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Factor	COPDGene		ECLIPSE	
	Coefficient (95% CI)	p value	Coefficient (95% CI)	p value
log(LAA950)*	-0.26 (-0.43, -0.08)	0.005	-0.07 (-0.17,-0.03)	0.19
Perc15*	4.68 (1.53, 7.82)	0.004	1.55 (-1.22,4.32)	0.27
SGRQ	3.00 (0.61-5.38)	0.014	-1.99 (-4.19, 0.21)	0.07

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3 Supplementary Table 1. Quantitative chest CT emphysema and SGRQ score in COPD
4 subjects with eosinophil counts ≥ 300 cells/ μ L. For log(LAA950) and Perc15, a subset of
5 subjects with quantitative CT data were analyzed (COPDGene n= 1119, ECLIPSE n=
6 1610) .Linear regression models are adjusted for age, sex, race, smoking status, BMI,
7 CT scanner model and WBC. For SGRQ, linear regression models are adjusted for age,
8 sex, race, and pack years smoking history.

9 LAA950 = low attenuation area at <950 HU; Perc15 = 15th percentile of the lung density
10 histogram; SGRQ = Saint George's Respiratory Questionnaire total score.

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Number of Exacerbations in prior year	Annual exacerbation rate during longitudinal follow up	
	Eosinophil < 300 cells/ μ L	Eosinophil \geq 300 cells/ μ L
0	0.29	0.35
1	0.81	0.79
\geq 2	1.42	2.39

19 (A)

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Number of exacerbation in prior year	Annual exacerbation rate			
	1 year		Overall study period	
	Eosinophil < 300 cells/ μ L	Eosinophil \geq 300 cells/ μ L	Eosinophil < 300 cells/ μ L	Eosinophil \geq 300 cells/ μ L
0	0.62	0.63	0.40	0.38
1	1.40	1.51	1.00	1.12
\geq 2	2.05	2.97	1.61	2.41

21 (B)

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23 Supplementary Table 2. Annual exacerbation rate in subgroups stratified by prior
 24 exacerbation frequency and blood eosinophil counts. (A) COPDGene Longitudinal
 25 Follow-up Study, (B) ECLIPSE one year and overall study period.

ECLIPSE overall study period				
Factors associated with exacerbation rate	Persistently elevated vs. low eosinophils (n= 90 vs. n=784)		Persistently elevated vs. fluctuating eosinophils (n= 90 vs. n=471)	
	IRR (95% CI)	p value	IRR (95% CI)	p value
Age	1.00(0.99-1.02)	0.75	1.00(0.99-1.02)	0.89
Non White race	0.76(0.41-1.34)	0.36	0.90(0.36-1.90)	0.80
Female	1.29(1.06-1.57)	0.009	1.38(1.10-1.73)	0.004
SGRQ total score*	1.01(1.01-1.02)	<0.001	1.01(1.00-1.01)	0.02
Post-bronchodilator FEV₁ % predicted †	0.98(0.97-0.98)	<0.001	0.99(0.98-0.99)	<0.001
GERD	1.32(1.07-1.62)	0.008	1.43(1.14-1.79)	0.002
Current smoking	1.10(0.89-1.35)	0.39	1.19(0.94-1.52)	0.16
previous exacerbations	2.77(2.27-3.39)	<0.001	3.00(2.38-3.82)	<0.001
WBC	1.00(0.95-1.05)	0.99	1.04(0.99-1.09)	0.1
Persistent eosinophils ≥ 300	1.48(1.11-1.96)	0.007	1.39(1.07-1.80)	0.01

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27 Supplementary Table 3. Persistent eosinophilia and exacerbation risk in ECLIPSE.

28 Risk of exacerbation in subjects with persistently elevated eosinophils compared to
 29 persistently low eosinophils and in subjects with persistently elevated eosinophils
 30 compared to fluctuating eosinophils.

31 *per 1 point increase in score, †per percentage point increase in FEV₁.

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Factor	COPDGene		ECLIPSE	
	Odds Ratio (95% CI)	p value	Odds Ratio (95% CI)	p value
Age	0.95 (0.93-0.97)	<0.001	0.94 (0.92-0.96)	<0.001
Female	1.68 (1.22-2.32)	0.001	2.16 (1.54-3.03)	<0.001
Non White race	1.37 (0.93-1.99)	0.11	2.69 (1.10-6.08)	0.02
BMI	1.03 (1.00-1.05)	0.03	1.04 (1.01-1.07)	0.007
Smoking (PY)	0.99 (0.98-0.99)	0.01	0.99 (0.98-0.99)	0.03
Eosinophil ≥ 300	1.51 (1.04-2.18)	0.03	1.69(1.15-2.48)	0.007

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37 Supplementary Table 4. Association between asthma-COPD overlap and eosinophilic
38 COPD, defined as blood eosinophil count ≥ 300 cells/ μ L. Odds ratio derived from
39 logistic regression. Asthma-COPD overlap defined based on doctor's diagnosis of
40 asthma before age of 40¹.

- 41 1. Hardin M, Cho M, McDonald M-L, Beaty T, Ramsdell J, Bhatt S, et al. The clinical
42 and genetic features of COPD-asthma overlap syndrome. *Eur Respir J*.
43 2014;44:341–50.

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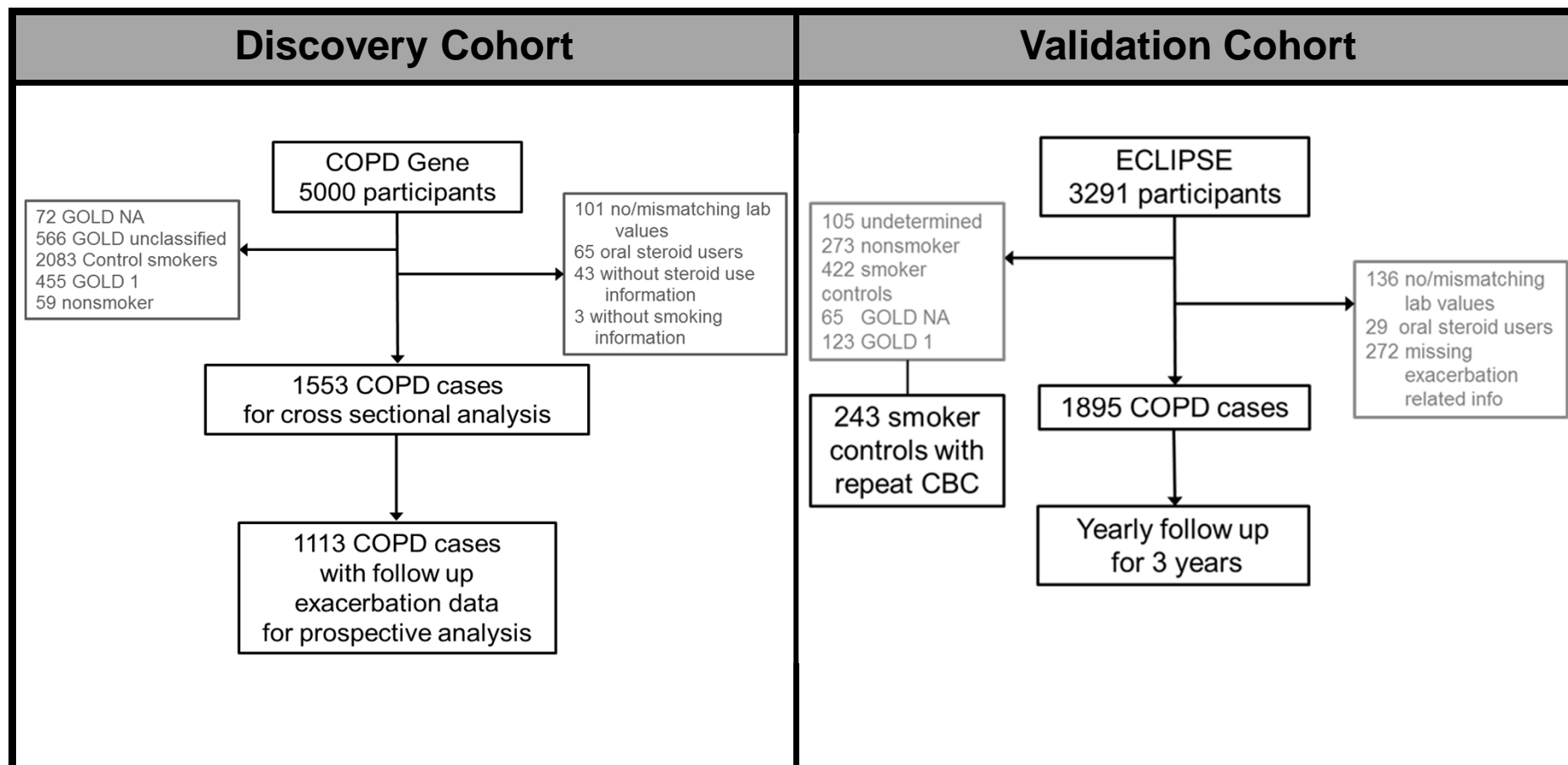
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Supplementary Figure 1. Study design and populations. COPD: chronic obstructive pulmonary disease, GOLD: Global initiative for chronic Obstructive Lung Disease, NA: not available

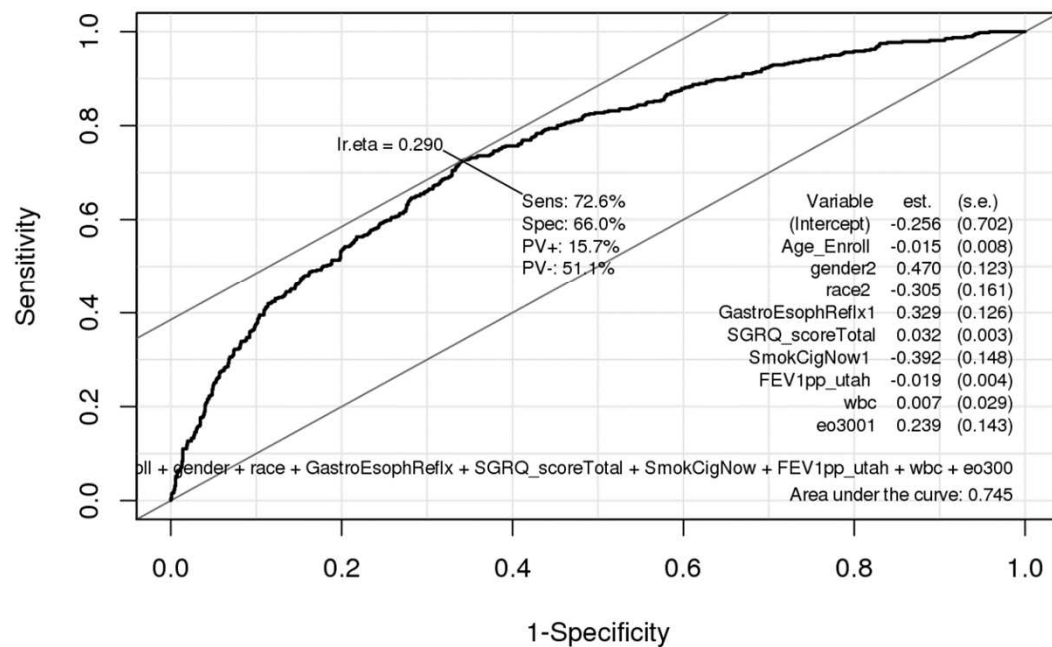
Supplementary Figure 2. Receiver operating characteristic (ROC) curve for eosinophil cutoff of 300 cells/ μ L in COPDGene. ROC analysis was based on logistic regression models (0 vs. any exacerbation history) adjusted for age, sex, race, gastroesophageal reflux, Saint George's Respiratory Questionnaire score, current smoking, post bronchodilator forced expiratory volume at 1 second percent predicted, white blood cell count, and eosinophil counts ranging from 100 to 400 cells/ μ L.

Supplementary Figure 3. Receiver operating characteristic (ROC) curve for eosinophil cutoff of 300 cells/ μ L in ECLIPSE. ROC analysis was based on logistic regression models (exacerbation rate ≥ 1 during overall study period vs. less than 1) adjusted for age, sex, race, previous exacerbation, gastroesophageal reflux, Saint George's Respiratory Questionnaire score, current smoking, post bronchodilator forced expiratory volume at 1 second percent predicted, white blood cell count, and eosinophil counts ranging from 100 to 400 cells/ μ L.

Supplementary Figure 4. Eosinophil cutoffs in COPD subjects not using inhaled corticosteroid. Risk estimates are derived from negative binomial regression models adjusted for age, sex, race, gastroesophageal reflux, Saint George's Respiratory Questionnaire score, current smoking, post bronchodilator forced expiratory volume at 1 second percent predicted, and white blood cell count. IRR: incidence rate ratio.

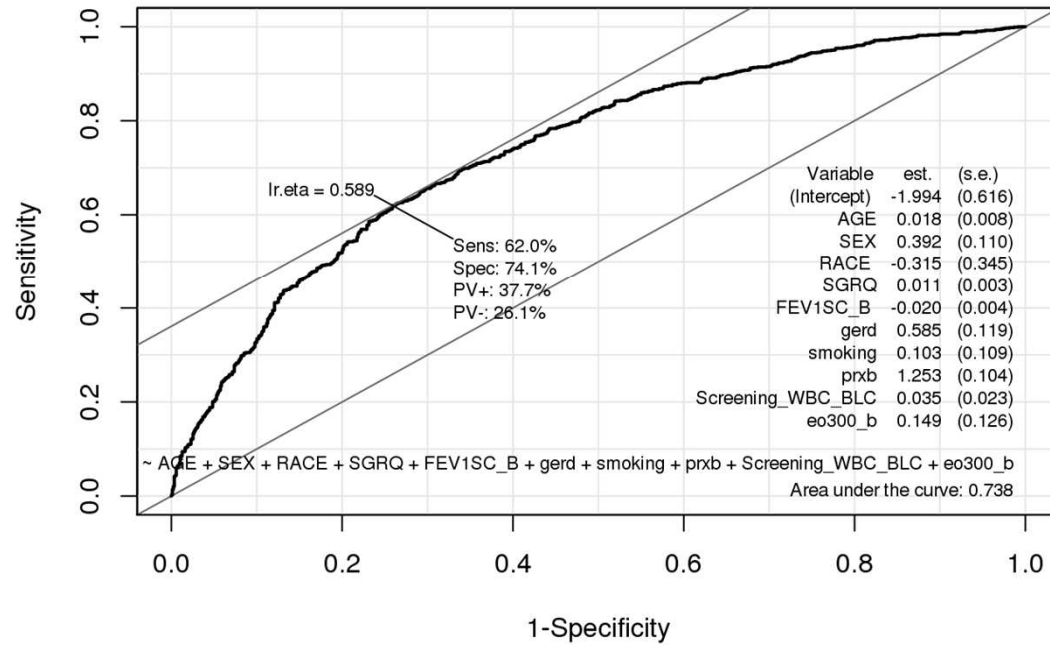


Supplementary Figure 1.



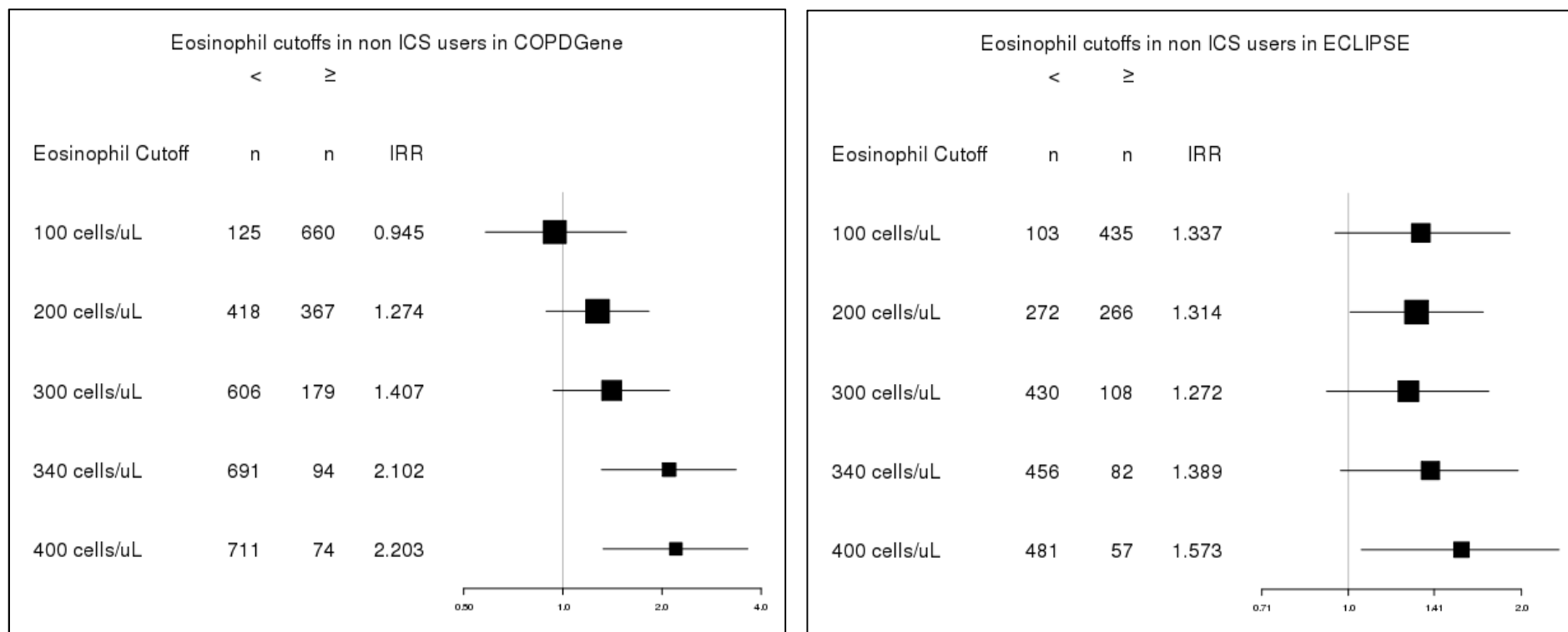
Eosinophil Cutoffs	Area under the curve	Sensitivity	Specificity
100 cells/ μ L	0.743	66.5	70.6
200 cells/ μ L	0.744	65.7	71.8
300 cells/ μ L	0.745	72.6	66.0
340 cells/ μ L	0.744	70.1	67.0
400 cells/ μ L	0.745	71.1	66.2

Supplementary Figure 2.



Eosinophil Cutoffs	Area under the curve	Sensitivity	Specificity
100 cells/ μ L	0.738	61.1	74.9
200 cells/ μ L	0.738	60.6	75.4
300 cells/ μ L	0.738	62	74.1
340 cells/ μ L	0.738	62.7	73.4
400 cells/ μ L	0.738	61.1	74.9

Supplementary Figure 3.



Supplementary Figure 4.