Supplement

This supplement contains supplementary material for

Estimating individual treatment effects on COPD exacerbations by causal machine learning on randomized controlled trials.

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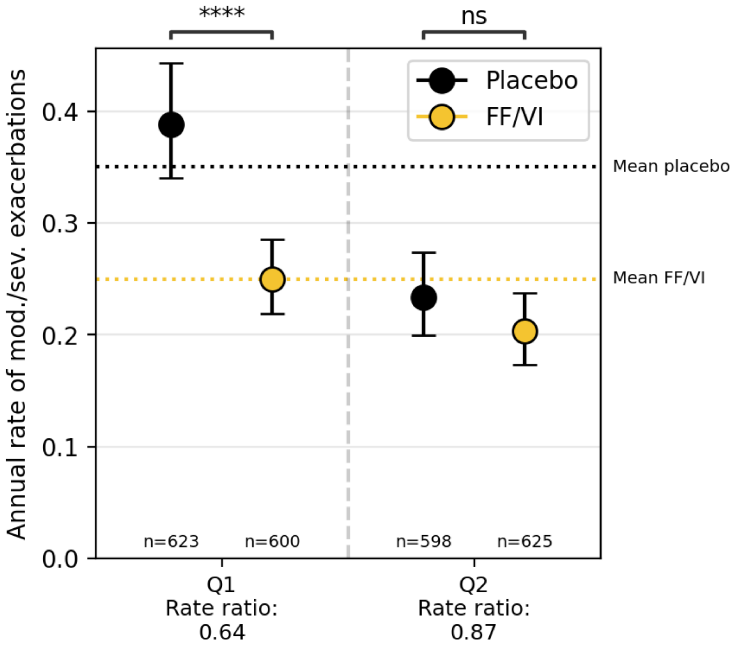
Two quantile to five quantile discretization in SUMMIT

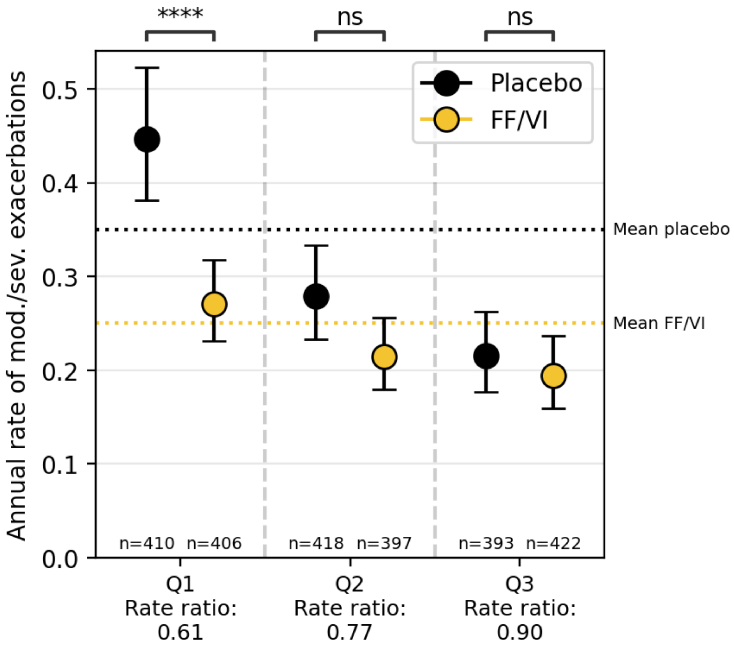
Two quantile discretization

Quantile 1/2
Placebo mean 0.39, 95% CI [0.34,0.44]
FF/VI mean 0.25, 95% CI [0.22,0.29]
Rate ratio: 0.64 (p=0.00002)
==========
Quantile 2/2
Placebo mean 0.23, 95% CI [0.20,0.27]
FF/VI mean 0.20, 95% CI [0.17,0.24]
Rate ratio: 0.87 (p=0.21648)



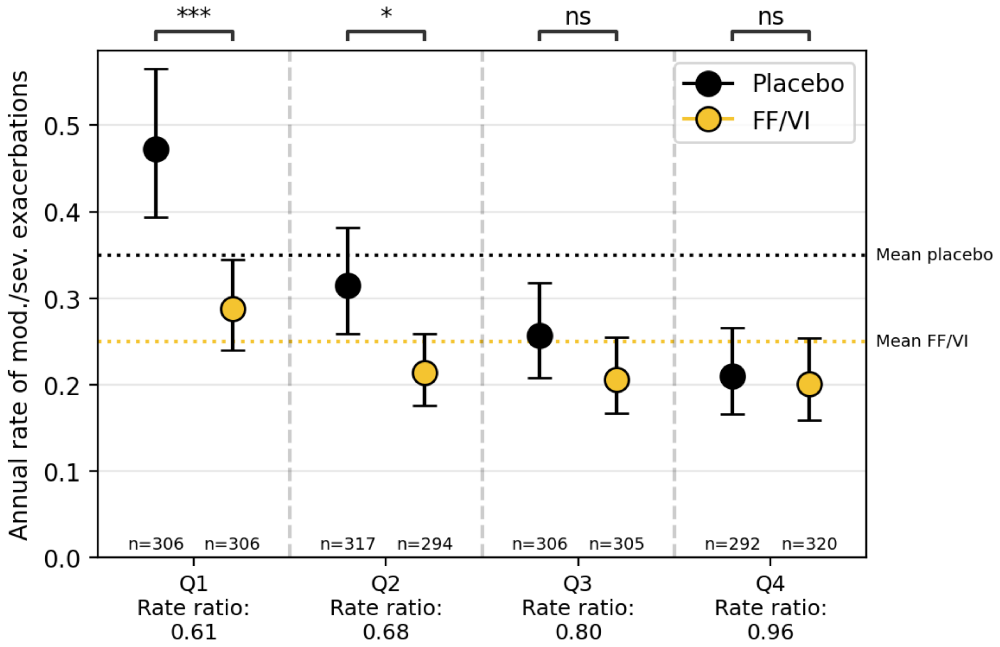
Three quantile discretization

Quantile 1/3
Placebo mean 0.45, 95% CI [0.38,0.52]
FF/VI mean 0.27, 95% CI [0.23,0.32]
Rate ratio: 0.61 (p=0.00004)
==========
Quantile 2/3
Placebo mean 0.28, 95% CI [0.23,0.33]
FF/VI mean 0.21, 95% CI [0.18,0.26]
Rate ratio: 0.77 (p=0.05296)
==========
Quantile 3/3
Placebo mean 0.22, 95% CI [0.18,0.26]
FF/VI mean 0.19, 95% CI [0.16,0.24]
Rate ratio: 0.90 (p=0.45657)



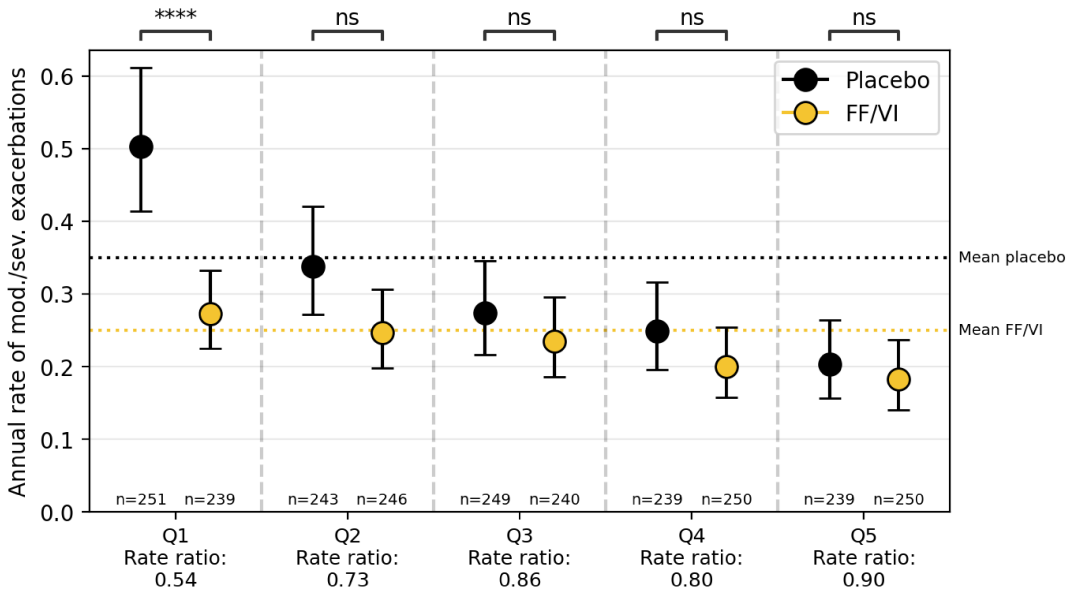
Four quantile discretization

Quantile 1/4
Placebo mean 0.47, 95% CI [0.39,0.57]
FF/VI mean 0.29, 95% CI [0.24,0.34]
Rate ratio: 0.61 (p=0.00037)
==========
Quantile 2/4
Placebo mean 0.31, 95% CI [0.26,0.38]
FF/VI mean 0.21, 95% CI [0.18,0.26]
Rate ratio: 0.68 (p=0.01051)
==========
Quantile 3/4
Placebo mean 0.26, 95% CI [0.21,0.32]
FF/VI mean 0.21, 95% CI [0.17,0.25]
Rate ratio: 0.80 (p=0.16305)
==========
Quantile 4/4
Placebo mean 0.21, 95% CI [0.17,0.27]
FF/VI mean 0.20, 95% CI [0.16,0.25]
Rate ratio: 0.96 (p=0.79411)



Five quantile discretization

Quantile 1/5
Placebo mean 0.50, 95% CI [0.41,0.61]
FF/VI mean 0.27, 95% CI [0.22,0.33]
Rate ratio: 0.54 (p=0.00008)
==========
Quantile 2/5
Placebo mean 0.34, 95% CI [0.27,0.42]
FF/VI mean 0.25, 95% CI [0.20,0.31]
Rate ratio: 0.73 (p=0.05602)
==========
Quantile 3/5
Placebo mean 0.27, 95% CI [0.22,0.35]
FF/VI mean 0.23, 95% CI [0.19,0.30]
Rate ratio: 0.86 (p=0.37346)
==========
Quantile 4/5
Placebo mean 0.25, 95% CI [0.20,0.32]
FF/VI mean 0.20, 95% CI [0.16,0.25]
Rate ratio: 0.80 (p=0.21500)
==========
Quantile 5/5
Placebo mean 0.20, 95% CI [0.16,0.26]
FF/VI mean 0.18, 95% CI [0.14,0.24]
Rate ratio: 0.90 (p=0.55786)



Characteristics of the subjects in IMPACT

	IMPACT (n=10355)
Age, years	65.3±8.3
Women	3485 (34%)
BMI, kg/m^2	26.6
Former smokers	6768 (65%)
Predicted postbronchodilator FEV1 (%)	45.5±14.8
Exacerbations in 12 months before study	
0	9 (<1%)
1	4691 (45%)
2	4487 (43%)
≥3	1168 (11%)
Mean COPD assessment test score	20.1±6.1
Treatment allocation	
Fluticasone furoate/umeclidinium/vilanterol	4151
Fluticasone furoate /vilanterol	4134
Umeclidinium/vilanterol	2070

Table S1 Baseline characteristics of the subjects in IMPACT. Data is presented as mean ± standard deviation or no. (%).
Abbreviations: BMI, body mass index; FEV1, forced expiratory volume in 1 second.

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Characteristics per quintile in SUMMIT

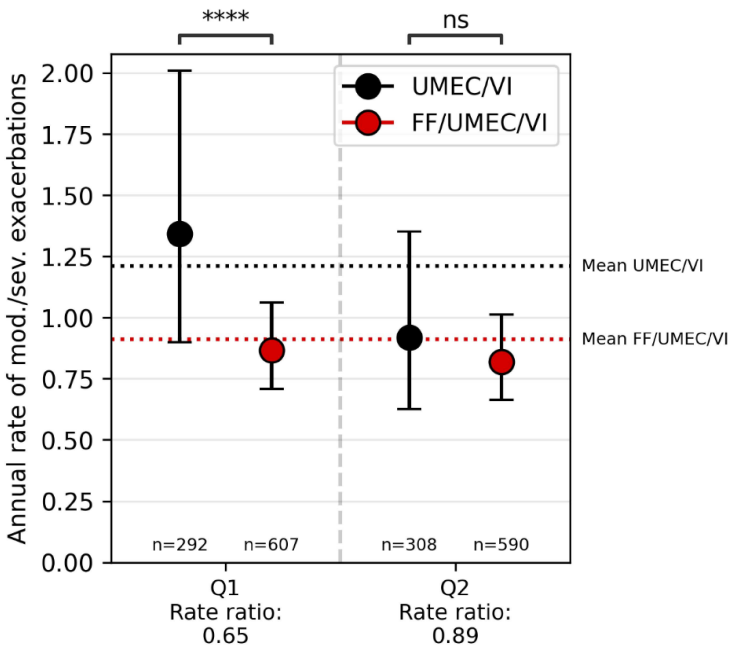
	Quantile 1		Quantile 2		Quantile 3		Quantile 4		Quantile 5	
	Control (n=251)	**Treated (n=239)**	**Control (n=243)**	**Treated (n=246)**	**Control (n=249)**	**Treated (n=240)**	**Control (n=239)**	**Treated (n=250)**	**Control (n=239)**	**Treated (n=250)**
Age	66.21±7.50	67.59±7.12	68.35±6.81	68.34±6.57	67.25±6.30	67.42±6.71	63.52±7.58	63.61±8.16	59.78±8.49	59.57±7.82
Sex	166/85 66% Male	161/78 67% Male	178/65 73% Male	167/79 68% Male	185/64 74% Male	187/53 78% Male	178/61 74% Male	196/54 78% Male	200/39 84% Male	215/35 86% Male
Height	162.98±9.02	163.23±9.61	165.41±8.48	164.89±8.68	167.90±6.66	167.89±6.48	170.06±7.47	170.33±6.88	176.15±8.56	176.00±8.43
Weight	71.82±16.22	72.82±18.96	76.04±17.70	74.93±16.27	78.85±16.53	79.02±17.97	82.33±17.59	82.71±17.15	87.77±22.23	89.99±21.69
BMI	26.98±5.57	27.13±5.76	27.65±5.49	27.48±5.25	27.87±5.19	27.95±5.73	28.45±5.83	28.50±5.69	28.19±6.67	28.95±6.46
Pack-years	40.61±24.80	38.82±23.67	42.82±27.05	38.20±21.95	41.37±23.19	39.45±22.94	37.48±20.86	39.79±23.94	40.17±27.74	42.90±28.28
FEV1 %pred	0.51±0.08	0.50±0.07	0.59±0.07	0.60±0.08	0.60±0.07	0.60±0.06	0.62±0.07	0.60±0.07	0.61±0.06	0.62±0.07
FVC %pred	0.76±0.15	0.74±0.15	0.79±0.13	0.78±0.12	0.79±0.14	0.80±0.12	0.80±0.13	0.80±0.13	0.80±0.12	0.81±0.14
Previous exacerbations	0.84±1.26	0.79±1.13	0.74±0.93	0.95±1.24	0.69±1.11	0.47±0.80	0.50±0.91	0.47±0.82	0.46±0.71	0.32±0.66
Use of β-agonists (yes/no)	76/175 (30%)	69/169 (29%)	53/189 (22%)	47/198 (19%)	35/213 (14%)	27/213 (11%)	28/210 (12%)	27/221 (11%)	18/221 (8%)	10/240 (4%)
Use of ICS (yes/no)	72/179 (29%)	69/169 (29%)	63/180 (26%)	54/190 (22%)	22/226 (9%)	19/221 (8%)	16/222 (7%)	21/227 (8%)	8/231 (3%)	7/243 (3%)
Diastolic blood pressure	78.99±8.88	78.40±8.60	79.36±9.36	79.10±9.41	78.80±9.09	79.03±9.35	79.49±9.07	78.64±9.95	80.63±9.48	79.55±10.39
Pulse rate	77.03±9.71	77.11±9.03	76.00±10.53	75.71±9.35	74.65±8.57	75.96±10.31	74.55±9.84	74.28±10.24	75.38±9.83	75.19±10.61

Table S2 Characteristics per quintile in SUMMIT. Data is presented as mean ± standard deviation or no. (%).
Abbreviations: BMI, body mass index; FEV1, Forced expiratory volume in 1 second; FVC, forced vital capacity.

Two quantile to five quantile discretization in IMPACT

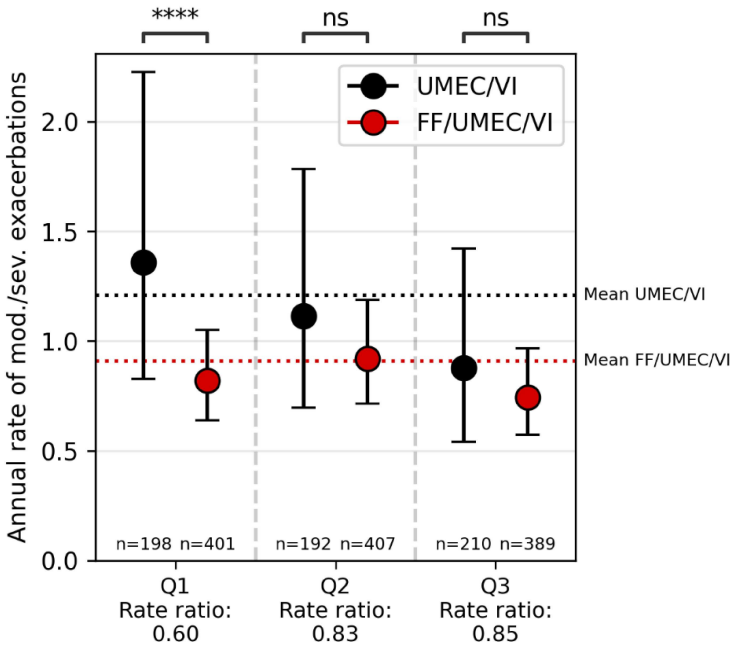
Two quantile discretization

Quantile 1/2
UMEC/VI mean 1.34, 95% CI [0.90,2.01]
FF/UMEC/VI mean 0.87, 95% CI [0.71,1.06]
Rate ratio: 0.65 (p=0.00002)
==========
Quantile 2/2
UMEC/VI mean 0.92, 95% CI [0.62,1.35]
FF/UMEC/VI mean 0.82, 95% CI [0.66,1.01]
Rate ratio: 0.89 (p=0.28649)



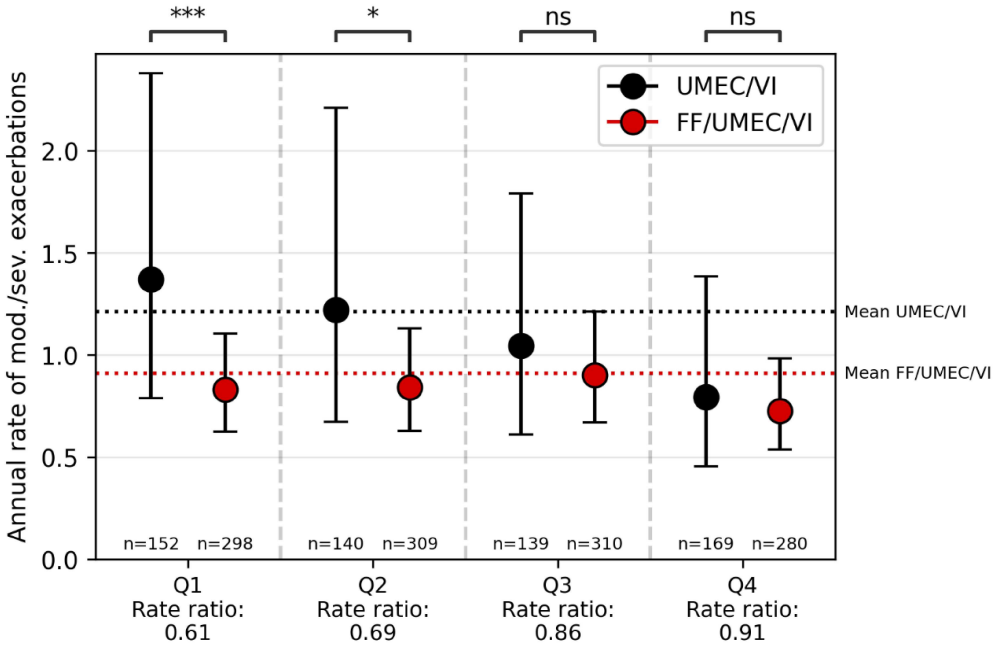
Three quantile discretization

Quantile 1/3
UMEC/VI mean 1.36, 95% CI [0.83,2.23]
FF/UMEC/VI mean 0.82, 95% CI [0.64,1.05]
Rate ratio: 0.60 (p=0.00007)
==========
Quantile 2/3
UMEC/VI mean 1.11, 95% CI [0.70,1.78]
FF/UMEC/VI mean 0.92, 95% CI [0.71,1.19]
Rate ratio: 0.83 (p=0.14167)
==========
Quantile 3/3
UMEC/VI mean 0.88, 95% CI [0.54,1.42]
FF/UMEC/VI mean 0.74, 95% CI [0.57,0.97]
Rate ratio: 0.85 (p=0.21311)



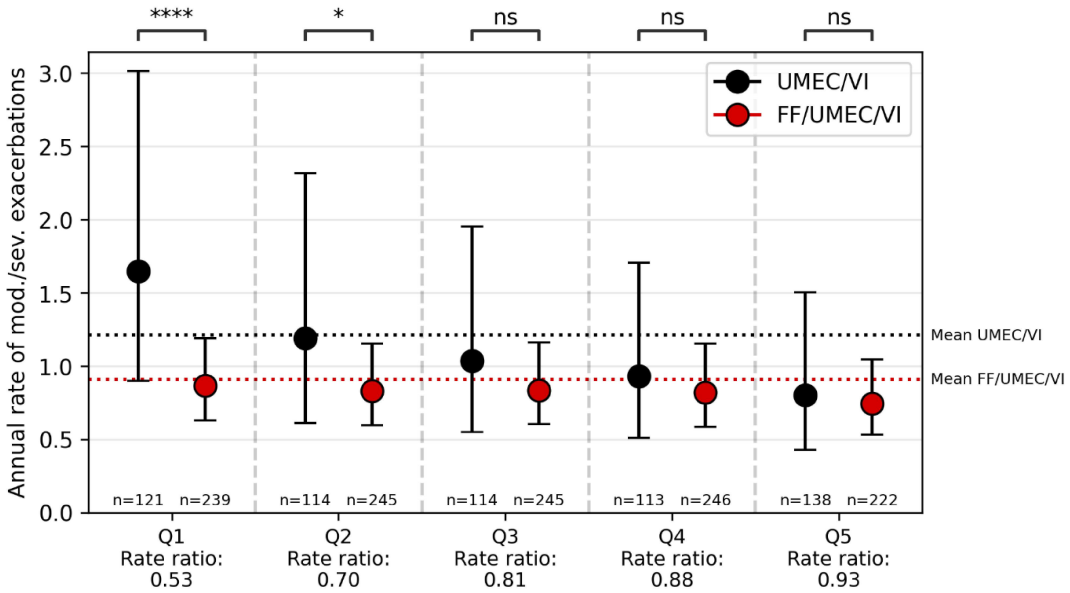
Four quantile discretization

Quantile 1/4
UMEC/VI mean 1.37, 95% CI [0.79,2.38]
FF/UMEC/VI mean 0.83, 95% CI [0.62,1.10]
Rate ratio: 0.61 (p=0.00060)
==========
Quantile 2/4
UMEC/VI mean 1.22, 95% CI [0.67,2.21]
FF/UMEC/VI mean 0.84, 95% CI [0.63,1.13]
Rate ratio: 0.69 (p=0.01345)
==========
Quantile 3/4
UMEC/VI mean 1.04, 95% CI [0.61,1.79]
FF/UMEC/VI mean 0.90, 95% CI [0.67,1.21]
Rate ratio: 0.86 (p=0.32839)
==========
Quantile 4/4
UMEC/VI mean 0.79, 95% CI [0.45,1.38]
FF/UMEC/VI mean 0.72, 95% CI [0.54,0.98]
Rate ratio: 0.91 (p=0.56167)



Five quantile discretization

Quantile 1/5
UMEC/VI mean 1.65, 95% CI [0.90,3.02]
FF/UMEC/VI mean 0.86, 95% CI [0.63,1.19]
Rate ratio: 0.53 (p=0.00008)
==========
Quantile 2/5
UMEC/VI mean 1.19, 95% CI [0.61,2.32]
FF/UMEC/VI mean 0.83, 95% CI [0.59,1.16]
Rate ratio: 0.70 (p=0.03284)
==========
Quantile 3/5
UMEC/VI mean 1.03, 95% CI [0.55,1.95]
FF/UMEC/VI mean 0.84, 95% CI [0.60,1.16]
Rate ratio: 0.81 (p=0.20132)
==========
Quantile 4/5
UMEC/VI mean 0.93, 95% CI [0.51,1.71]
FF/UMEC/VI mean 0.82, 95% CI [0.58,1.15]
Rate ratio: 0.88 (p=0.46342)
==========
Quantile 5/5
UMEC/VI mean 0.80, 95% CI [0.43,1.50]
FF/UMEC/VI mean 0.75, 95% CI [0.53,1.05]
Rate ratio: 0.93 (p=0.67733)



Characteristics per quintile in IMPACT

	Quantile 1		Quantile 2		Quantile 3		Quantile 4		Quantile 5	
	Control (n=121)	**Treated (n=239)**	**Control (n=114)**	**Treated (n=245)**	**Control (n=114)**	**Treated (n=245)**	**Control (n=113)**	**Treated (n=246)**	**Control (n=138)**	**Treated (n=222)**
Age	65.42±8.17	65.79±8.13	66.90±8.22	65.93±8.39	65.40±7.52	65.26±7.79	64.43±8.18	65.04±7.84	63.65±9.47	64.16±8.70
Sex	87/38 70% Male	166/69 71% Male	68/50 58% Male	155/86 64% Male	86/48 64% Male	147/78 65% Male	69/41 63% Male	151/98 61% Male	76/37 67% Male	158/89 64% Male
Height	169.01±9.59	167.04±9.53	166.67±9.68	167.18±8.98	167.04±9.23	166.77±9.78	167.78±9.90	167.20±9.75	167.54±9.12	167.83±8.32
Weight	74.27±17.96	71.80±17.92	70.91±18.29	73.62±18.78	74.92±20.81	74.52±20.21	78.45±22.53	76.55±18.56	80.09±17.48	78.99±20.94
BMI	25.91±5.50	25.61±5.56	25.44±5.90	26.28±6.22	26.65±6.31	26.69±6.46	27.69±6.75	27.32±6.07	28.45±5.24	27.94±6.66
Pack-years	47.92±26.51	46.20±24.10	44.63±24.40	51.49±27.82	47.70±25.49	45.39±26.01	46.32±25.69	46.49±24.99	44.25±32.11	40.69±25.54
Years smoked	41.10±9.99	40.01±11.41	40.58±11.78	40.69±11.44	39.49±10.55	39.12±11.20	38.32±10.25	37.79±10.71	34.95±10.45	34.87±10.40
FEV1 %pred	38.18±13.67	39.52±15.43	37.89±13.20	37.99±15.17	39.86±12.39	40.63±13.91	45.02±14.12	44.61±13.17	52.69±15.20	49.29±17.23
FVC %pred	43.82±13.86	44.22±14.89	41.82±14.42	41.94±15.07	44.51±12.23	43.76±13.93	47.63±14.13	48.33±13.78	55.02±14.14	52.39±15.02
Previous exacerbations	1.76±1.01	1.80±1.01	1.58±0.72	1.74±1.00	1.66±0.89	1.61±0.74	1.76±0.69	1.78±0.92	1.96±0.86	1.67±0.66
Total CAT score	19.18±8.20	20.26±7.08	19.08±6.70	20.82±6.79	18.27±6.65	18.76±6.10	16.47±6.25	17.59±6.96	14.56±6.47	14.04±6.00
Systolic blood pressure	124.94±14.12	126.72±15.71	125.61±14.06	127.00±14.79	128.84±15.30	129.02±16.32	131.33±14.88	132.30±14.68	137.58±16.72	135.90±15.82
Diastolic blood pressure	74.71±10.74	75.76±10.01	76.72±9.01	75.47±9.37	75.99±8.09	77.54±9.48	79.14±9.06	78.33±8.77	79.41±9.26	80.86±9.91
Eosinophils/ leukocytes	5.63±3.94	6.15±4.23	2.64±1.38	2.21±1.34	2.21±1.16	1.90±1.13	1.71±1.00	1.94±1.01	1.69±0.98	1.69±0.97
Eosinophils	0.42±0.32	0.45±0.31	0.19±0.11	0.17±0.11	0.18±0.11	0.15±0.09	0.14±0.09	0.16±0.09	0.14±0.08	0.13±0.08
Neutrophils	4.69±1.67	4.70±1.82	4.81±1.69	5.22±1.82	5.21±1.84	5.31±1.96	5.64±1.80	5.65±2.60	5.58±1.82	5.36±2.18

Table S3 Characteristics per quintile in IMPACT. Data is presented as mean ± standard deviation or no. (%).
Abbreviations: BMI, body mass index; FEV1, Forced expiratory volume in 1 second; FVC, forced vital capacity.

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Explanation Q-score

Limited by the fundamental problem of causal inference, models for estimating individual treatment effects (ITEs) cannot be validated in the classical way of comparing predictions against ground truth labels. It is therefore infeasible to validate a single prediction. We attempted to overcome this by developing a new score which validates predictions for a group of subjects (consisting of treated and control subjects) in a stratified way. Patients can be grouped in two ways; based on baseline characteristics or based on predicted ITE. For this score, we chose the latter since this focuses purely on the predictions of the model which already takes into account the baseline characteristics of the subjects. The intuition behind the Q-score is that in subjects, treated and control, within a subgroup of similar predicted ITEs, a similar subgroup average treatment effect should observed. Subgroups are made using quantiles based on predicted ITE. As ITE predictions should be valid independent of the number of quantiles chosen, the Q-score measures prediction errors over multiple quantile-based discretizations. The score quantifies the performance of the prediction model against the benchmark prediction: the average treatment effect.

Given a causal inference model $\mathcal{M}$, input dataset $X = \{x_i\}_{i=1}^{M}$ with M feature vectors $x_i \in \mathbb{R}^N$ with N features, outcomes $Y = \{y_i\}_{i=1}^{M}$ with $y_i \in \mathbb{R}$, assignment vectors $W = \{w_i\}_{i=1}^{M}$ with $w_i \in \{0,1\}$, predicted individual treatment effects $T = \{t_i\}_{i=1}^{M}$ with $t_i \coloneqq \mathcal{M}(x_i) \in \mathbb{R}$. The ordering of i is chosen such that T is sorted in ascending order. We define $Q(\mathcal{M}; X, Y, W)$ as the Q-score of model $\mathcal{M}$ given the input dataset X, the outcomes Y and the treatment assignments W:

$$Q(\mathcal{M}; X, Y, W) \coloneqq 1 - \frac{L_Q(\mathcal{M}; X, Y, W)}{L_{ATE}(\mathcal{M}; X, Y, W)}$$

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with L_Q the quantile loss function of model $\mathcal{M}$ and L_{ATE} the loss function of the average treatment effect over the quantiles determined by model $\mathcal{M}$. The Q-score has range $]-\infty, 1]$ and evaluates how model $\mathcal{M}$ performs against the standard ATE prediction, i.e., every subject is predicted to have the average treatment effect as individual treatment effect. We define L_Q as

$$L_Q(\mathcal{M}; X, Y, W) \coloneqq \sum_{i=2}^{\frac{M}{2}} w(i) * \left(L_Q^i(\mathcal{M}; X, Y, W)\right)$$

and L_{ATE} as

$$L_{ATE}(\mathcal{M}; X, Y, W) \coloneqq \sum_{i=2}^{\frac{M}{2}} w(i) * \left(L_{ATE}^i(\mathcal{M}; X, Y, W)\right)$$

with $w(i)$ a self-chosen weight function. L_Q^i is defined as the loss function of $\mathcal{M}$ for quantile cut i, i.e., the quantile-based discretization of T into i quantiles, which depends on $\mathcal{M}$:

$$L_Q^i(\mathcal{M}; X, Y, W) \coloneqq \sqrt{\frac{1}{i}\sum_{j=1}^{i} L_Q^{i,j}(\mathcal{M}; X, Y, W)^2}$$

with $L_Q^{i,j}$ the loss function of the j^{th} quantile of quantile cut i. Analogue, L_{ATE}^i is the loss function of ATE for quantile cut i:

$$L_{ATE}^i(\mathcal{M}; X, Y, W) \coloneqq \sqrt{\frac{1}{i}\sum_{j=1}^{i} L_{ATE}^{i,j}(\mathcal{M}; X, Y, W)^2}\,.$$

We then define $q^{i,j}$ as the range of treatment effects in the j^{th} quantile of quantile cut i and *quantile average treatment effect* as the treatment effect in a quantile. The loss $L_Q^{i,j}$ in the

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j^{th} quantile of quantile cut i is defined as the difference between the observed quantile treatment effect, i.e., the difference between the mean outcomes of the treated ($\mu_{w=1}^{i,j}$) and untreated ($\mu_{w=0}^{i,j}$) subjects in that quantile, and the expected quantile average treatment effect $E[t|t \in q^{i,j}]$, based on the distribution of the treatment effects $P(t)$ and the range $q^{i,j}$:

$$L_Q^{i,j}(\mathcal{M}; X, Y, W) \coloneqq \left(\mu_{w=1}^{i,j} - \mu_{w=0}^{i,j}\right) - E[t|t \in q^{i,j}]$$

$$\coloneqq \left[\left(\frac{\sum_k y_k \, I_{q^{i,j}}(t_k) w_k}{\sum_k I_{q^{i,j}}(t_k) w_k}\right) - \left(\frac{\sum_k y_k \, I_{q^{i,j}}(t_k)(1-w_k)}{\sum_k I_{q^{i,j}}(t_k)(1-w_k)}\right)\right] - \frac{\int_{t \in q^{i,j}} tP(t)dt}{\int_{t \in q^{i,j}} P(t)dt}$$

with indicator function $I_{q^{i,j}}(t) \coloneqq \begin{cases} 1 \text{ if } t \in q^{i,j} \\ 0 \text{ if } t \notin q^{i,j} \end{cases}$.

And analogue for $L_{ATE}^{i,j}$ where we use $ATE = \mu_{w=1} - \mu_{w=0}$:

$$L_{ATE}^{i,j}(\mathcal{M}; X, Y, W) \coloneqq (\mu_{w=1} - \mu_{w=0}) - E[t|t \in q^{i,j}]$$

$$\coloneqq \left[\left(\frac{\sum_k y_k \, w_k}{\sum_k w_k}\right) - \left(\frac{\sum_k y_k \, (1-w_k)}{\sum_k (1-w_k)}\right)\right] - \frac{\int_{t \in q^{i,j}} tP(t)dt}{\int_{t \in q^{i,j}} P(t)dt}.$$

For practical reasons we reduced the number of quantile cuts, $\frac{M}{2} - 1$, and used only powers of 2, i.e., we computed $\sum_{i=2}^{\frac{M}{2}} \left(L_Q^i(\mathcal{M}; X, Y, W)\right)$ and $\sum_{i=2}^{\frac{M}{2}} \left(L_{ATE}^i(\mathcal{M}; X, Y, W)\right)$ for L_Q and L_{ATE}, respectively. To compute the expected quantile treatment effect, we used kernel density estimation to estimate the probability density function given the treatment effects computed by the model $\mathcal{M}$ itself. We then sampled over a linear space in each quantile to obtain an estimate of the expected quantile treatment effect. Another option is to compute the expected quantile treatment effect from the ITE predictions in the training set.

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Parameter grids for the grid search during model development

Table S3. Parameter grid for the grid search procedure of Causal Forest

Model	Parameter	Values
Causal Forest	Number of estimators	[10, 25, 50, 100, 200, 500, 1000, None]
	Criterion	[heterogeneity, mean square error]
	Maximum depth	[5, 10, 25, 50, None]
	Maximum features	[square root, log2, number of features]
	Minimum samples leaf	[1, 2, 4, 5, 10]
	Minimum samples split	[2, 3, 5, 10]

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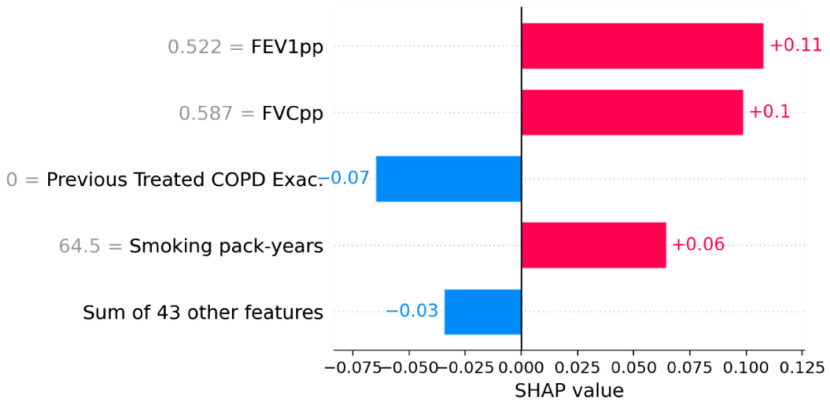

Personalized analysis 1: a non-responder in SUMMIT

This subject is predicted to have a reduction of 0.01 exacerbations per year (ITE: -0.01) according the causal forest model. FEV1 %predicted (52.2%), FVC %predicted (58.7%) and smoking pack-years (64.5) were the main contributors (evidence for, red bars) to the non-response. There was counter-evidence from exacerbation history and the other parameters.

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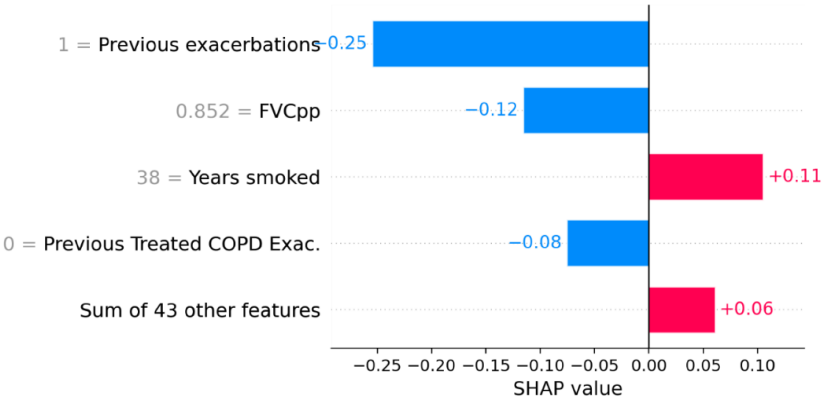

Personalized analysis 2: a super responder in SUMMIT

This subjected is predicted to have a reduction of 0.43 exacerbations per year (ITE: -0.43) according to the causal forest model. Number of previous exacerbations (1), FVC %predicted (85%) and number of previous treated exacerbations (0) were the main contributions to the good response of this subjects. However, there was counter-evidence from years smoked (38) and the other parameters.

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Parameter list in SUMMIT

This list contains all the parameters that were considered as input for the machine learning models in SUMMIT. The parameters that were used after filtering for missing data or considered clinically relevant by experienced clinicians are indicated in bold.

Baseline characteristics

Age, Country, **BMI**, Race, **Height**, **Weight**, **Sex**, Region, **Previous Hospitalised COPD Exacerbations**, **Previous Treated COPD Exacerbations**, **Previous Treated/Hosp. COPD Exacerbations**, **mMRC at baseline**, CAT score.

Cardiovascular entry criteria

Met entry criteria, **history of CV disease**, established CAD, established PAD, previous stroke, previous myocardial infarction, Diabetes mellitus with target organ disease, Being treated for Hypertension, Being treated for Hypercholesterolemia, Being treated for peripheral arterial disease, Being treated for diabetes mellitus.

Cardiovascular history

Ever Treated with Medication for Ventricular Arrhythmia, **Ever had Carotid, Abdominal or Femoral Bruits**, **Ever Diagnosed with Congestive Heart Failure**, Any Target Organ Damage (Diabetes Mellitus), **Ever Diagnosed with Diabetes Mellitus**, Diabetes Mellitus End Organ Damage: Eyes, Diabetes Mellitus End Organ Damage: Kidneys (DM), Diabetes Mellitus End Organ Damage: Limbs/extremities, **Family History of Stroke or Myocardial Infarction in Either Parent or Sibling**, **Ever Diagnosed with Hypercholesterolemia**, **Ever Diagnosed with Hypertension**, **Hypertension End Organ Damage: Kidneys**, **Hypertension End Organ Damage: Heart**, **Hypertension End Organ Damage: Central Nervous System**, Any Target

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Organ Damage (Hypertension), **Ever had Implantable Cardiac Defibrillator**, Indicator of Ischaemic Heart Disease, **Ever Hospitalised for Myocardial Infarction**, Indicator of Vascular Disease, Ever had Carotid, Abdominal or Femoral Bruits with associated Abdominal Aortic Aneurysm, Ever had Carotid, Abdominal or Femoral Bruits with associated Central Nervous System Signs, Ever had Carotid, Abdominal or Femoral Bruits with associated Claudication, **Established Peripheral Arterial Disease (confirmed by Clinical Signs or Imaging Studies)**, **Ever Treated with Medication for Carotid or Aorto-Femoral Vascular Disease**, **Had Surgery for Carotid or Aorto-Femoral Vascular Disease**, **Ever had Coronary Artery Bypass Graft or Percutaneous Coronary Intervention**, **Ever Hospitalised for Cerebrovascular Accident**, **Ever had Transient Ischemic Attack (confirmed by Healthcare Professional)**, **Receiving Prescription Treatment for Hypercholesterolemia at Study Entry**, **Receiving Prescription Treatment for Diabetes Mellitus at Study Entry**, **Receiving Prescription Treatment for Hypertension at Study Entry**, **Receiving Prescription Treatment for Peripheral Arterial Disease at Study Entry**.

EQ5D

EQ5D Mobility, EQ5D Self-Care, EQ5D Usual Activities, EQ5D Pain/Discomfort, EQ5D Anxiety/Depression, EQ VAS Score.

Prior COPD therapy

Tiotropium taken in 12 months prior to Screening, **Any ICS use in 12 months prior to Screening**, Any LABA use in 12 months prior to Screening, Summary of medication taken in 12 months prior to Screening, **Long acting B2 agonists taken in 12 months prior to Screening**, Inhaled corticosteroids taken in 12 months prior to Screening, **LABA/ICS combination product taken in 12 months prior to Screening**.

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Laboratory results

Calcium, Carbon Dioxide, Creatinine, Glucose, Hematocrit, Potassium, Erythrocytes Mean Corpuscular HGB Concentration, Erythrocytes Mean Corpuscular Volume, Mean Platelet Volume, Platelets, Erythrocytes Distribution Width, Sodium, Leukocytes, 30-day Intermountain Risk Score, 1-year Intermountain Risk Score, 5-year Intermountain Risk Score.

Pulmonary function tests (post-bronchodilator)

FEV1, **FEV1 %predicted**, FVC, **FVC %predicted**.

Pulse wave velocity (PWV)

Pulse Wave Velocity, Central Mean Arterial Pressure, Central Pulse Pressure, Augmentation Index, Heart Rate Variability, Central Systolic blood pressure, Central Diastolic blood pressure.

Saint-George's Respiratory Questionnaire (SGRQ)

SGRQ Symptoms Score, SGRQ Activities Score, SGRQ Impacts Score, SGRQ Total Score.

Substance use

Current Smoking Status, Smoking Status Based on Date of Stopping, **Smoking Status at Screening**, **Years Smoked**, **Smoking Pack Years**, **Number of Cigarettes Smoked Per Day**.

Vital signs

Diastolic blood pressure, **systolic blood pressure**, **pulse rate**.

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Parameter list in IMPACT

This list contains all the parameters that were considered as input for the machine learning models in IMPACT. The parameters that were used after filtering for missing data or considered clinically relevant by experienced clinicians are indicated in bold.

Baseline characteristics

Age, BMI, height, weight, sex, ethnicity, race, GOLD stage, previous moderate/severe COPD exacerbations, previous moderate COPD exacerbations, previous severe COPD exacerbations, past history of pneumonia, COPD assessment test score.

Electrocardiography

PR Interval, QRS Duration, QT Interval, QTcB Interval, QTcF Interval, ECG Mean Heart Rate.

EQ5D

VAS score, Utility score.

Laboratory results

BLOOD Eosinophils, BLOOD Eosinophils/Leukocytes, BLOOD Hematocrit, BLOOD Hemoglobin, BLOOD Neutrophils, BLOOD Neutrophils/Leukocytes, BLOOD Platelets, SERUM OR PLASMA Albumin, SERUM OR PLASMA Creatinine, BLOOD Basophils, BLOOD Basophils/Leukocytes, SERUM Glucose, BLOOD Lymphocytes, BLOOD Lymphocytes/Leukocytes, BLOOD Monocytes, BLOOD Monocytes/Leukocytes, BLOOD Neutrophils, BLOOD Neutrophils/Leukocytes, BLOOD Neutrophils, Segmented, BLOOD Neutrophils, Segmented/Leukocytes, BLOOD Platelets, BLOOD Erythrocytes, BLOOD Leukocytes, SERUM OR PLASMA Albumin, SERUM OR PLASMA Alkaline Phosphatase, SERUM

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OR PLASMA Alanine Aminotransferase, SERUM OR PLASMA Aspartate Aminotransferase, SERUM OR PLASMA Direct Bilirubin, SERUM OR PLASMA Bilirubin, SERUM OR PLASMA Indirect Bilirubin, SERUM OR PLASMA Calcium, SERUM OR PLASMA Creatine Kinase, SERUM OR PLASMA Chloride, SERUM OR PLASMA Carbon Dioxide, SERUM OR PLASMA Creatinine, SERUM OR PLASMA Gamma Glutamyl Transferase, SERUM OR PLASMA Potassium, SERUM OR PLASMA Phosphate, SERUM OR PLASMA Protein, SERUM OR PLASMA Sodium, SERUM OR PLASMA Urate, SERUM OR PLASMA Urea ENZYMATIC COLORIMETRY

Pulmonary function tests

FEV1, **FEV1 %predicted**, **FVC**, **FVC %predicted**, **FEV1 reversibility**.

Saint-George's Respiratory Questionnaire (SGRQ)

SGRQ Symptoms Score, SGRQ Activities Score, SGRQ Impact Score, SGRQ Total Score.

Substance use

Smoking status at baseline, number of pack-years, years smoked, smoking history, cigarettes smoked per day.

Vital signs

Diastolic blood pressure, systolic blood pressure, pulse rate, oxygen saturation, respiratory rate.

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