Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation®

Original Research

Machine Learning Prediction of Progression in Forced Expiratory Volume in 1 Second in the COPDGene® Study

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Abstract

Background: The heterogeneous nature of chronic obstructive pulmonary disease (COPD) complicates the identification of the predictors of disease progression. We aimed to improve the prediction of disease progression in COPD by using machine learning and incorporating a rich dataset of phenotypic features.

Methods: We included 4496 smokers with available data from their enrollment and 5-year follow-up visits in the COPD Genetic Epidemiology (COPDGene®) study. We constructed linear regression (LR) and supervised random forest models to predict 5-year progression in forced expiratory in 1 second (FEV_1) from 46 baseline features. Using cross-validation, we randomly partitioned participants into training and testing samples. We also validated the results in the COPDGene 10-year follow-up visit.

Results: Predicting the change in FEV_1 over time is more challenging than simply predicting the future absolute FEV_1 level. For random forest, R-squared was 0.15 and the area under the receiver operator characteristic (ROC) curves for the prediction of participants in the top quartile of observed progression was 0.71 (testing) and respectively, 0.10 and 0.70 (validation). Random forest provided slightly better performance than LR. The accuracy was best for Global initiative for chronic Obstructive Lung Disease (GOLD) grades 1–2 participants, and it was harder to achieve accurate prediction in advanced stages of the disease. Predictive variables differed in their relative importance as well as for the predictions by GOLD.

Conclusion: Random forest, along with deep phenotyping, predicts FEV_1 progression with reasonable accuracy. There is significant room for improvement in future models. This prediction model facilitates the identification of smokers at increased risk for rapid disease progression. Such findings may be useful in the selection of patient populations for targeted clinical trials.

Abbreviations: chronic obstructive pulmonary disease, **COPD**; COPD Genetic Epidemiology study, **COPDGene®**; linear regression, **LR**; forced expiratory volume in 1 second, **FEV_1**; receiver operator characteristic, **ROC**; Global initiative for chronic Obstructive Lung Disease, **GOLD**; computed tomography, **CT**; annualized 5-year changes in FEV_1, **ΔFEV_1**; root mean squared error, **RMSE**; increase in the mean squared errors, **IncMSE**; area under the curve, **AUC**; body mass index, **BMI**; low attenuation area below -950 Hounsfield units, **%LAA-950**; 15th percentile point, **Perc15**; forced vital capacity, **FVC**; modified Medical Research Council, **mMRC**; St George's Respiratory Questionnaire, **SGRQ**; preserved ratio-impaired spirometry, **PRISm**; interquartile, **IQR**; forced expiratory flow rate between 25% and 75% of the vital capacity, **$FEV_{25\%-75\%}$**

Funding Support: This work was supported by National Heart, Lung, and Blood Institute K08 HL141601, R01 HL124233, R01 HL126596, R01 HL147326, U01 HL089897, and U01 HL089856. The COPDGene® study (NCT00608764) is also supported by the COPD Foundation through contributions made to an Industry Advisory Board that has included AstraZeneca, Bayer Pharmaceuticals, Boehringer-Ingelheim, Genentech, GlaxoSmithKline, Novartis, Pfizer, and Sunovion.

Date of Acceptance: May 18, 2022 | **Published Online Date:** May 20, 2022

Citation: Boueiz A, Xu Z, Chang Y, et al. Machine learning prediction of progression in forced expiratory volume in 1 second in the CODPGene® study. ***Chronic Obstr Pulm Dis.*** 2022;9(3):349-365. doi: https://doi.org/10.15326/jcopdf.2021.0275

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Keywords:

COPD; disease progression; 5-year changes in FEV_1; prediction; random forest machine learning

This article has an online data supplement.

Note: The abstract from this work was presented at the American Thoracic Society International Conference in 2018 and published in the *American Journal of Respiratory and Critical Care Medicine:* Boueiz A, Chang Y, Cho MH, et al. Machine learning prediction of 5-year progression of FEV1 in the COPDGene Study. *Am J Respir Criti Care Med.* 2018;197(A7430).

Introduction

Chronic obstructive pulmonary disease (COPD) continues to be a major cause of disability and death in the United States and globally.[1-4] Novel therapies that slow disease progression could result in an improvement in COPD patients' health status and have a substantial impact on health care utilization. The development of such therapies will be aided by improved tools for predicting disease progression, enabling the selection of high-risk groups for targeted treatment.

Predictive models incorporate multiple sources of information to make patient-specific predictions and are widely used in multiple areas of medical practice. Existing models of disease progression in COPD have been limited in the scope of variables assessed.[5-9] COPD exhibits significant variation in clinical and radiologic presentation as well as disease progression.[6,10-12] This disease heterogeneity complicates the identification of the predictors of COPD progression and limits the accuracy of predictive models. Furthermore, COPD often progresses slowly over decades and true disease progression over short time periods can be difficult to detect with existing measurements.

In this study, we aimed to improve the prediction of COPD progression by applying machine learning to a rich dataset of clinical, demographic, patient-reported variables and imaging features in the COPD Genetic Epidemiology (COPDGene®) study. We hypothesized that deep phenotyping at the initial study visit along with random forest modeling, which exploits complex non-linear relationships and interactions among the risk factors, would facilitate the prediction of the rates of disease progression as measured by forced expiratory volume in 1 second (FEV_1), a key aspect of COPD.

Methods and Materials

Study Populations

The COPDGene study is an ongoing, multi-institutional, longitudinal study to investigate the epidemiologic and genomic characteristics of COPD.[13] COPDGene enrolled self-identified non-Hispanic White and African-American smokers across the full spectrum of disease severity as defined by the Global initiative for chronic Obstructive Lung Disease (GOLD) spirometric grading system.[14] Participants were aged 45 to 80 years at study enrollment and had at least a 10 pack-year lifetime smoking history. COPDGene collects longitudinal data at 5-year intervals; the 10-year study visit is ongoing. Visit 1 and Visit 2 were completed and Visit 3 is ongoing. At each study visit, participants underwent comprehensive phenotyping, which included spirometry, questionnaire assessment, and inspiratory and expiratory chest computed tomography (CT) scans, all of which were done according to a standard procedure with consistent quality control across centers.

Derivation cohort - COPDGene Study Visit 1 and Visit 2: We analyzed 4496 smokers with complete CT scans and relevant covariate data at the baseline visit

(Visit 1) and 5-year follow-up visit (Visit 2) in the COPDGene cohort.

Temporal validation cohort - COPDGene Study Visit 3: During Phase 3 of the COPDGene Study, enrolled participants returned for their 10-year follow-up visit. At the time of this analysis, 1833 smokers had completed their 10-year follow-up visit and had available 10-year spirometric and radiologic data. To predict their outcome values at Year 10 (Visit 3), we entered their 5-year (Visit 2) predictor data into the models trained in the derivation cohort. The FEV_1 values for Visit 3 were observed. Our models were trained using only data from Visit 1 and Visit 2, where predictors were at Visit 1 and responses were Visit 2 values or the change in values between Visit 2 and Visit 1. In this setting, cross-validation was used to assess model performance. To provide further *temporal* validation of our models, we tested our already-trained models (no further parameter fitting) by using Visit 2 values for the predictors. This allowed us to compare the predicted Visit 3 values against the observed Visit 3 values to assess the accuracy of each prediction model in the temporal validation cohort.

The COPDGene study design, participant enrollment, and phenotype measurements have been previously reported[13] and additional information is included in the online data supplement.

Outcome Variables

We constructed models to predict annualized follow-up FEV_1 and 5-year changes in FEV_1 (ΔFEV_1). ΔFEV_1 (mL/year) was calculated by subtracting the Visit 1 value from the Visit 2 value and dividing by the time between Visit 1 and Visit 2. Negative values represent a lower value of the outcome at Visit 2 (i.e., worsening of the disease over the 5-year period with greater loss of FEV_1). From the prediction models of ΔFEV_1, we also derived the prediction of Visit 2 FEV_1 by adding the predicted 5-year change to the observed Visit 1 value.

Feature Selection

Candidate predictors consisted of 46 baseline demographic, clinical, physiologic, and imaging variables that were available in the COPDGene population at Visit 1 and had correlation coefficients of less than 0.90 with the other variables. We set the threshold to 0.9 to ensure that only secondary/redundant features are removed, rather than features with potentially complementing information. To confirm this, we reran our experiments with removal of variables with correlation coefficients ≥0.7 and we compared the performance accuracies.

Training, Testing, and Validation Samples

We trained a prediction model for ΔFEV_1 in 4496 participants with data from COPDGene Visit 1 and Visit 2 using a nested, 10-fold cross validation procedure. The inner fold of cross validation was used for parameter tuning. In the outer fold, our studied derivation cohort was randomly partitioned into 10 mutually exclusive subsets (folds) of approximately equal size, using nine folds for training and one-fold for testing each time for 10 times. This entire procedure was repeated 5 times to account for the random variability of the partitioning procedure and provide more accurate estimates of the performance. This repeated resampling procedure created an ensemble of 50 models over which we averaged the predictions, and we then validated the performance of this model using data from COPDGene Visit 3 that had not been used in any aspect of the model training process (temporal validation).

Random Forest Supervised Machine Learning

Supervised random forest is an ensemble learning method that predicts outcomes by fitting a series of decision trees and aggregating the results across trees. This method can capture non-linear dependencies and has been shown to perform well for a range of tasks.[15] It begins building each tree by randomly selecting participants for the tree with replacements (bootstrap samples). Participants not selected in bootstrapping represent the out-of-bag set. For each bootstrap sample, a decision tree is trained by recursive binary partition of the data until the minimum node size is reached. At each node split, an optimal feature (and its split-point) is identified from a randomly selected subset of features by minimizing a loss measure. The random selection of features reduces the correlation between trees, leading to variance reduction and improved generalization performance. It also allows a moderately informative feature to assert its importance to the prediction. Once an ensemble of trees is grown, the prediction for a new sample is made by aggregating predictions (e.g., averaging for regression and majority vote for classification) from individual trees. In our study, we fixed the number of trees at 500 and tuned the hyperparameters (the bootstrap sampling fraction, the minimal node size and the number of features to use at each split) by minimizing root mean squared error (RMSE) using a nested 10-fold cross-validation within the training data.

Random Forest Variable Importance and Their Effects on the Prediction

We calculated variable importance scores as the aggregated increase in the mean squared errors (IncMSE) of predictions estimated with out-of-bag samples when the values of a given variable are randomly permuted.[16,17] The larger the increase in prediction error when permuted, the higher the variable importance score (IncMSE), and the more important the variable is to the prediction. Since the raw permutation importance has better statistical properties, the importance values were not normalized.[18] Therefore, they cannot be used to compare variable importance across prediction tasks, but they can be used within the same prediction task to rank variables by their contribution to the accuracy of the final model.

Prediction Performance

We assessed the accuracy of each prediction model using the RMSE and R-squared metrics, indicators of the goodness of fit of a set of predictions to the observed values. For the prediction of ΔFEV_1, we also assessed the ability of the models to correctly identify participants in the top quartile of disease progression (i.e., greatest decline in FEV_1) as quantified by the areas under the receiver operator characteristic ROC curves (AUC-ROC).

Linear Regression

To compare the performance of random forest to that of a more traditional modeling approach, the same set of predictors was evaluated in linear regression models.

Statistical Analyses

We performed a complete case analysis. Descriptive characteristics were reported respectively as percentages and medians with interquartile ranges for categorical and continuous variables. Variables were analyzed using the *t*-test for normally distributed variables, the Wilcoxon rank sum test for non-normally distributed variables, and Chi-square tests for categorical variables. To identify differences in the quality of prediction and variable importance in participants with different levels of COPD severity, we also constructed prediction models separately in various GOLD subgroups. All tests of significance were 2-tailed with a significance threshold of *P*-value <0.05.

Results

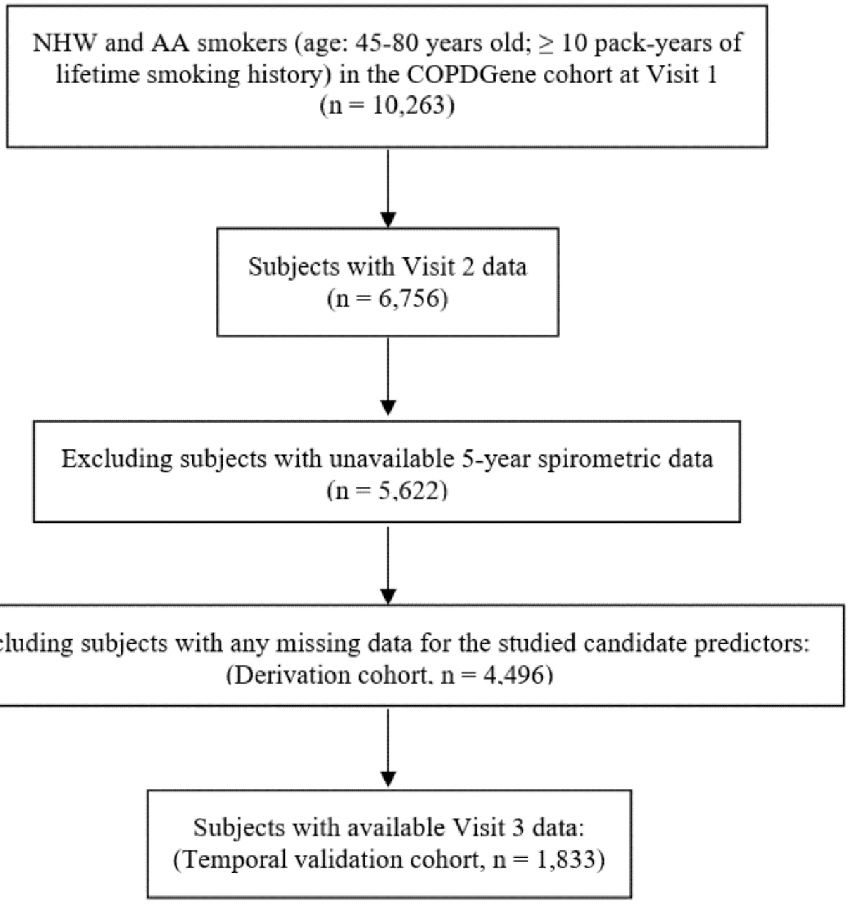
Participant Characteristics

In total, 4496 COPDGene participants (median age: 60; 51% men; 73% non-Hispanic Whites) had complete phenotypic data and were included in the analysis. The participant flow diagram is shown in Figure 1.

Characteristics of "Rapid FEV_1 Progressors" in COPDGene: To describe the characteristics of participants who were "rapid FEV_1 progressors" and test the null hypothesis that there is no systematic difference in patient characteristics between the 2 groups, we examined the characteristics of participants in the top quartile of progression to those in the bottom quartile (Table 1). Compared to participants in the bottom quartile of ΔFEV_1, those in the top quartile (rapid FEV1 progressors) had a higher proportion of males with less severe spirometric impairment at baseline but with higher exposure to smoking (pack years and percentage of current smoking), more advanced radiologic disease (total emphysema and gas trapping), more bronchodilator responsiveness, more dyspnea and chronic bronchitis symptoms, and a lower rate of obesity and metabolic syndrome. The many significant *P*-values support the alternative hypothesis and shed light on the factors that may be associated with or even contribute to the rapid FEV_1 progression. The significant differences between the rapid and slow progressors also underpin the clinical relevance of identifying rapid progressors using a prediction model.

The median change in FEV_1 was -37 (interquartile [IQR]: -66, -9)mL/year (Figure 2). Fifty-seven percent of the studied participants had a rate of decline in FEV_1 of more than 30mL/year over the 5-year period and 7% had an increase in FEV_1 of more than 30mL/year. Rapid FEV_1 progressors had a median change of -91mL/year compared to 11mL/year for slow spirometric progressors (Table 1). When assessed according to the severity of airflow limitation, the rate of FEV_1 decline was inversely

Figure 1. Participants' Flow Diagram and General Framework of the Study


NHW and AA smokers (age: 45-80 years old; ≥ 10 pack-years of lifetime smoking history) in the COPDGene cohort at Visit 1 (n = 10,263)
Subjects with Visit 2 data (n = 6,756)
Excluding subjects with unavailable 5-year spirometric data (n = 5,622)
Excluding subjects with any missing data for the studied candidate predictors: (Derivation cohort, n = 4,496)
Subjects with available Visit 3 data: (Temporal validation cohort, n = 1,833)

NHW=non-Hispanic Whites; AA=African Americans; COPDGene=COPD Genetic Epidemiology study

related to the GOLD grade, with medians of ΔFEV_1 of -46, -38, -31, -16mL/year for GOLD 1–4, respectively.

Prediction Performance for Follow-up Forced Expiratory Volume in 1 Second and 5-year Change in Forced Expiratory Volume in 1 Second

We constructed the prediction models using a nested cross-validation procedure and we assessed the prediction performance in the COPDGene 10-year follow-up visit. A schematic representation of our model is shown in Figure 3. The list of candidate predictors is provided in Table 2. In the cross-validation testing samples, on average, 89.6% of the variance in follow-up FEV_1 values were explained and the AUC-ROC curves for the prediction of participants in the top quartile of observed disease progression was 0.97 (Table 3 and Figure 4). This high performance was maintained in the temporal validation with an R-squared value of 0.91 and AUC of 0.98 (Table 3). For the prediction of the change in FEV_1 over time (ΔFEV_1), the average R-squared value was 0.15 and AUC was 0.71 in the testing samples and respectively, 0.10 and 0.70 in the validation cohort.

The random forest model had slightly better performance for the prediction of ΔFEV_1 compared to linear regression (Table 3). The percentage of variance explained by random forest versus linear regression was 14.7% versus 12.3%. The indirect approach arithmetically transforms the predictions from modeling change in FEV_1 to follow-up FEV_1 predictions, and the best follow-up FEV_1 prediction is achieved via an indirect approach with random forest modeling change in FEV_1. In all cases by all metrics, random forest modeling change in FEV_1 leads to the best prediction directly in change in FEV_1 and indirectly in follow-up FEV_1. These results demonstrate consistently the superiority of random forest versus

Table 1. Characteristics of the Rapid Spirometric Progressors

	Top Quartile Progressors (n=1124)	Bottom Quartile Progressors (n=1124)	*P*-value
Age (years)	58.3 [51.9, 65.0]	59.7 [52.3, 66.6]	***<0.001***
Male (%)	66.0%	51.2%	***<0.001***
Non-Hispanic Whites (%)	72.3%	69.6%	0.098
Height (cm)	173.0 [166.7, 180.0]	170.0 [162.6, 177.5]	***<0.001***
BMI	27.7 [24.5, 31.7]	29.3 [25.6, 33.9]	***<0.001***
Pack Years of Smoking	40.5 [29.9, 57.0]	38.0 [25.7, 52.5]	***<0.001***
Current Smoking (%)	56.1%	45.2%	***<0.001***
Total Emphysema (%LAA-950)	2.7 [0.7, 7.2]	1.7 [0.5, 5.0]	***0.003***
U/L Ratio	0.38 [0.00, 0.91]	0.41 [0.00, 0.92]	0.43
Airway Wall Thickening (%)	49.6 [44.3, 55.2]	50.1 [44.6, 56.3]	0.09
Pi10	2.1 [1.8, 2.5]	2.2 [1.9, 2.6]	***0.01***
Gas Trapping (%)	15.9 [7.6, 30.3]	12.3 [5.5, 25.0]	***<0.001***
FEV_1 (percentage predicted)	86.4 [68.9, 99.7]	78.9 [60.9, 91.5]	***<0.001***
FEV_1/FVC	0.71 [0.61, 0.79]	0.72 [0.62, 0.79]	***<0.001***
Pre/Post-Bronchodilator FEV_1 (% change)	5.5 [1.8, 11.0]	2.8 [-1.4, 7.9]	***<0.001***
Pre/Post-Bronchodilator FVC (% change)	3.1 [-1.0, 8.8]	1.0 [-3.6, 6.7]	***0.04***
MMRC Dyspnea Score			
0	563 (50.1%)	529 (47.1%)	0.37
1	171 (15.2%)	177 (15.7%)	
2	143 (12.7%)	137 (12.2%)	
3	166 (14.8%)	199 (17.7%)	
4	81 (7.2%)	82 (7.3%)	
SGRQ Score	31.8±25.9	29.3±24.5	***0.03***
Chronic Bronchitis (%)	21.1%	16.4%	***0.004***
Metabolic Syndrome (%)	16.0%	20.3%	***0.01***
Obesity (%)	35.1%	45.0%	**< 0.001**
GOLD:			
PRISm	75 (6.7%)	194 (17.3%)	***<0.001***
0	546 (48.6%)	468 (41.6%)	
1	138 (12.3%)	65 (5.8%)	
2	272 (24.2%)	221 (19.7%)	
3	90 (8.0%)	138 (12.3%)	
4	3 (0.3%)	38 (3.4%)	
5-year Change in FEV_1 (mL/year)	-91.0 [-117.0, -77.0]	11.0 [0.0, 32.0]	***<0.001***

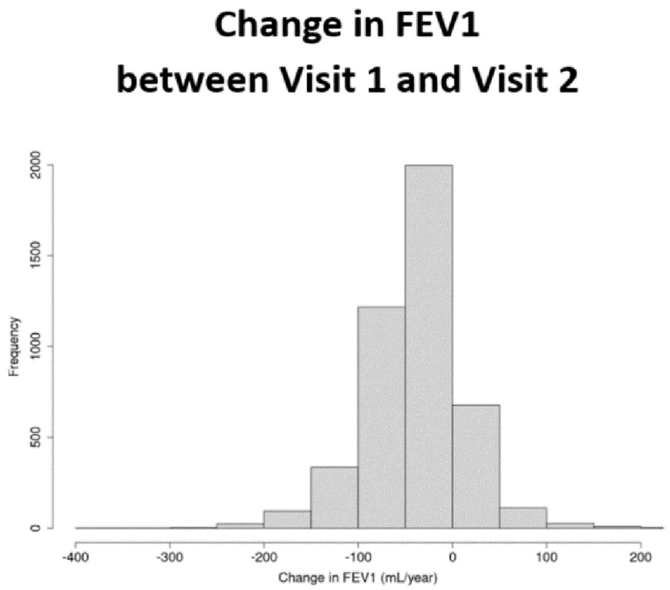
All values are from Visit 1.

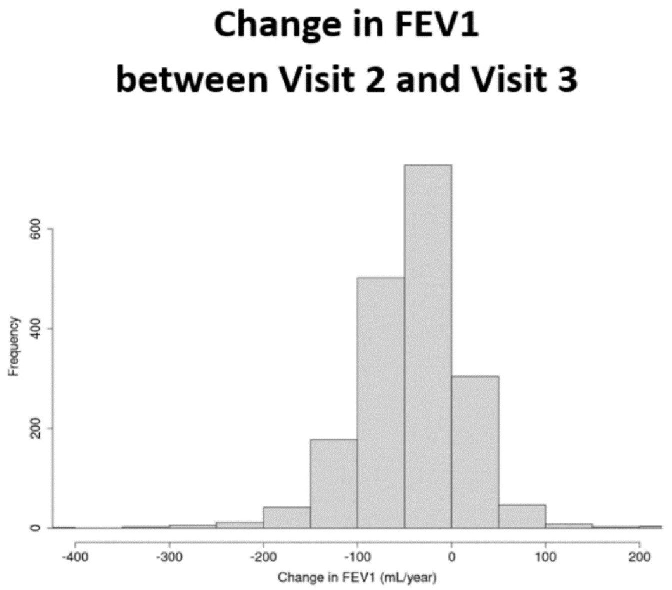
"Change between Visit 1 and Visit 2 per year" variables are defined as (Value at Visit 2-Value at Visit 1) / Time between Visit 1 and Visit 2 in years. Variables are expressed as mean and standard deviation for continuous normally distributed variables, median, and interquartile range (25th to 75th percentile) for continuous non-normally distributed variables, and percentages for categorical variables. *P*-values are obtained using *t*-test for the continuous normally distributed variables, Wilcoxon rank sum test for the continuous non-normally distributed variables, and Chi-square test for the proportions. *P*-values < 0.05 are **bolded** and *italicized*.

Definitions: Emphysema is the percentage of computed tomography low attenuation area below -950 Hounsfield units at end-inspiration using Thirona software (% LAA-950); U/L ratio is the ratio of %LAA-950 in upper lung third to %LAA-950 in lower lung third; Airway wall thickening area percentage is the percentage of the wall area compared with the total bronchial area for segmental airways; Pi10 is the square root of the wall area of a hypothetical airway of 10-mm internal perimeter. Exacerbation frequency is the percentage of participants reporting at least one COPD exacerbation in the previous year; Metabolic syndrome=3 of these 4: BMI ≥ 30 (measured), diabetes mellitus, hypertension, and high cholesterol (all self-report); obesity= BMI≥30.

BMI=body mass index; %LAA-950=low attenuation area below -950 Hounsfield units; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; mMRC=modified Medical Research Council; SGRQ=St George's Respiratory Questionnaire; GOLD=Global initiative for chronic Obstructive Lung Disease; PRISm=preserved ratio-impaired spirometry

Figure 2. Histograms of Change in Forced Expiratory Volume in 1 Second[a] Between Visit 1 and Visit 2 and Between Visit 2 and Visit 3

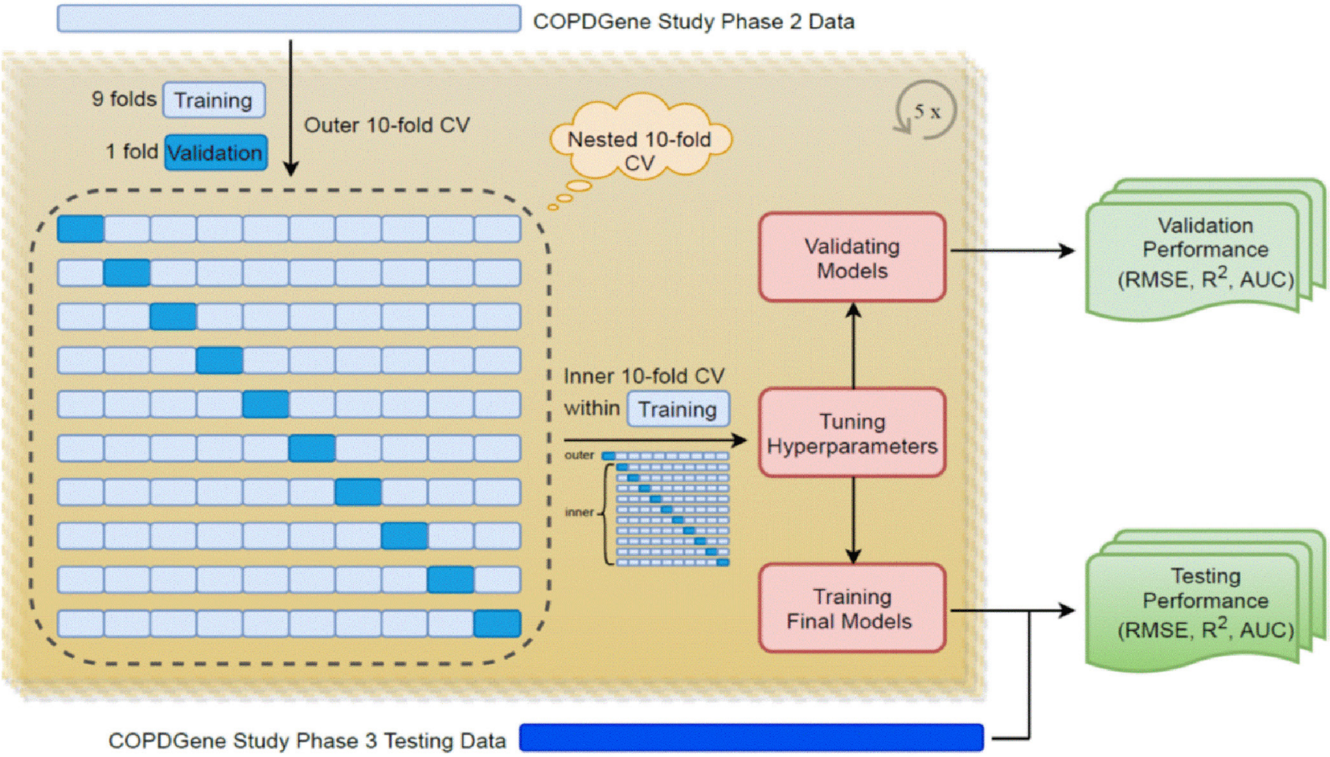




[a] ΔFEV_1; mL/year

FEV_1=forced expiratory volume in 1 second

Figure 3. Random Forest Modeling Framework



RMSE=root mean square error; AUC=area under the curve; COPDGene=COPD Genetic Epidemiology study

Table 2. Variables Included in the Prediction Algorithms

Demographics:
Age at study enrollment
Sex
Race
BMI
Height
Pack years of smoking
Current smoking
Age at smoking initiation
Family History:
Family history of COPD, chronic bronchitis, or emphysema
Functional Measures:
mMRC Dyspnea Scale
SGRQ
6-minute Walk Distance
COPD Characteristics:
Chronic bronchitis (chronic cough and phlegm for ≥3 months/year for at least 2 consecutive years)
Blue bloater (chronic bronchitis, BMI>25, resting oxygen saturation <90%)
Pink puffer (emphysema>10%, BMI≤20, resting oxygen saturation ≥90%)
Number of COPD exacerbations over the prior year (number of self-reported acute worsening of respiratory symptoms that required the use of antibiotics and/or systemic steroids in the previous year)
History of severe COPD exacerbation (self-report of COPD exacerbation requiring an emergency department visit or hospital admission)
Need for courses of systemic steroids
Poor exercise capacity (6-minute walk distance <500 feet)
Hypoxemia (resting oxygen saturation ≤88%)
Severe early-onset COPD (age<55 years, FEV$_1$<50% predicted)
Comorbidities:
Diabetes mellitus (self-report)
Hypertension (self-report)
Dyslipidemia (self-report)
Pneumothorax (self-report)
Gastroesophageal reflux disease (self-report)
Osteoporosis (self-report)
Coronary artery disease (self-report of heart attack, coronary artery disease, angina, angioplasty, or coronary artery bypass graft)
Congestive heart failure (self-report)
Peripheral vascular disease (self-report)
Metabolic syndrome (3 of these 4: BMI≥30 (measured), self-reported diabetes mellitus, hypertension, and high cholesterol)
Physician diagnosis of asthma before age 40 (Self-report)
Asthma/COPD overlap (Self-report)
Obstructive sleep apnea (Self-report)
Spirometry:
Post-bronchodilator FEV$_1$
Post-bronchodilator FVC
FEV$_1$/FVC
Post-bronchodilator FEF$_{25\%-75\%}$
Pre/Post- bronchodilator FEV$_1$ (% change)
Pre/Post- bronchodilator FVC (% change)
GOLD
Radiology:
Total emphysema (%LAA-950)
Emphysema distribution (upper over lower lung third %LAA-950 ratio)
Gas trapping (percentage of low attenuation area less than -856HU at end-expiration)
CT-measured total lung volumes at end-inspiration
Airway wall thickness (obtained along the center line of the lumen, in the middle third of the airway segment, for one segmental airway of each lung lobe)
Pi10 (square root of the wall area of a hypothetical airway of 10-mm internal perimeter)

BMI=body mass index; COPD=chronic obstructive pulmonary disease; mMRC=modified Medical Research Council; SGRQ=St George's Respiratory Questionnaire; FEV$_1$=forced expiratory volume in 1 second; FVC=forced vital capacity; FEF=forced expiratory flow rate between 25% and 75% of the vital capacity; GOLD=Global initiative for chronic Obstructive Lung Disease; %LAA-950=low attenuation area below -950 Hounsfield units; CT=computed tomography

linear regression and the merit of modeling change in FEV$_1$ compared with modeling follow-up FEV$_1$.

Candidate predictors consisted of variables that were available in the COPDGene population at Visit 1 and had correlation coefficients of less than 0.90 with the other variables. We set the threshold to 0.9 to ensure that only secondary/redundant features are removed, rather than features with potentially complementing information. To confirm this, we reran our experiments with 7 variables removed using a correlation criterion of 0.7 (CT-measured total lung volumes at end-inspiration, FEV$_1$ to forced vital capacity (FVC) ratio, GOLD spirometric grade, airway wall thickness, post-bronchodilator FEV$_1$, sex, and adjusted 15th percentile point (Perc15) density. We found that by setting the correlation threshold to 0.7, the resulting predictive performance decreased, particularly for the follow-up FEV$_1$ (median RMSE increased from 269.71 to 278.60

Table 3. Prediction Performance of Random Forest and Linear Regression in the Cross-Validation Testing Samples and Temporal Validation Cohort

	Random Forest		Linear Regression	
	COPDGene Visit 1 / Visit 2 Testing	COPDGene Visit 2 / Visit 3 Temporal Validation	COPDGene Visit 1 / Visit 2 Testing	COPDGene Visit 2 / Visit 3 Temporal Validation
RMSE				
Follow-up FEV$_1$	269.711 [259.252, 276.476]	236.742	270.166 [260.796, 276.134]	234.978
Change in FEV$_1$ (mL/year)	**46.913** [45.647, 48.795]	**52.289**	48.003 [46.187, 49.262]	52.819
Follow-up FEV$_1$ (indirect)	**258.872** [249.820, 268.046]	**231.377**	263.583 [253.860, 270.307]	233.926
R-squared				
Follow-up FEV$_1$	0.896 [0.890, 0.903]	0.913	0.896 [0.889, 0.903]	0.915
Change in FEV$_1$ (mL/year)	**0.147** [0.126, 0.173]	**0.104**	0.123 [0.097, 0.147]	0.0857
Follow-up FEV$_1$ (indirect)	**0.904** [0.895, 0.912]	**0.917**	0.900 [0.894, 0.909]	0.915
AUC				
Follow-up FEV$_1$	0.974 [0.970, 0.979]	0.975	0.974 [0.970, 0.979]	0.975
Change in FEV$_1$ (mL/year)	**0.706** [0.688, 0.724]	**0.704**	0.698 [0.682, 0.715]	0.685
Follow-up FEV$_1$ (indirect)	**0.977** [0.973, 0.982]	**0.976**	0.975 [0.972, 0.980]	0.976

The derivation cohort (COPDGene Study Visit 1 and Visit 2) was randomly partitioned into training and testing samples using 10-fold cross validation. This procedure was repeated 5 times to account for the random variability of the partitioning procedure. This repeated resampling procedure created an ensemble of 50 models over which we averaged the predictions, and we then validated the performance of this model using data from COPDGene Visit 3 (temporal validation). To predict the outcome values at Year 10 (Visit 3), we entered the participants' 5-year (Visit 2) predictor data into the models trained in the derivation cohort. Besides directly modeling follow-up FEV$_1$ and change in FEV$_1$ (mL/year), we also considered an indirect model on follow-up FEV$_1$ where the prediction from modeling change in FEV$_1$ (mL/year) is arithmetically converted to prediction of follow-up FEV$_1$. The prediction performance for change in FEV$_1$ (mL/year) is shaded with grey color and the best performance in predicting follow-up FEV$_1$ and change in FEV$_1$ (mL/year) are in **bold**.

Variables are expressed as median and interquartile range (25th to 75th percentile) when applicable.

COPD=chronic obstructive pulmonary disease; COPDGene=COPD Genetic Epidemiology study; RMSE=root mean square error; FEV$_1$=forced expiratory volume in 1 second; AUC=area under the receiver operator characteristic curve for prediction of participants in the top quartile of COPD progression

for follow-up FEV$_1$ and from 46.91 to 47.04 for change in FEV$_1$).

Setting the number of trees to the default of 500 provided a good compromise between performance and computational efficiency in our datasets, as evidenced by the 10-fold cross-validation loss curves with respect to the number of trees shown in Figure 1S in the online supplement.

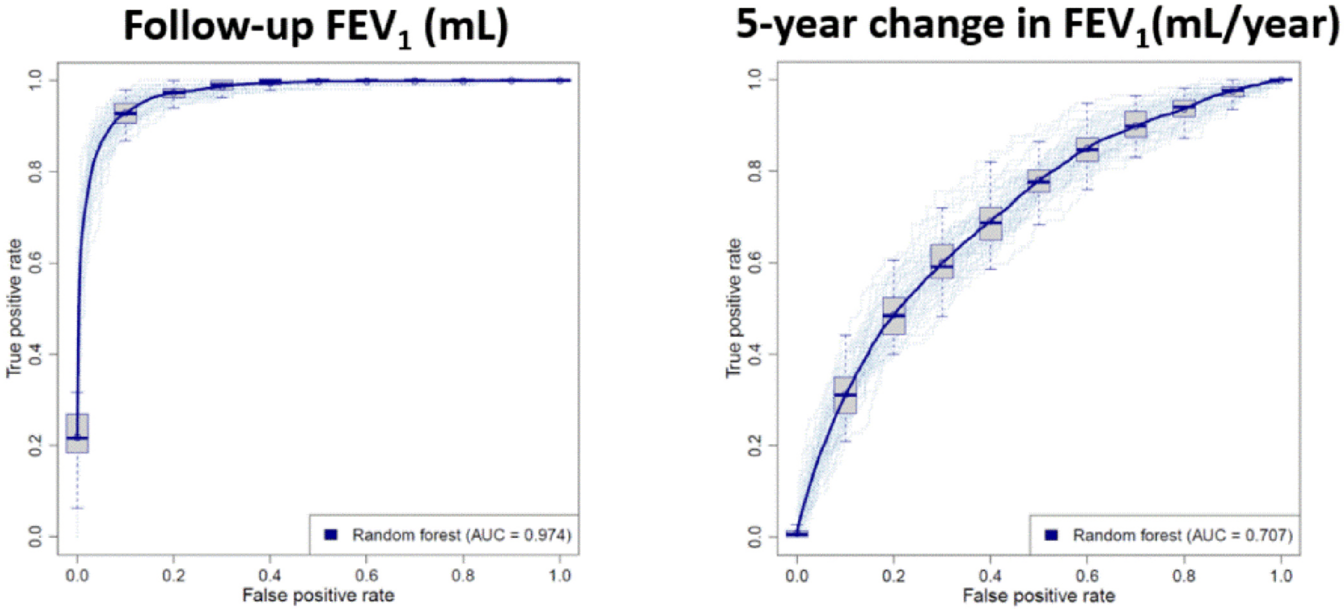
Analysis of Signal to Noise Ratio for 5-year Change in Forced Expiratory Volume in 1 Second

Changes in spirometric measures are more commonly used endpoints in COPD clinical trials. Predicting future FEV$_1$ values is not the same as predicting the changes of FEV$_1$ over the same period, since the ΔFEV$_1$ over a fixed time period generally contributes a relatively small amount to the overall variance of FEV$_1$ at a given time point. Given the often gradual rate of progression of COPD, 5 years is a relatively short observation period, and one of the concerns is that the signal to noise ratio in our progression variables is insufficient for reliable prediction. To determine the signal-to-noise characteristics of our progression variables, we calculated the expected signal-to-noise ratio using previously published values[19] of measurement error for FEV$_1$. An important parameter in these calculations is the extent of correlation in errors between the 2 study measurements. Since empiric data were unavailable, we assumed independence between these errors; therefore, these estimates likely represent a lower bound on the proportion of noise in these measures. We estimated that measurement error accounted for at least 22% of the variance of ΔFEV$_1$ (calculations are included in the supplement). Thus, the theoretical upper bound for prediction performance of ΔFEV$_1$ was 78%.

Important Predictors and Their Effects on Prediction

Figure 5 shows the ranking of the top-20 predictors based on their importance scores in the random forest models. Several of the known COPD disease progression

Figure 4. Receiver Operator Characteristic Curves of the Performance of the Random Forest Follow-up Forced Expiratory Volume in 1 Second and 5-year Change in Forced Expiratory Volume Models[a]



[a]Correctly identified participants in the top quartiles of spirometric progression in the COPDGene Visit 1/Visit 2 cross-validation testing samples.
Solid lines represent the average performance, and colored dots represent the performance in each of the sampling iterations.
FEV_1=forced expiratory volume in 1 second; AUC=area under the curve

risk factors were present as top-ranked risk factors in our models and other new predictors were identified. The most important variables for FEV_1 progression included baseline spirometry, CT-measured total lung volume, bronchodilator responsiveness, gas trapping, total emphysema, and smoking exposure. Variables like the number of COPD exacerbations in the prior year, selected comorbidities, and dyspnea scores were of less importance.

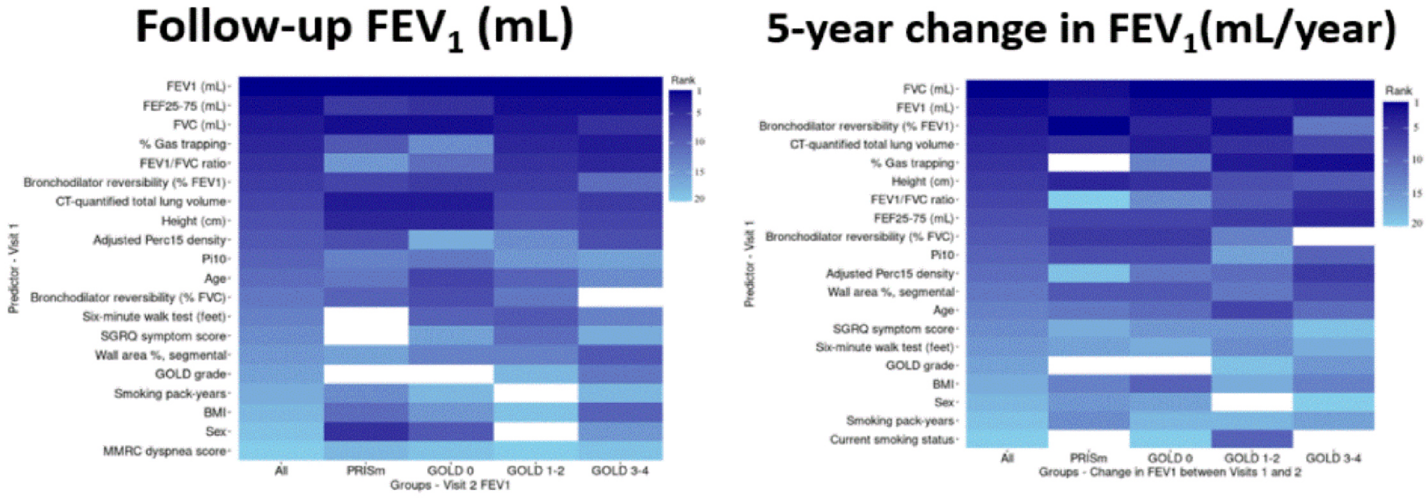
Prediction of COPD Progression Stratified by Global Initiative for Chronic Obstructive Lung Disease Grade

To determine whether progression was determined by different variables at different GOLD spirometric grades, we examined the performance of random forest prediction models for pre-specified subgroups of smokers stratified by GOLD grade (n=4496 [*Overall*], 499 [*preserved ratio-impaired spirometry (PRISm)]*, 2116 [*GOLD 0*], 1318 [*GOLD 1-2*], and 563 [*GOLD 3-4*]). We observed significant differences in predictive performance across these subgroups. The model performance accuracy was best for GOLD 1–2 and it was harder to achieve accurate prediction in advanced stages of the disease. The area under the ROC curves for the prediction of participants in the top quartile of disease progression was 0.66 (GOLD 0), 0.73 (GOLD 1–2), and 0.58 (GOLD 3–4). The predictors of disease progression were also different by GOLD grade (Figure 5). For instance, bronchodilator responsiveness seems to be less important and emphysema and airway disease more important in the prediction of ΔFEV_1 in participants at more advanced stages of the disease.

Effects of Accounting of Smoking Status in Both Baseline and Follow-up Visits on the Prediction Performance

At Visit 1, 47% of the studied participants were current smokers and 53% were former smokers. At Visit 2, 37% of the studied participants were current smokers and 63% were former smokers. At Visit 3, 30.6% of the studied participants were current smokers and 69.4% were former smokers. In terms of change of the smoking status between visits, 35% remained current smokers at

Figure 5. Heatmaps of the Top-20 Predictors of Visit 2: (A) Forced Expiratory Volume in 1 Second[a] and (B) Change in Forced Expiratory Volume in 1 Second[b]



[a] mL
[b] mL/year

The x-axis contains the group assignments (All, PRISm, GOLD0, GOLD 1-2, and GOLD 3-4). The y-axis includes the top-20 predictors ranked by their importance scores in the predictive models built in the "All" group (decreasing order with the best predictors on top). Darker shades of blue indicate a higher rank of the predictor. White cells indicate variables that do not fall within the top-20 ranks. The sample sizes were [n=4,496 (*All*), 499 (*PRISm*), 2116 (*GOLD 0*), 1318 (*GOLD 1-2*), and 563 (*GOLD 3-4*)].

Definitions: Bronchodilator reversibility (%) FEV_1 is the percentage of participants with post-bronchodilator increase in FEV_1 of at least 12% from baseline. Adjusted Perc15 density is the cut off value in HU below which 15% of all voxels are distributed on a lung CT scan (per convention, adjusted Perc15 density values are reported as the HU + 1000). Gas trapping (%) is the percentage of lung voxels with a density less than -856 HU at end exhalation. Pi10 is the square root of the wall area of a hypothetical airway of a 10-mm internal perimeter; % Segmental airway wall thickness is the percentage of the wall relative to the total bronchial area for the segmental airways.

FEV_1=forced expiratory volume in 1 second; $FEF_{25\%-75\%}$=forced expiratory flow at 25%–75% of forced vital capacity; CT=computed tomography; SGRQ=St George's Respiratory Questionnaire; GOLD=Global initiative for chronic Obstructive Lung Disease; BMI=body mass index; mMRC=modified Medical Research Council; PRISm=preserved ratio-impaired spirometry; HU=Hounsfield units

Visit 1 and Visit 2 and 50.7% remained former smokers at Visit 1 and Visit 2. A total of 11.9% were current smokers at Visit 1 and former smokers at Visit 2 and 2.2% were former smokers at Visit 1 and current smokers at Visit 2. A total of 27.9% of studied participants remained current smokers at Visit 2 and Visit 3 and 63% remained former smokers at Visit 2 and Visit 3. A total of 6.4% were current smokers at Visit 2 and former smokers at Visit 3 and 2.7% were former smokers at Visit 2 and current smokers at Visit 3. We reran our prediction models adding the smoking status variable at Visit 2 in the derivation cohort (and Visit 3 smoking status for the temporal cohort). No major effect on the prediction performance was noted as shown in Table 1S in the online supplement.

Discussion

This current study showed that the prediction of change in FEV_1, which is more relevant for disease progression, is more challenging than predicting the absolute FEV_1 level. Our prediction models for ΔFEV_1 represent the current state of the art for prediction of prospective change in FEV_1. But there is significant room for improvement in future models. The most important predictive variables came from a wide range of clinical, spirometric, and imaging features. Baseline spirometry, CT-measured total lung volumes, and bronchodilator responsiveness dominated the prediction. In addition, the predictive performance and the relative importance of predictors differed by GOLD grade.

Several screening tools are available to identify patients with undiagnosed COPD and to predict outcomes in patients with COPD.[1,8,9,20-25] While Zafari et al and Chen et al developed and validated risk models to accurately predict lung function trajectory,[8,9] our study is the first to apply advanced machine learning methods, use an extensive set of phenotypic measurements and comorbidities, predict not only the follow-up values but also the more relevant change variables, and identify the relative importance of the predictors at various stages of the disease. With respect to the outcomes evaluated in these 2 papers, our predictive models gave similar performance for the prediction of future values of FEV_1. Our study added the prediction of prospective changes in FEV_1 that were not reported in these previously published studies. Predicting the change over time is more challenging than simply predicting the future value, since the change typically represents a small proportion of the overall variance in a given pair of FEV_1 measurements separated by 5 years or less. However, it is important to assess the ability of models to predict prospective changes since this is an important outcome for clinical trials.

Given the superiority of non-linear models compared with linear models with regards to exploiting complex relationships and interactions among the risk factors,[26] we chose random forest as our primary model due to its flexibility and generalizability, and the fact that the interpretation of decision trees are more natural to clinicians than some of the other black-box models. Despite hundreds of trees, the ensemble method (bagging) and the base learner (decision tree) in random forest are easier to understand and interpret than many other black-box models with more sophisticated ensemble methods (e.g., boosting) or base learners (e.g., kernels, neural networks).[27] The similar performance of cross-validation and temporal validation attests to the generalizability of our models rather than overfitting, which would result in poor temporal validation performance compared to cross-validation performance. The sharp performance gap between predicting follow-up FEV_1 and (rate of) change in FEV_1 seems nonintuitive at first glance. To explain this in other terms, imagine that a predictive model for change in height was developed for a cohort of adults. A model that predicted "height 5 years from baseline" by simply substituting the baseline height value would be very accurate, since there is little to no change in adult height over that timeframe. While FEV_1 does change over a 5-year timeframe, the absolute amount of change is usually small relative to baseline FEV_1 volumes. Thus, predicting the *total* FEV_1 in 5 years is a much easier (but less clinically relevant) problem than predicting the *change* in FEV_1 over 5 years. The key rationale is that 5 years is a short time period in terms of COPD progression, leading to a high correlation of FEV_1 values between 2 visits (therefore, high prediction performance with follow-up FEV_1) and a low signal-to-noise ratio in the FEV_1 5-year progression measurements (hence, poor prediction performance with change in FEV_1). Despite this, there may still be merit in modeling the change in FEV_1 even with a short 5-year period, as we found a modest improvement in predicting follow-up FEV_1 using models built to predict change in FEV_1 that can then be transformed to follow-up FEV_1 (median RMSE: 258.87 and 231.38 for follow-up FEV_1 at Visit 2 and Visit 3, respectively). This improvement could be attributed to the change in FEV_1 models taking into account the uneven time lapse between visits.

Random forests offer superior prediction of disease progression relative to linear regression, and this improved performance stems from the ability of these models to more efficiently capture non-linear interactions between predictors. The predictive accuracy of our models may potentially be further improved by including additional predictors (such as DLCO, pulmonary vascular measures, and relevant molecular biomarkers) and exploring other machine learning algorithms (such as deep learning). At present, these models are not ready for clinical use but could be useful in the design of COPD clinical trials to enrich the study populations by patients who are most likely to experience rapid disease progression and benefit from therapeutic interventions. For clinical use, better performing models that have been more extensively validated in multiple additional and relevant target populations are necessary.

Rapid decline in lung function has previously been associated with a range of factors such as smoking exposure, bronchodilator reversibility, higher baseline FEV_1, higher baseline FVC, exacerbations in the prior year, low body mass index (BMI), African American race, female sex, emphysema, upper lobe emphysema predominance, and CT-detected small airway abnormalities.[5,6,8,28-33] Our study detected several of these known COPD disease progression risk factors and identified other new predictors for FEV_1 decline. Our study is the first, to our knowledge, to demonstrate that the patterns of predictors vary by GOLD spirometric grade. The intriguing variations in the importance of different risk factors depending on the studied subgroup may help inform further exploration of predictive risk factors and future development of new risk prediction algorithms.

Compared to participants in the bottom quartile of ΔFEV_1, those in the top quartile (rapid FEV_1 progressors) had less severe spirometric impairment and more advanced radiologic disease (total emphysema and gas trapping) at baseline. It is possible that the association of less severe spirometric impairment at baseline with more rapid FEV_1 progression is an artifact related to the inability to lose sufficient FEV_1 at the same rate compared to when disease is more severe (a physiologic floor in FEV_1 which, once reached, results in a diminished FEV_1 response to additional cigarette exposure). It is also possible that the association between more severe emphysema with more rapid FEV_1 decline may represent a "winner's curse." However, it is important to note that baseline FEV_1 was accounted for in our analyses as this variable was among the predictors in the prediction models. In addition, the fact that our cross-validation and temporal validation performances are similar argues against the presence of large winner's curse effects.

The relative unimportance of certain traditional risk factors such as COPD exacerbations in the prior year, selected comorbidities, race, and sex in our machine learning predictive models may be consistent with the disparate results from previous studies. For example, although some publications have suggested a significant excess loss of FEV_1 for each COPD exacerbation,[29,34,35] others have reported minimal 6 or no relationship.[36] Such discrepancy may also result from differences in methodology between studies as well as differences in sample size, study duration, study population, and variable definitions. The relative unimportance of certain traditional risk factors in our models may also indicate that, while these risk factors may attain statistical significance in some models, they do not provide much additional predictive value after considering more important risk factors.

Dimensionality and collinearity are important factors to consider in building and interpreting prediction models. While our data has a reasonable dimensionality in respect to the sample size, random forest performs well with high dimensional data.[37] Collinearity is more of a challenge for interpreting the feature relevance ratings than the prediction performance. It is worth noting that the permutation-based feature importance scores we utilized in this study capture the marginal importance of a feature; additional approaches for capturing conditional/partial feature importance in the presence of associated features have been proposed.[18] However, there is a heuristic component to these diverse feature importance scoring techniques, and there is currently no consensus or clear theoretical underpinning for them. It has been argued that there is a marginal-partial feature importance dimension, and the researcher must determine where he/she falls on this dimension based on his/her perspective on variable importance and the research question under consideration.[38]

The random forest's tunability of the number of trees hyperparameter has not been thoroughly investigated until recent years. For mean squared error loss in regression (and other loss functions in classification), it has been theoretically proven that increasing the number of trees does not lead to overfitting and that setting it to a computationally feasible large number is more favored than tuning the hyperparameter.[39] Setting the number of trees to the default of 500 provided a good compromise between performance and computational efficiency in our datasets.

This study has a number of strengths. Analyses were performed within a well-characterized cohort that included participants at all stages of disease severity. In addition, by focusing on prediction rather than the study of individual risk factors, our results provide useful context regarding the relative importance of specific predictors. By constructing models in participants stratified by GOLD spirometric grade, we demonstrated that patterns of optimal predictors vary by specific disease outcome and GOLD grade. Validation of our findings in the temporal cohort represents another strength of our paper.

Our study also has limitations. We only used 2 measurements of lung function separated by approximately 5 years. The large sample size available helped to overcome some of the inherent challenges in low signal-to-noise ratio with studies of COPD progression over a relatively short period of time. However, with longer follow-up and more measurements in future studies, we will be better able to isolate measurement noise from real disease progression which will result in greater predictive accuracy. Our analysis was based on participants who had completed their second study visit, and it is possible that patients who were lost to follow-up differed from those available for analysis. Many of the patients with airflow obstruction were receiving therapy for their disease. Although no existing pharmacotherapy has been conclusively shown to affect the rates of disease progression, this still may have influenced our results. However, we chose not to include pharmacotherapy data in these analyses in order to reduce biases likely present in patient-reported pharmaco-epidemiologic data.[40,41] It is recognized that as the number of potential risk factors increases, the complexity of the models can cause overfitting. We addressed this by appropriate hyperparameter tuning and by evaluating the performance of our predictive models in cross-validation and in the temporal cohort. Lastly, because COPDGene is one of the few available studies with deeply phenotyped participants at all stages of disease severity, extensive clinical, spirometric, and imaging features, and follow-up data, there is currently no other appropriate replication cohort for the analyses performed, and lack of validation in an independent set of participants limits the generalizability of our findings. It will be important for future investigations to validate these findings in independent large cohorts of similarly well-characterized smokers with the same or greater length of follow-up time.

Conclusion

Random forest machine learning in conjunction with deep phenotyping improves the prediction accuracy of COPD progression. The present study improves our ability to identify patients at risk for rapid disease progression, and these models may be useful for the development of targeted disease-modifying therapies.

Acknowledgements

Author Contributions: Drs. Boueiz and Castaldi had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. COPDGene investigators were instrumental in the design and implementation of the COPDGene study and collected and analyzed data cited in this article. All authors have reviewed, approved and endorsed all content and conclusions of this article.

The authors wish to thank the thousands of patients who participated in the COPDGene study over the last 10 years.

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Declaration of Interest

Dr. Castaldi reports grants from the National Institutes of Health during the conduct of the study, grants and other from GlaxoSmithKline, and personal fees from Novartis, outside the submitted work. Dr. Silverman reports grants from the National Institutes of Health during the conduct of the study, and grants and other from GlaxoSmithKline, outside the submitted work.

All other authors have nothing to disclose.

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