Online Supplement
Changes in Lung Volumes with Spirometric Disease Progression in COPD

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Study design

Lung volumes measured by plethysmography in seated posture extractable from the VA EHR PFT data (n=71,356) and lung volumes measured by CT in supine posture from the COPDGene (n=7,969) and SPIROMICS (n=2,552) cohorts were examined over the spectrum of the spirometric airflow obstruction. VA EHR PFT data contained total lung capacity (TLC), VC, IC, residual volume (RV), and functional residual capacity (FRC). COPDGene CT data contained TLC and FRC while SPIROMICS CT data contained TLC and RV.

Longitudinal changes in the lung volumes were computed for patients/subjects who had *both* spirometric *and* lung volume data available in a follow-up visit. For SPIROMICS cohort, although spirometry data were available from multiple visits, lung volumes measurements were only available at baseline and 1-year follow-up visits (the 5-year SPIROMICS II CT-measured lung volumes were not available at the time of this analysis). For COPDGene cohort, CT-measured lung volumes were available from three visits (baseline, 5-year, and 10-year visits), although there was a significant decrease in the number of participants at the 10-year visit at the time of this analysis. For VA EHR cohort, we identified the patients with available full PFT data ≥1 year or ≥3 years after their index PFT. These timeframes were chosen to match the follow-up time intervals available from the SPIROMICS and COPDGene cohorts.

In all three cohorts, patients/subjects with preserved ratio and impaired spirometry or PRISm (those with normal FEV_1/FVC but reduced FEV_1, as defined originally by COPDGene investigators)[1] were excluded from this analysis, as they may have had a “restrictive” impairment affecting their lung volumes. Similarly, patients/subjects who showed improvements in their

follow-up spirometry, resulting in an improvement in their GOLD stage, were also excluded from this analysis, as they may represent a subgroup with a reversible disease pathology distinct from the rest of the cohort. Overall, the longitudinal analysis included those whose spirometry in follow-up visit stayed the same or worsened.

VA EHR study design details

The procedural details of the VA EHR data extraction have been previously described.[2] For the current study, retrospective VA EHR data available from the nationwide VA Informatics and Computing Infrastructure (VINCI) database between January 1, 1985 and March 1, 2020 were interrogated for all patients at risk for COPD, defined as ever smokers ≥40 and <90 years of age, who had at least one full PFT with body plethysmography performed at ≥40 years of age available in VINCI database. Patient ≥90 years of age at the time of their first spirometry were excluded due to concerns about the validity of determination of spirometric COPD based on any reference equations. Smoking status was assigned based on documented International Statistical Classification of Diseases and Related Health Problems (ICD)-9th and ICD-10th revisions diagnosis codes for smoking, report of smoking in VA EHR "Health Factor", or recorded diagnosis of smoking on PFT report. Ever smoker status was defined by having at least one smoking diagnosis documented in the EHR using the above criteria. Patients with diagnoses of restrictive, fibrotic, or interstitial lung diseases as documented by ICD-9 or ICD-10 diagnosis codes, or allergic lung diseases (except for asthma) were excluded. Patients with diagnosis of asthma who were considered to be at risk for COPD were not excluded to avoid exclusion of those with overlap disease. Detailed list of ICD-9 and ICD-10 codes used are available at the end of Supplemental Methods below.

Medical records of eligible patients were interrogated to identify the very first PFT that included pre- and post-albuterol spirometry and lung volume measurement by plethysmography. Full PFT data including plethysmography were available from 37 Veterans Affairs Medical Centers across the United States. Data from other Veterans Affairs Medical Centers were not used due to lack of availability of coded PFT data that would be obtainable through VINCI.

For cross-sectional analysis, data were derived from all patients identified as described above. For longitudinal analysis, data were derived from a subset of the identified patients who had a repeat set of PFT including pre- and post-bronchodilator spirometry and plethysmography ≥1 year and ≥3 years after their index PFT. These timeframes were chosen to provide follow-up time intervals that would be relevant to those available from the COPDGene and SPIROMICS cohorts, as described below.

The University of California San Francisco Institutional Review Board (IRB) and the Veterans Health Administration Research and Development Committee approved this study.

COPDGene Study Design

The COPDGene study is a U.S.-based multicenter observational prospective study designed to identify genetic factors associated with COPD that has enrolled 10,263 current and former smokers with or without a reported COPD diagnosis.[10] The COPDGene study inclusion criteria were: non-Hispanic White or African-American, current or former smokers (≥10 pack-years), and age 45 to 80 years. Subjects reporting a medical diagnosis of active lung diseases other than asthma, emphysema, chronic bronchitis, or COPD were excluded (e.g., lung cancer). The goals of the COPDGene study have been to characterize phenotypes of tobacco smokers using spirometry, chest computerized tomographic (CT) scans (at full inspiration [TLC] and

normal exhalation [FRC]), medical history and questionnaires regarding respiratory symptoms and to perform genome-wide association studies (GWAS). Furthermore, baseline plethysmographic lung volume measurements were performed in a limited number of subjects at a single center in COPDGene study and were available for analysis (n=391). No follow-up plethysmographic lung volume measurements were available from COPDGene cohort. Local IRB approvals to enroll participants in COPDGene study were obtained and all subjects provided informed consent to participate in the study.

For cross-sectional analysis, data were derived from all enrolled subjects who had a history of smoking tobacco, had undergone pre- and post-bronchodilator spirometry (two inhalations of albuterol 90 μg per inhalation with repeat spirometry 15 minutes later), and had baseline chest CT imaging with radiographic lung volumes (TLC and FRC) available. For longitudinal analysis, data were derived from subjects who had completed their 5-and 10-year follow-up visits (visits 2 and 3, respectively) and had pre- and post-bronchodilator spirometry and chest CT imaging with radiographic lung volumes (TLC and FRC) available.

SPIROMICS Study Design

SPIROMICS is a multicenter observational study that enrolled 2,975 participants from 2010 through 2015.[11] The study included persons 40 to 80 years of age who were either never-smoking healthy persons or current and former smokers who had a smoking history ≥20 pack-years, with or without a clinical diagnosis of obstructive lung disease. Participants were categorized using the GOLD staging system according to the results on spirometry performed before and after four inhalations each of albuterol 90 μg per inhalation and ipratropium 18 μg per inhalation.[3] Current asthma was an exclusionary criterion but current and former smokers who

had a concomitant diagnosis of asthma earlier in life were not excluded. CT thoracic images at full inspiration (TLC) and full exhalation (RV) were obtained following administration of the same regimen of short-acting bronchodilators used for measurement of post-bronchodilator spirometry. Subjects were followed for a target follow-up time of three years with planned annual serial spirometry and symptoms questionnaires, as previously described.[4,5] The current analysis does not include data from SPIROMICS 2 study.

For cross-sectional analysis, data were derived from all enrolled subjects who had a history of smoking tobacco, had undergone pre- and post-bronchodilator spirometry, and had chest CT imaging with radiographic lung volumes (TLC and RV) available. For longitudinal analysis, data were derived from subjects who had completed their 1-year follow-up visit (visit 2), underwent pre- and post-bronchodilator spirometry, and had chest CT imaging with radiographic lung volumes (TLC and RV) available.

CT Indices of Lung Volumes, Air Trapping, Emphysema, and Small Airways for COPDGene and SPIROMICS Cohorts

The detailed protocol and quality assessment of COPDGene CT scans have been described previously.[6] Briefly, subjects underwent two volumetric chest CT examinations, one at full inspiration (TLC) and one at the end of a normal expiration (FRC). Three manufacturers and 11 different CT scanner models were used in the study including with 16-detector (1,083 subjects), 40-detector (12 subjects), 64-detector (1667 subjects), and 128-detector (1300 subjects) scanners.[7] Anonymized scans were transferred to a central imaging laboratory for quantitative analysis using a standardized protocol with image reconstruction at sub-millimeter slice thickness with smooth and edge-enhancing algorithms.[6-8]

The detailed protocol and quality assessment of SPIROMICS CT scans have been described previously.[9] Briefly, SPIROMICS has an established quantitative CT lung assessment system (QCT-LAS), which includes scanner-specific imaging protocols for lung assessment at TLC and RV. Written breath-holding instructions were supplied to the CT technologists, who were instructed to coach the subject, as in a pulmonary function laboratory, to achieve both TLC and RV with a series of proceeding deep inspirations. To provide imaging speeds that allow proper breath-holds from subjects, only 64-detector rows or higher scanners were used.

Spirometry gating of the CT scan acquisition was not performed in either COPDGene or SPIROMICS studies.

Statistical Analysis

Predicted values and ranges for PFT measurements for spirometry and lung volumes in VA EHR data were calculated using NHANES and Stocks and Quanjer predicted formulas, respectively;[10,11] COPDGene and SPIROMICS used NHANES reference equations for calculation of spirometric percent predicted values.[10] Percent predicted of normal values for CT measured lung volumes in the COPDGene and SPIROMICS were not available. Bronchodilator responsiveness was defined as ≥12% and ≥200mL increase in FEV_1 after bronchodilators administration as a matter of consistency with previous publications from these cohorts.

For cross-sectional analyses, the distributions of the baseline lung volumes were examined across airflow obstruction as measured by the post-bronchodilator FEV_1 as a continuous variable. To understand the nature of relationship between lung volumes and spirometry variables, we performed a Locally Weighted Scatterplot Smoothing (LOWESS) analysis of the relative distribution of the lung volume variables versus FEV_1 and found that

many lung volumes variables had a nonlinear association with FEV_1. To generate better fits, we thus chose to examine the association of lung volumes versus partitions of FEV_1 based on the arbitrary but clinically well-known Global Initiative for Obstructive Lung Disease (GOLD) categorization. The GOLD stages were determined using the post-bronchodilator FEV_1 %predicted.[12] To account for random effect of study sites, the comparisons among each of the five baseline lung volume measurements (TLC, VC, RV, FRC, and IC, measured by plethysmography in VA EHR and CT imaging in COPDGene and SPIROMICS) with respect to the baseline GOLD stages were assessed using mixed-effects linear regression, with a random effect of study sites and fixed effect covariates, including age, sex, height, and body mass index (BMI). BMI instead of weight was used as a covariate based on previous studies demonstrating BMI to have significant effects on lung volumes measurements even in people with normal lung function.[13,14] Smoking status (current versus former) was also included as a covariate only in analyses of COPDGene and SPIROMICS data, as it was not available in VA EHR data, although all patients in VA EHR had history of smoking. No adjustment for race or ethnicity was done, as at least one recent study has shown that, compared to a universal approach for adjustment of values, lung function-adjusted for race may less accurately reflect clinically relevant outcomes.[15]

Longitudinal changes in lung volume measurements and additional covariates (including changes in age, height, and BMI) were calculated by subtracting the follow-up values from those from baseline visit. Changes in lung volumes were stratified by the baseline GOLD stages of the patients/subjects and then compared across the subsequent GOLD stages at follow-up visits. To account for random effect of study sites, this analysis was performed using mixed-effects linear regression, with a random effect of sites within each of the three cohorts, and fixed effects of baseline age, sex, height, BMI, and smoking status as well as changes in age, height, BMI, and

smoking status. The same modeling was examined for each of the baseline GOLD stages. To assess the pattern of change in lung volumes from initially mild disease onward, average changes in lung volumes for those smokers with preserved spirometry (denoted for simplicity of comparison terminology as GOLD-0) at baseline with respect to subsequent GOLD stages were examined using one-sample t-tests with the null hypothesis of changes in lung volumes being zero. Comparisons of baseline lung volumes and their longitudinal changes for those patients/subjects with GOLD-0 at baseline with respect to subsequent GOLD stages were examined using two-sample t-tests. P-values and 95% confidence intervals (95% CI) for relative differences from mixed-effects linear regression modeling were estimated by Satterthwaite's degrees of freedom method via R package, 'lmerTest'. Statistical significance was defined as a P-value <0.05.

VA EHR study design details

The International Statistical Classification of Diseases and Related Health Problems (ICD)-9th and ICD-10th revisions diagnosis codes used for the United States Department of Veterans Affairs electronic health records (VA EHR) cohort are listed below:

<u>Diagnosis of COPD</u>

- Chronic obstructive lung disease: ICD-9: 496
- Chronic bronchitis: ICD-9: 491.xx
- Pulmonary emphysema: ICD-9: 492.x
- Chronic bullous emphysema: ICD-9: 429.0
- COPD: ICD-10: J44.0, J44.1and J44.9
- Chronic bronchitis: ICD-10: J41.0, J41.1 and J41.8

- Pulmonary emphysema: ICD-10: J43.0, J43.1, J43.2, J43.8 and J43.9

Diagnosis of tobacco smoking or tobacco use

- Tobacco use disorder: ICD-9 305.1
- History of tobacco use: ICD-9 V15.82
- Tobacco: ICD-9 989.84
- Smoking cessation counseling: ICD-9 V65.42
- Tobacco Use: ICD-10 Z72.0
- Tobacco Abuse Counseling: ICD-10 Z71.6
- Nicotine dependence, cigarettes: ICD-10 F17.21
- Nicotine dependence, other tobacco product: ICD-10 F17.29
- Nicotine dependence, unspecified: ICD-10 F17.20
- Personal History of Nicotine Dependence: ICD-10 Z87.891

Diagnosis of asthma

- Asthma: ICD-9: 493.xx (493.1 was excluded)
- Bronchospasm: ICD-9: 519.11
- Asthma: ICD-10: J45.909, J45.998
- Unspecified asthma: ICD-10: J45.90
- Cough variant asthma: ICD-10: J45.991
- Acute bronchospasm: ICD-10: J98.01
- Moderate persistent asthma, uncomplicated: ICD-10: J45.40
- Mild intermittent asthma with status asthmaticus: ICD-10: J45.22

- Mild intermittent asthma, uncomplicated: ICD-10: J45.20
- Unspecified asthma with status asthmaticus: ICD-10: J45.902
- Unspecified asthma with (acute) exacerbation: ICD-10: J45.901

Diagnosis of ILD

- ILD: ICD-9: 518.89, 508.1, 714.81, 770.7
- Hypersensitivity pneumonitis: ICD-9: 495
- Silicosis: ICD-9: 502
- Asbestosis: ICD-9: 501
- Berylliosis: ICD-9: 503
- Sarcoidosis: ICD-9: 135
- Acute interstitial pneumonitis: ICD-9: 516.3
- Hamman-Rich Syndrome: ICD-9: 516.3
- Post Inflammatory Pulmonary Fibrosis: ICD-9: 515
- ILD: ICD-10: J84.9
- Pneumoconiosis due to other dust containing silica: ICD-10: J62.8
- Pneumoconiosis due to asbestos and other mineral fibers: ICD-10: J61
- Berylliosis: ICD-10: J63.2
- Sarcoidosis, unspecified: ICD-10: D86.9
- Pulmonary fibrosis, unspecified: ICD-10: J84.10
- Other specified interstitial pulmonary diseases: ICD-10: J84.89
- Interstitial emphysema: ICD-10: J98.2
- Respiratory bronchiolitis interstitial lung disease: ICD-10: J84.848; J84.115

- Other interstitial pulmonary diseases with fibrosis in diseases classified elsewhere: ICD-10: J84.17
- Acute interstitial pneumonitis: ICD-10: J84.114
- Idiopathic pulmonary fibrosis: ICD-10: J84.112

Diagnosis of AERD

- Samter's triad, Exacerbated Respiratory disease, Samter's Syndrome: ICD-9: 493.1
- Other specified respiratory disorders: ICD-10: J98.8

Diagnosis of ABPA

- Allergic bronchopulmonary aspergillosis: ICD-9: 518.6
- Allergic bronchopulmonary aspergillosis: ICD-10: B44.81

Cystic fibrosis

- ICD-9: 277.0
- Cystic fibrosis: ICD-10: E84
- Congenital cystic lung: ICD-10: Q33.0

Diagnosis of Lung Cancer

- Lung cancer: ICD-9: 162, 162.2, 162.3, 162.4, 162.5, 162.8, 162.9
- Lung cancer: ICD-10: C34.00, C34.10, C34.20, C34.30, C34.80, C34.90
- Malignant neoplasm of pleura: ICD-9: 163
- Malignant neoplasm of pleura: ICD-10: C38.4

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SUPPLEMENTAL TABLES

Table S1- Characteristics of patients in longitudinal follow-up in VA EHR.

VA EHR	Baseline (V1)	One-year Follow-up (V1 + ≥1 year)	Three-year Follow-up (V1 +≥3 years)
Demographics			
Number of Subjects (N)	71,356	8,902	4,612
Age (years)	63.4±10.0	65.9±9.1	66.5±8.8
Sex [Female n (%)]	2,634 (3.7%)	328 (3.7%)	172 (3.7%)
Height (cm)	176±8	176±7	176±7
Weight (kg)	86.3±19.8	86.5±19.9	86.3±19.9
BMI (kg/m^2)	27.9± 6.0	28.0±6.1	27.9±6.1
Years of Follow-up	-	3.9±2.6	5.6±2.5
Spirometric indices			
FEV_1 (L)	2.24±0.85	1.90±0.80	1.91±0.78
FEV_1 (% predicted)	68±25	59±23	60±23
FVC (L)	3.60±0.93	3.35±0.92	3.38±0.92
FVC (% predicted)	82±18	78±19	79±19
FEV_1/FVC	0.61±0.14	0.56±0.14	0.56±0.14
FEV_1/FVC (% predicted)	81±18	74±19	74±18
FEF_{25-75} (L)	1.49±1.10	1.11±0.91	1.10±0.88
FEF_{25-75} (% predicted)	54±40	43±34	43±33
Bronchodilator responsiveness by FEV_1 (mL)	155±204	147±183	151±180
Bronchodilator responsiveness by FEV_1 (%)	9.2±12.8	10.3±13.4	10.3±13.0

No. of subjects w bronchodilator responsiveness by FEV_1 [n (%)]	18,142 (25.4%)	2,348 (26.4%)	1,236 (26.8%)
Lung volume indices by plethysmography			
IC (L)	2.61±0.81	2.41±0.77	2.39±0.77
TLC (L)	6.76±1.41	6.77±1.44	6.81±1.44
TLC (% predicted)	98±19	98±20	99±20
RV (L)	3.22±1.30	3.46±1.36	3.48±1.34
RV (% predicted)	131±51	138±53	138±52
RV/TLC	0.47±0.13	0.50±0.13	0.50±0.12
RV/TLC (% predicted)	120±31	126±32	126±30
FRC (L)	4.15±1.34	4.36±1.39	4.42±1.39
FRC (% predicted)	116±36	121±38	123±37
FRC/TLC	0.61±0.11	0.64±0.11	0.64±0.11
FRC/TLC (% predicted)	106±19	111±19	111±18
VC (L)	3.54±0.93	3.31±0.90	3.33±0.90

Footnote: Data from subjects of three cohorts are presented as mean ± standard deviation or number of patients with positive value for the variable (n) out of the total number of patients (N) and percentage of patients (%). Reference equations: for VA EHR, percent predicted of normal values of spirometry and lung volumes were calculated using NHANES and Quanjar predicted formulas, respectively.[10,11] Bronchodilator responsiveness was defined as ≥12% and ≥200mL increase in FEV_1 after bronchodilators administration. Abbreviations: BMI=body mass index; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; FEF_{25-75}=maximum airflow at mid-lung volume; FEF_{75}=maximum airflow after 75% of lung volume exhaled;

IC=inspiratory capacity; TLC=total lung capacity; RV=residual volume; FRC=functional residual capacity; VC=vital capacity.

Table S2- Characteristics of subjects in longitudinal follow-up in COPDGene.

COPDGene	All V1	V2	V3
Demographics			
Number of Subjects (N)	7,969	3,712	750
Age (years)	60.1 ± 9.1	65.5 ± 8.7	69.9 ± 8.3
Sex [Female n (%)]	3,584 (45.0%)	1,776 (47.8%)	377 (50.3%)
Height (cm)	170 ± 9	169 ± 10	169 ± 10
BMI (kg/m^2)	28.3 ± 5.9	28.4 ± 6.0	27.9 ± 6.0
Years of Follow-up	-	5.53 ± 0.77	10.00 ± 0.35
Current Smoker [n (%)]	4,035 (50.6%)	1,528 (37.5%)	233 (29.0%)
Smoking History (pack-years)	44.7 ± 25.0	44.0 ± 23.8	45.2 ± 22.8
Spirometric indices			
FEV_1 (L)	2.27 ± 0.97	2.19 ± 0.90	2.06 ± 0.87
FEV_1 (% predicted)	77 ± 27	80 ± 27	80 ± 28
FVC (L)	3.41 ± 1.02	3.24 ± 0.97	3.11 ± 0.99
FVC (% predicted)	90 ± 18	90 ± 18	90 ± 20
FEV_1/FVC	0.65 ± 0.17	0.66 ± 0.16	0.65 ± 0.16
FEV_1/FVC (% predicted)	84 ± 21	87 ± 20	86 ± 21
FEF_{25-75} (L)	1.73 ± 1.32	1.67 ± 1.22	1.49 ± 1.13
FEF_{25-75} (% predicted)	65 ± 45	71 ± 48	70 ± 50
Reversibility in FEV_1 (mL)	98 ± 165	98 ± 155	84 ± 131
Reversibility in FEV_1 (%)	6 ± 10	6 ± 9	5 ± 8
Bronchodilator responsiveness by FEV_1 [n (%)]	988 (12.4%)	433 (11.7%)	63 (8.4%)
Lung Volumes indices by CT			
TLC (L)	5.71 ± 1.41	5.65 ± 1.41	5.58 ± 1.45

FRC (L)	3.40 ± 1.14	3.31 ± 1.07	3.45 ± 1.13
FRC/TLC	0.59 ± 0.12	0.58 ± 0.12	0.61 ± 0.12
IC (L)	2.38 ± 0.91	2.38 ± 0.93	2.20 ± 0.88
Average Pi10	2.34 ± 0.62	2.25 ± 0.58	2.30 ± 0.61
PRM^{EMPH}	6.20 ± 10.70	5.40 ± 9.83	-
$PRM^{Air\ trapping}$	17.1 ± 13.7	17.6 ± 13.5	-
Exp_{-856}	23.6 ± 20.5	22.5 ± 19.9	27.0 ± 21.1
$Insp_{-950}$	7.23 ± 10.40	6.41 ± 9.86	8.65 ± 9.94

Footnote: Data from subjects with baseline data and follow-up data are presented as mean ± standard deviation or number of patients with positive value for the variable (n) out of the total number of patients (N) and percentage of patients (%). Reference equations: measures of pulmonary function and percent predicted of normal values were calculated using NHANES predicted formulas.[10] Bronchodilator responsiveness was defined as ≥12% and ≥200mL increase in FEV_1 after bronchodilators administration. Abbreviations: BMI=body mass index; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; FEF_{25-75}=maximum airflow at mid-lung volume; CT=computed tomography; TLC=total lung capacity; FRC= functional residual capacity; IC=inspiratory capacity; Average Pi10= the average for the square root of wall area of a hypothetical airway with 10mm internal perimeter; PRM^{EMPH}=parametric response mapping of functional small airway disease as measures of emphysema; $PRM^{Air\ trapping}$=parametric response mapping of percent air trapping; Exp_{-856}=percent of the lung voxels with attenuation <-856 Hounsfield Unit on the expiratory CT images; $Insp_{-950}$=percent of the lung voxels on inspiratory CT images with attenuation < -950 Hounsfield Units.

Table S3- Characteristics of subjects in longitudinal follow-up in SPIROMICS.

SPIROMICS	All V1	V2
Demographics		
Number of Subjects (N)	2,552	1,748
Age (years)	63.6 ± 8.9	65.0 ± 8.8
Sex [Female n (%)]	1,158 (45.4%)	799 (45.7%)
Height (cm)	170 ± 10	170 ± 10
BMI (kg/m^2)	27.4 ± 5.3	27.9 ± 5.3
Years of Follow-up	-	1.1 ± 0.2
Current Smoker [n (%)]	1,012 (39.7%)	641 (36.7%)
Smoking History (pack-years)	49.3 ± 27.2	49.5 ± 25.8
Spirometric Indices		
FEV_1 (L)	2.09 ± 0.91	2.08 ± 0.89
FEV_1 (% predicted)	73 ± 27	74 ± 26
FVC (L)	3.46 ± 1.02	3.46 ± 1.01
FVC (% predicted)	92 ± 19	93 ± 18
FEV_1/FVC	0.59 ± 0.17	0.59 ± 0.17
FEV_1/FVC (% predicted)	78 ± 21	78 ± 21
FEF_{25-75} (L)	1.40 ± 1.14	1.37 ± 1.12
FEF_{25-75} (% predicted)	56 ± 42	57 ± 43
Reversibility in FEV_1 (mL)	192 ± 171	187 ± 160
Reversibility in FEV_1 (%)	13.2 ± 13.9	13 ± 13
Bronchodilator responsiveness by FEV_1 [n (%)]	785 (30.8%)	511 (29.2%)
SVC (L)	3.53 ± 1.05	3.55 ± 1.05
Lung Volumes indices by CT		
TLC (L)	5.09 ± 1.33	5.08 ± 1.32
RV (L)	2.78 ± 1.15	2.73 ± 1.12
RV/TLC	0.54 ± 0.15	0.54 ± 0.14
VC (L)	2.31 ± 0.93	2.34 ± 0.90

Average Pi10	3.72 ± 0.10	3.72 ± 0.10
PRM^{EMPH} (%)	6.8 ± 10.7	/
PRM^{fSAD} (%)	21.1 ± 15.3	/
Exp_{-856}	25.7 ± 21.7	25.2 ± 21.4
$Insp_{-950}$	8.3 ± 10.5	8.2 ± 10.4

Footnote: Data from subjects with baseline data and follow-up data are presented as mean ± standard deviation or number of patients with positive value for the variable (n) out of the total number of patients (N) and percentage of patients (%). Reference equations: measures of pulmonary function and percent predicted of normal values were calculated using NHANES predicted formulas.[10] Bronchodilator responsiveness was defined as ≥12% and ≥200mL increase in FEV_1 after bronchodilators administration. Abbreviations: BMI=body mass index; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; FEF_{25-75}=maximum airflow at mid-lung volume; SVC=slow vital capacity; CT=computed tomography; TLC= total lung capacity; RV=residual volume; VC=vital capacity; Average Pi10= the average for the square root of wall area of a hypothetical airway with 10mm internal perimeter; PRM^{EMPH}=parametric response mapping of functional small airway disease as measures of emphysema; PRM^{fSAD}=parametric response mapping of functional small airway disease; Exp_{-856}=percent of the lung voxels with attenuation <-856 Hounsfield Unit on the expiratory CT images; $Insp_{-950}$=percent of the lung voxels on inspiratory CT images with attenuation < -950 Hounsfield Units.

SUPPLEMENTAL FIGURE LEGENDS

Figure S1- Locally Weighted Scatterplot Smoothing (LOWESS) visualization of the lung volumes with respect to FEV_1. Scatter plots of the lung volumes with respect to FEV_1 and FEV_1 % prediction with superimposed LOWESS curves were presented for the cohorts. Abbreviations: VA EHR=Veterans Affairs electronic health records; FEV1=forced expiratory volume in 1 second; TLC=total lung capacity; VC= vital capacity; IC=inspiratory capacity; RV=residual volume; FRC=functional residual capacity.

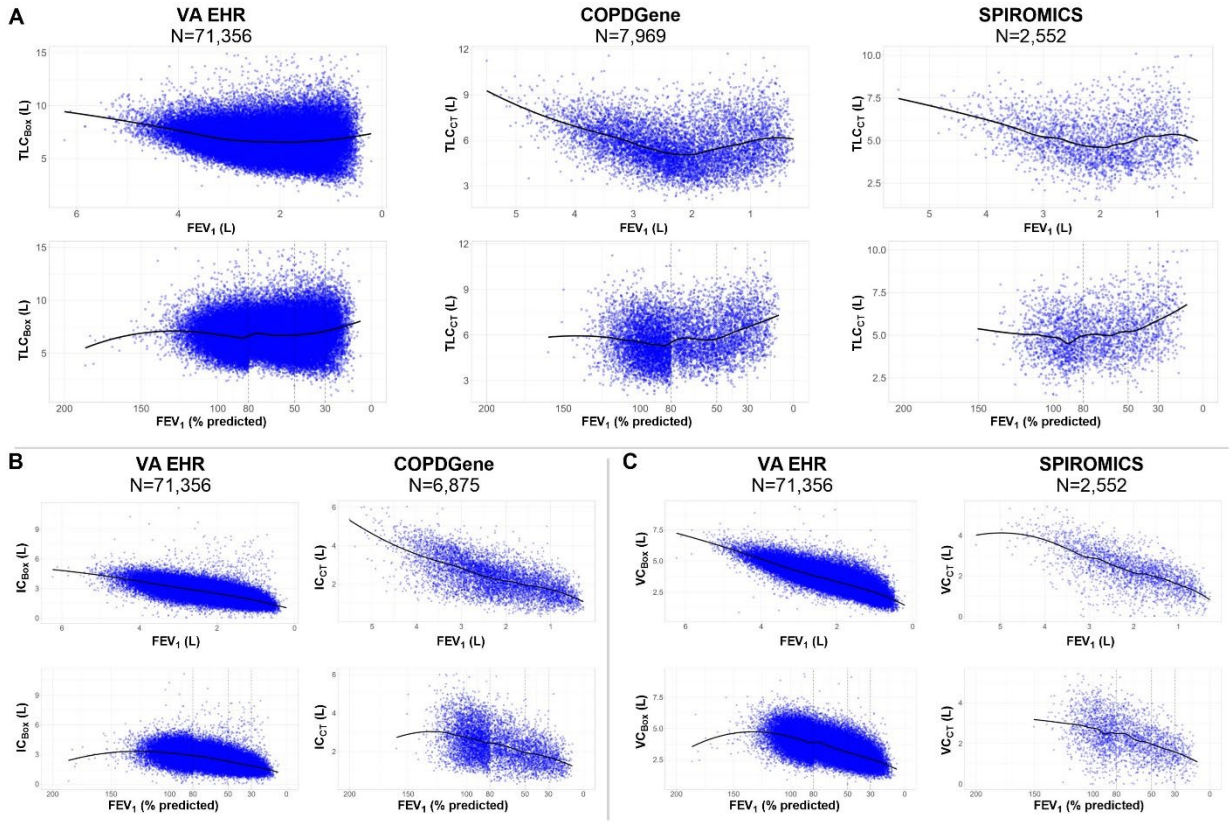


Figure S2- Longitudinal changes in TLC, IC, and FRC with disease progression in COPD in COPDGene cohort. Changes in the total lung capacity (Δ TLC), inspiratory capacity (Δ IC), and functional residual capacity (Δ FRC) with disease progression in patients from different GOLD stages of COPD in COPDGene cohort are represented using regression coefficient (ß or parameter estimate) and 95% confidence interval with adjustment for age, sex, height, and body mass index. Each row represents the changes in patients from one baseline GOLD category COPD (e.g., changes for patients with baseline GOLD-0 in the first row and patients with baseline GOLD-1 in second row, etc.). Lung volumes and capacities in COPDGene was measured by computed tomography (CT) in supine position. Abbreviations: GOLD= Global Initiative for Obstructive Lung Disease; V1= first visit; F/U= Follow-up visit.

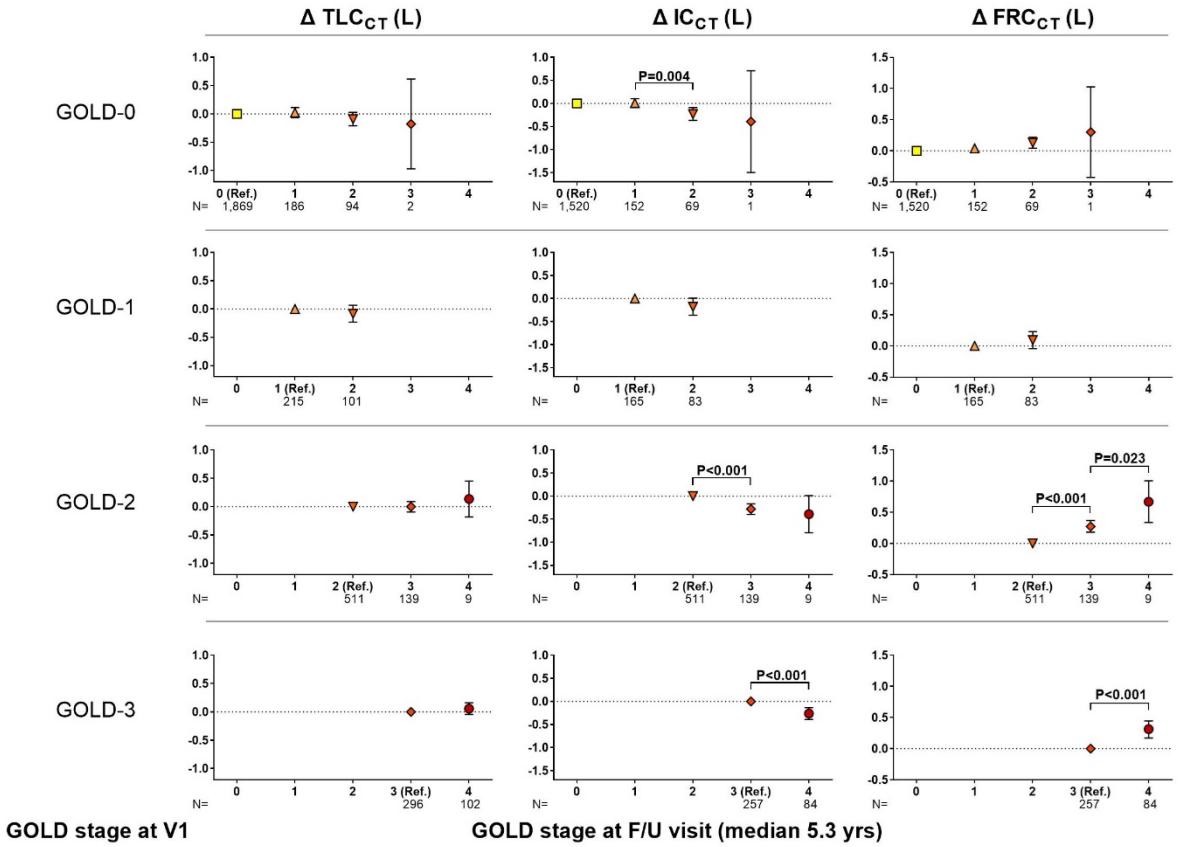


Figure S3- Longitudinal changes in TLC, VC, and RV with disease progression in COPD in SPIROMICS cohort. Changes in the total lung capacity (Δ TLC), vital capacity (Δ VC), and residual volume (Δ RV) with disease progression in patients from different GOLD stages of COPD in SPIROMICS cohort are represented using regression coefficient (ß or parameter estimate) and 95% confidence interval with adjustment for age, sex, height, and body mass index. Each row represents the changes in patients from one baseline GOLD category COPD (e.g., changes for patients with baseline GOLD-0 in the first row and patients with baseline GOLD-1 in second row, etc.). Lung volumes and capacities in SPIROMICS was measured by computed tomography (CT) in supine position. Abbreviations: GOLD= Global Initiative for Obstructive Lung Disease; V1= first visit; F/U= Follow-up visit.

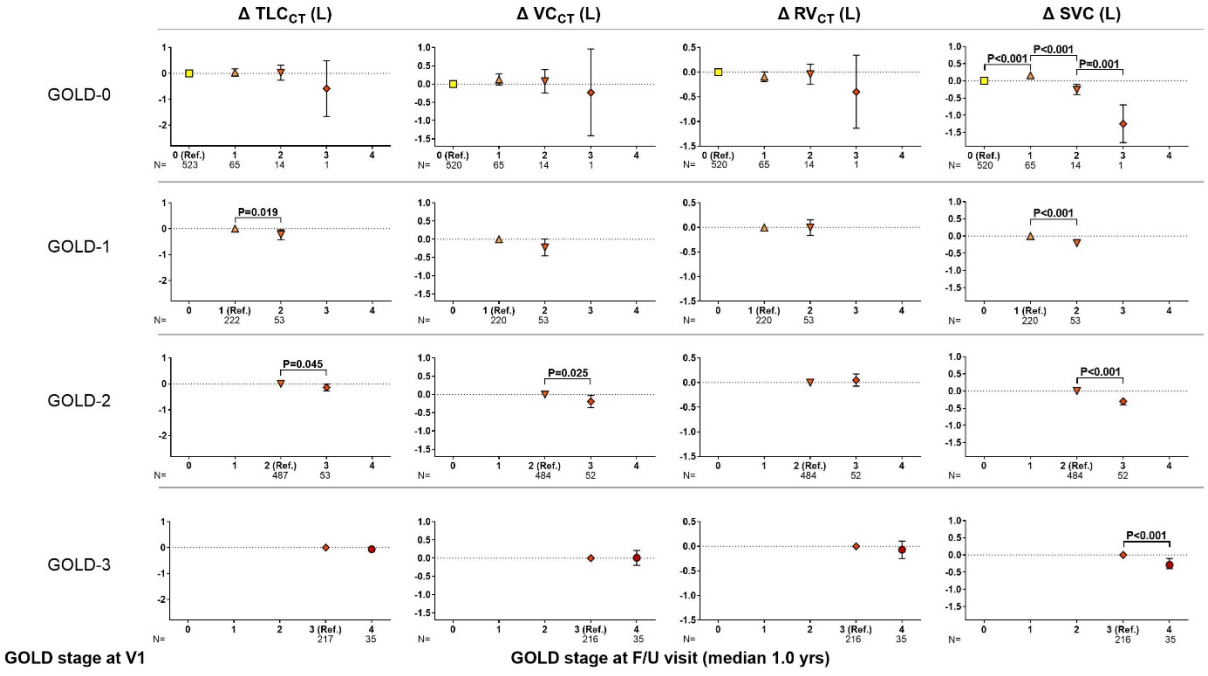


Figure S4- Longitudinal changes in TLC, VC, RV, IC, and FRC with disease progression in COPD in VA EHR cohort for subsequent visits of at least 3 years from the first visit.

Changes in the total lung capacity (Δ TLC), vital capacity (Δ VC), residual volume (Δ RV), inspiratory capacity (Δ IC), and functional residual capacity (Δ FRC) with disease progression in patients from different GOLD stages of COPD in VA EHR cohort are represented using regression coefficient (ß or parameter estimate) and 95% confidence interval with adjustment for age, sex, height, and body mass index. Each row represents the changes in patients from one baseline GOLD category COPD (e.g., changes for patients with baseline GOLD-0 in the first row and patients with baseline GOLD-1 in second row, etc.). Lung volumes and capacities in VA EHR were measured by plethysmography (Box) in seated position. Abbreviations: GOLD= Global Initiative for Obstructive Lung Disease; V1= first visit; F/U= Follow-up visit.

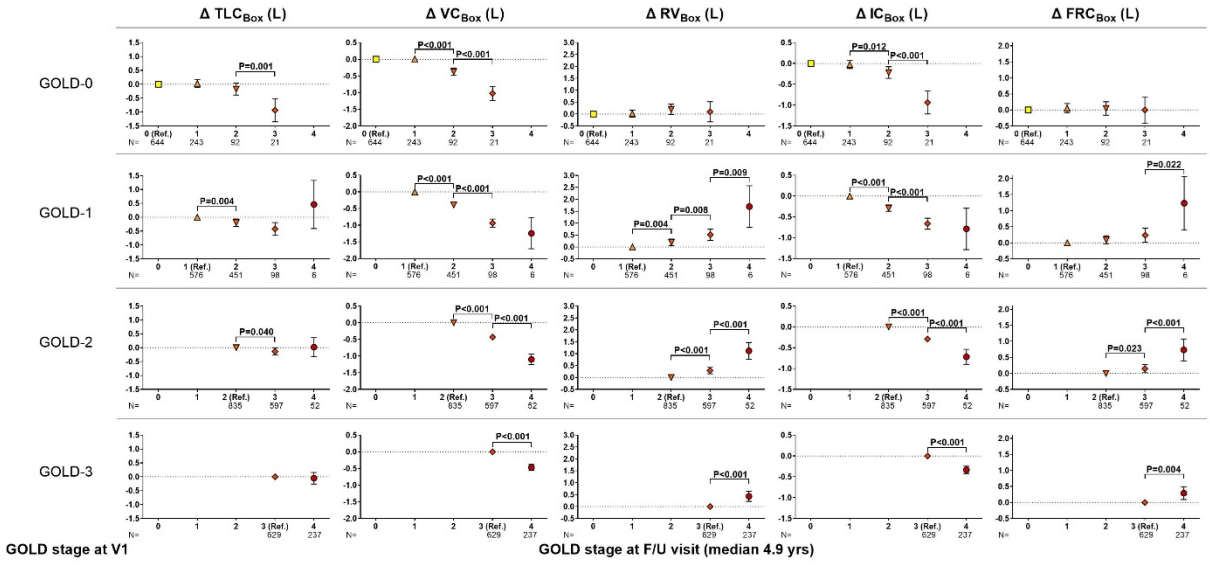
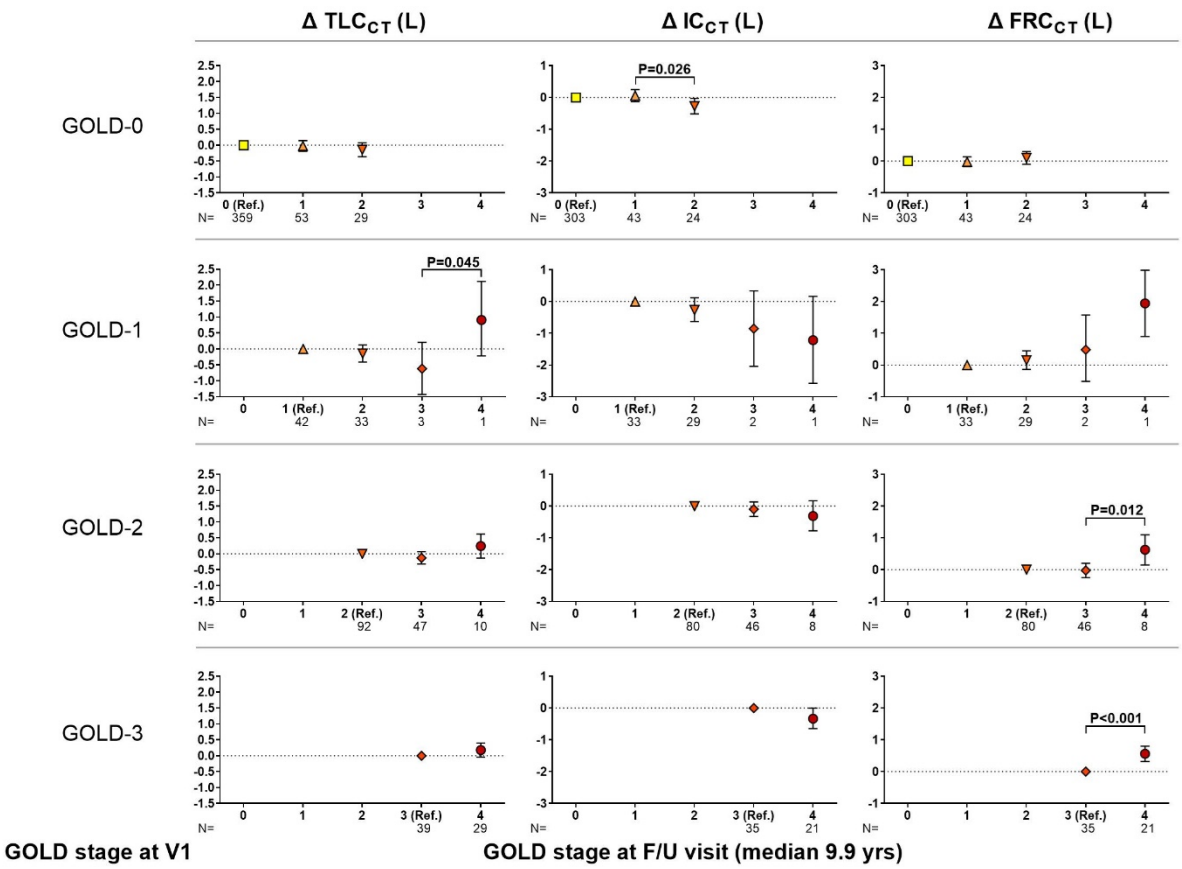


Figure S5- Longitudinal changes in TLC, IC, and FRC with disease progression in COPD in COPDGene cohort between the first and the third visits. Changes in the total lung capacity (Δ TLC), inspiratory capacity (Δ IC), and functional residual capacity (Δ FRC) with disease progression in patients from different GOLD stages of COPD in COPDGene cohort are represented using regression coefficient (ß or parameter estimate) and 95% confidence interval with adjustment for age, sex, height, and body mass index. Each row represents the changes in patients from one baseline GOLD category COPD (e.g., changes for patients with baseline GOLD-0 in the first row and patients with baseline GOLD-1 in second row, etc.). Lung volumes and capacities in COPDGene was measured by computed tomography (CT) in supine position. Abbreviations: GOLD= Global Initiative for Obstructive Lung Disease; V1= first visit; F/U= Follow-up visit.


Δ TLC$_{CT}$ (L)
Δ IC$_{CT}$ (L)
Δ FRC$_{CT}$ (L)
GOLD-0
GOLD-1
GOLD-2
GOLD-3
P=0.026
P=0.045
P=0.012
P<0.001
N= 359 53 29
N= 303 43 24
N= 303 43 24
N= 42 33 3 1
N= 33 29 2 1
N= 33 29 2 1
N= 92 47 10
N= 80 46 8
N= 80 46 8
N= 39 29
N= 35 21
N= 35 21
GOLD stage at V1
GOLD stage at F/U visit (median 9.9 yrs)