Group, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; Royal Liverpool Hospital, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; Jorvik Medical Centre, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; Haxby Group Practice, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; Pickering Medical Practice, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; Atherstone Surgery, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; Strensall Health Care Centre, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; Thornton Medical Centre, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; Wythenshawe Hospital, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; James Cook University Hospital, South Tees NHS Foundation Trust, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; Bollington Medical Centre, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; Belfast City Hospital, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; Aneurin Bevan University Health Board - Royal Gwent Hospital, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; South Tyneside District Hospital, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; Southampton General Hospital, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; Broomfield Hospital, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; Royal Brompton and Harefield NHS Foundation Trust, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; West Hertfordshire NHS Trust, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439; and Castle Hill Hospital, East Midlands–Leicester Central Research Ethics Committee, 16/EM/0439. Details of the ethical approval for the 43 sites in the USA are as follows (site name, ethics committee or institutional review board, approval number or reference): Plains Clinical Research Center, Quorum, QR31645/7; Colorado Springs Pulmonary Consultants, PC, Quorum, QR31645/11; Atco Medical Associates, P.C., Quorum, QR31645/9; Daria B. Lee, MD–Research, Quorum, QR31645/4; Hutchinson Clinic PA, Quorum Review IRB, 31645; Novel Research of New York, Quorum Review IRB, NA; Veterans Affairs Long Beach Healthcare System, Long Beach VAMC Research Health Care Group (151), 001182; Northern Pines Health Center, Quorum, QR31645/10; Gotham Cardiovascular Research, PC, Quorum, QR31645/8; University of Texas Health Science Center, UT Health San Antonio, HSC20170346H; Miami VA Healthcare System, Miami VA Healthcare System Human Studies Subcommittee, 116161-9 (1251.13); Center For Allergy The Lung Center of Penn Highlands Dubois, Western Institutional Review Board, Quorum IRB QR31645/38; Rush University Medical Center, Institutional Review Board #2 at Rush University Medical Center, ORA Number: 16030803-IRB01-AM03; Genesis Clinical Research and Consulting, LLC, Quorum, QR31645/3; Loma Linda VA-Pulmonary and Critical Care Section, VA Loma Linda Healthcare System-605/Research Service (151), ID: Anholm 1212; The North Florida and South Georgia Veterans Health System, University of Florida, IRB201602286; Urban Health Plan, Quorum Review IRB, 31645; St. Francis Sleep, Allergy and Lung Institute, Quorum Review IRB, 31645; Sentral Clinical Research, Quorum Review IRB, 31645; Comprehensive Internal Medicine Inc, Quorum Review IRB, 31645; Advanced Allergy Parikh Institute for Research, Quorum Review IRB, 31645; Homestead Associates in Research, Inc, Quorum, QR31645/15; Clinical Trials Center, Quorum, QR31645/21; Midwest Allergy Sinus Asthma, Quorum Review IRB, 31645; Portland Clinical Research, Quorum Review IRB, 31645; New York Allergy and Sinus Centers, Quorum Review IRB, 31645; Dominion Medical Associates, Inc, Quorum Review IRB, 31645; Montefiore Medical Center, Brany, 17-10-108-01; University of Michigan, Quorum Review IRB, 31645; Austin Regional Clinic, Quorum, QR31645/24; Allergy and Asthma Center, Quorum, QR31745/30; University of

Colorado, Quorum Review IRB, 31645; Parikh Institute for Research LLC, Quorum Review IRB, 31645; National Clinical LLC, Quorum Review IRB, 31645; Breathe America, Quorum, QR31645/31; BRCR Global, Quorum Review IRB, 31645; Breathe America Albuquerque, Quorum, QR31645/32; Advance Clinical Research, Quorum Review IRB, 31645; Live Oak Allergy Allergy, Asthma and Immunology Associates, P.C., Quorum, QR31645/36; and Capital Allergy and Respiratory Disease Center, Quorum Review IRB, 31645.

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REFERENCES

1 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2023 report). 2023. Available: https://goldcopd.org
2 Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. 2022. Available: http://www.ginasthma.org
3 Mekov E, Nuñez A, Sin DD, *et al*. Update on Asthma-COPD Overlap (ACO): A Narrative Review. *Int J Chron Obstruct Pulmon Dis* 2021;16:1783–99.
4 Bafadhel M, Pavord ID, Russell REK. Eosinophils in COPD: just another biomarker? *Lancet Respir Med* 2017;5:747–59.
5 Couillard S, Do WIH, Beasley R, *et al*. Predicting the benefits of type-2 targeted anti-inflammatory treatment with the prototype Oxford Asthma Attack Risk Scale (ORACLE). *ERJ Open Res* 2022;8:00570-2021.
6 Couillard S, Laugerud A, Jabeen M, *et al*. Derivation of a prototype asthma attack risk scale centred on blood eosinophils and exhaled nitric oxide. *Thorax* 2022;77:199–202.
7 Rabe KF, Martinez FJ, Ferguson GT, *et al*. Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD. *N Engl J Med* 2020;383:35–48.
8 Pavord ID, Beasley R, Agusti A, *et al*. After asthma: redefining airways diseases. *Lancet* 2018;391:350–400.
9 Couillard S, Shrimanker R, Chaudhuri R, *et al*. Fractional Exhaled Nitric Oxide Nonsuppression Identifies Corticosteroid-Resistant Type 2 Signaling in Severe Asthma. *Am J Respir Crit Care Med* 2021;204:731–4.
10 Çolak Y, Afzal S, Nordestgaard BG, *et al*. Combined value of exhaled nitric oxide and blood eosinophils in chronic airway disease: the Copenhagen General Population Study. *Eur Respir J* 2018;52:1800616.
11 Reddel HK, Gerhardsson de Verdier M, Agustí A, *et al*. Prospective observational study in patients with obstructive lung disease: NOVELTY design. *ERJ Open Res* 2019;5:00036-2018.
12 Graham BL, Steenbruggen I, Miller MR, *et al*. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *Am J Respir Crit Care Med* 2019;200:e70–88.
13 ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide, 2005. *Am J Respir Crit Care Med* 2005;171:912–30.
14 Unalli OS, Ozarda Y. Stability of hematological analytes during 48 hours storage at three temperatures using Cell-Dyn hematology analyzer. *J Med Biochem* 2021;40:252–60.
15 Schapkaitz E, Pillay D. Prolonged storage-induced changes in haematology parameters referred for testing. *Afr J Lab Med* 2015;4:208.
16 Wasserstein RL, Lazar NA. The ASA Statement on *p* -Values: Context, Process, and Purpose. *Am Stat* 2016;70:129–33.
17 Sivapalan P, Bikov A, Jensen JU. Using Blood Eosinophil Count as a Biomarker to Guide Corticosteroid Treatment for Chronic Obstructive Pulmonary Disease. *Diagnostics (Basel)* 2021;11:236.
18 Kostikas K, Brindicci C, Patalano F. Blood Eosinophils as Biomarkers to Drive Treatment Choices in Asthma and COPD. *Curr Drug Targets* 2018;19:1882–96.
19 Blakey JD, Price DB, Pizzichini E, *et al*. Identifying Risk of Future Asthma Attacks Using UK Medical Record Data: A Respiratory Effectiveness Group Initiative. *J Allergy Clin Immunol Pract* 2017;5:1015–24.
20 Kerkhof M, Freeman D, Jones R, *et al*. Predicting frequent COPD exacerbations using primary care data. *Int J Chron Obstruct Pulmon Dis* 2015;10:2439–50.
21 Alcázar-Navarrete B, Ruiz Rodríguez O, Conde Baena P, *et al*. Persistently elevated exhaled nitric oxide fraction is associated with increased risk of exacerbation in COPD. *Eur Respir J* 2018;51:1701457.
22 Kharitonov SA, Robbins RA, Yates D, *et al*. Acute and chronic effects of cigarette smoking on exhaled nitric oxide. *Am J Respir Crit Care Med* 1995;152:609–12.
23 Malerba M, Radaeli A, Olivini A, *et al*. Exhaled nitric oxide as a biomarker in COPD and related comorbidities. *Biomed Res Int* 2014;2014:271918.
24 Reddel HK, Vestbo J, Agustí A, *et al*. Heterogeneity within and between physician-diagnosed asthma and/or COPD: NOVELTY cohort. *Eur Respir J* 2021;58:2003927.
25 Price DB, Buhl R, Chan A, *et al*. Fractional exhaled nitric oxide as a predictor of response to inhaled corticosteroids in patients with non-specific respiratory symptoms and insignificant bronchodilator reversibility: a randomised controlled trial. *Lancet Respir Med* 2018;6:29–39.
26 Chipps BE, Jarjour N, Calhoun WJ, *et al*. A Comprehensive Analysis of the Stability of Blood Eosinophil Levels. *Ann Am Thorac Soc* 2021;18:1978–87.