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Association between functional small airways disease and FEV_1 decline in COPD

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Acquisition, analysis, or interpretation of data: All authors
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At a Glance Commentary:

Scientific Knowledge on the Subject

Airflow obstruction is influenced by both small airways disease and emphysema. The small conducting airways are the major site of airflow obstruction in chronic obstructive pulmonary disease (COPD), and histologic data suggest small airway abnormality may precede emphysema. The impact of these components of COPD on lung function decline remains unknown.

What This Study Adds to the Field

In a population of current and former smokers, we demonstrate that the rate of FEV_1 decline is greatest in mild COPD. A novel, CT biomarker demonstrates functional small airways disease contributes to lung function decline particularly in mild disease, even amongst individuals without airflow obstruction.

Abstract

Background: The small conducting airways are the major site of airflow obstruction in COPD and may precede emphysema development. We hypothesized a novel CT biomarker of small airways disease predicts FEV_1 decline.

Methods: We analyzed 1,508 current and former smokers from COPDGene with linear regression to assess predictors of change in FEV_1 (ml/year) over 5 years. Separate models for non-obstructed and obstructed subjects were generated using baseline clinical and physiologic predictors in addition to two novel CT metrics created by Parametric Response Mapping (PRM), a technique pairing inspiratory and expiratory CT images to define emphysema (PRM^{emph}) and functional small airways disease (PRM^{fSAD}), a measure of non-emphysematous air trapping.

Results: Mean (SD) rate of FEV_1 decline in ml/year for GOLD 0-4 was as follows: 41.8 (47.7), 53.8 (57.1), 45.6 (61.1), 31.6 (43.6), and 5.1 (35.8) respectively (trend test for grades 1-4, $p<0.001$). In multivariable linear regression, for non-obstructed participants, PRM^{fSAD} but not PRM^{emph} was associated with FEV_1 decline, $p<0.001$. In GOLD 1-4 participants, both functional small airways disease (PRM^{fSAD}) and emphysema (PRM^{emph}) were associated with FEV_1 decline ($p<0.001$ and $p=0.001$, respectively). Based on the model, the proportional contribution of the two CT metrics to FEV_1 decline, relative to each other, was 87% vs. 13% and 68% vs. 32% for PRM^{fSAD} and PRM^{emph} in GOLD 1/2 and 3/4, respectively.

Conclusions: Both CT assessed functional small airways disease and emphysema are associated with FEV_1 decline, but the association with functional small airways disease has greatest importance in mild-to-moderate stage COPD where the rate of FEV_1 decline is the greatest.

Abstract Word Count: 256

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Introduction

Cigarette smoking is associated with an accelerated decline in the forced expiratory volume in 1 second (FEV_1), resulting in airflow obstruction in a significant proportion of smokers.(1) FEV_1 is influenced by both airway resistance and reduced elastic recoil due to emphysema.(2) The small conducting airways <2 mm in diameter that offer little resistance to airflow in normal lungs become the major site of airflow obstruction in persons with chronic obstructive pulmonary disease (COPD), (3, 4) representing a "silent zone" within the lung where obstructive airway disease can accumulate without being noticed.(3-5) In fact, histologic and micro CT data from explanted lung tissue suggest that widespread narrowing and destruction of the smaller airways actually occurs before emphysematous lesions become large enough to be visible on standard CT imaging.(6) Unfortunately, the resolution of current clinical CT imaging prevents direct visualization of small airways disease beyond the subsegmental bronchi.

While small airways disease can be assessed by "gas trapping", defined as the percent of voxels < -856 Hounsfield Units (HU) on expiratory CT, a significant limitation of this approach is that many lung regions that trap gas on exhalation will also show emphysematous destruction when fully inflated to total lung capacity (TLC).(7) A recently developed CT analytic method, Parametric Response Mapping (PRM), matches inspiratory and expiratory images on a voxel-by-voxel basis to examine the change in density between inspiratory and expiratory images.(8) By applying separate density thresholds to the inspiratory and expiratory voxel measurements, we are able to discriminate emphysema (PRM^{emph}) from non-emphysematous air trapping, termed functional small airways disease (PRM^{fSAD}), see Figure 1 and Supplemental Figure E1.

While emphysema defined as the percent of voxels <-950 HU on inspiratory CT has previously been associated with lung function decline, the relative contribution of CT defined

small airways disease has not been examined.(9) Here we present an analysis of a large multicenter study of current and former smokers to understand the relative contribution of small airways disease and emphysema to subsequent lung function decline across the disease severity spectrum over a five year period of observation. Some of the results in this manuscript have been previously reported in the form of an abstract. (10)

Methods

Study population and assessments

Subjects participating in the follow-up phase of COPDGene (Genetic Epidemiology of COPD), a large multicenter longitudinal observational cohort study were included in this analysis. Written informed consent was obtained from each subject and the study was approved by the institutional review boards of all 21 participating centers. Current and former smokers with ≥ 10 pack-year smoking history, with and without airflow obstruction were enrolled.(11) Inclusion criteria also included non-Hispanic White or African American race; exclusion criteria included a history of other lung disease except asthma, prior surgical excision involving a lung lobe or greater, active cancer, metal in the chest and history of chest radiation therapy. The original COPDGene cohort enrolled 10,192 individuals. 1,508 GOLD 0-4 subjects who had completed a second COPDGene visit approximately 5 years after the first visit with acceptable pulmonary function and CT scans from visit 1 and 2 by November 2014 were included for this analysis (see Supplemental Figure E2, Consort Diagram).

At both visits, spirometry was performed before and after administration of 180 mcg of albuterol (ndd Easy-One spirometer, Andover, MA). Bronchodilator reversibility was defined as at least 12% and 200 ml increase in FEV_1 and/or forced vital capacity (FVC)

postbronchodilator.(12); post bronchodilator values were used for analyses.(12) COPD was defined by post-bronchodilator $FEV_1/FVC < 0.70$ at baseline visit per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.(13) Disease severity was defined by GOLD grade. "GOLD 0" was defined as by post-bronchodilator $FEV_1/FVC \geq 0.70$ at baseline visit and FEV_1% predicted $\geq$ 80. Participants with $FEV_1/FVC>0.70$ but with FEV_1 <80% predicted were deemed to have Preserved Ratio Impaired Spirometry (PRISm) and were not included in the analyses.(14)

Data on demographics, smoking burden, respiratory morbidity, exacerbations and comorbidities used in this analysis were recorded at the baseline visit. Respiratory disease related health impairment and quality of life was assessed using the St George's Respiratory Questionnaire (SGRQ),(15) and dyspnea using the Modified Medical Research Council (MMRC) dyspnea score.(16) History of exacerbations in the previous year was obtained at the time of initial visit, with exacerbations defined as acute worsening of respiratory symptoms that required use of either antibiotics or systemic steroids.(13)

At the baseline visit, paired inspiratory and expiratory scans were obtained at maximal inspiration (total lung capacity, TLC) and end-tidal expiration (functional residual capacity, FRC).(11) Emphysema was quantitated using the percentage of low attenuation units <-950 HU at TLC, and gas trapping using the percentage of low attenuation units <-856 HU at end-expiration using Slicer software (www.Slicer.org).(17) Using funds from NHLBI Grant # R01 HL122438, PRM analysis was also performed on paired registered inspiratory and expiratory images to distinguish functional small airways disease (PRM^{fSAD}) from emphysema (PRM^{emph}) by Imbio LLC, Minneapolis, MN, USA using Lung Density Analysis™ software.(8) Briefly, PRM^{fSAD} was defined as areas of lung that are >-950 HU on inspiration but also <-856 HU on

expiration. PRM^{emph} was defined as areas of lung that are <-950 HU on inspiration and <-856 HU on expiration. (See Supplemental Figure E1).

Statistical analyses

All statistical analyses were performed in SAS 9.3 (Cary, NC). Comparisons were performed using two-sample t-tests for continuous variables and chi-squared statistics for categorical variables. Linear regression was used to study univariate and multivariable associations between potential predictors and change in FEV_1 (ml/year). The outcome of change in FEV_1 for each individual was calculated by subtracting visit 1 FEV_1 from visit 2 FEV_1 and dividing by the time between visits to calculate change in ml/year. In addition to PRM CT metrics which were the covariates of interest, age, sex, race, height, smoking history and scanner type were included as covariates in all multivariable regression models regardless of univariate statistical significance. Otherwise, only parameters associated with FEV_1 change at a significance level of $p<0.05$ were retained in the multivariable model. Linear regression analyses were repeated separately for GOLD 0 participants and also for GOLD 1-4 participants. Among GOLD 1-4 participants, the contribution to FEV_1 decline for each CT metric was calculated by multiplying the parameter estimate from the multivariate model by the mean CT metric value for the corresponding disease stage and dividing that value by the sum of this product for both metrics (PRM^{fSAD} and PRM^{emph}). $P<0.05$ was considered statistically significant for all analyses.

Results

Subject characteristics

Results for 1,508 participants with complete data needed for multivariable regression analyses are reported here (Consort Diagram, Supplemental Figure E2). Baseline demographics and lung function are reported in Table 1, categorized by severity of airflow obstruction according to GOLD grade. Imaging metrics show an increase in emphysema with increasing GOLD spirometry grade as measured by both density analysis (Emphysema) and PRM (PRM^{emph}) and an increase in small airways disease (PRM^{fSAD}) as well.

FEV_1 change over time

The median follow-up time for the entire cohort was 64 months (range 49 to 79) with a mean (SD) rate of decline in FEV_1 of 41.1 (52.0) ml/year (Figure 2). For GOLD 0 participants, mean rate of FEV_1 decline was 41.8 (47.7) ml/year. Those with GOLD grade 1 had the most rapid rate of decline 53.8 (57.1) ml/year, with progressively slower rates of decline with increasing GOLD grades: 45.6 (61.1), 31.6 (43.6), and 5.1 (35.8) for GOLD grades 2 to 4 respectively (trend test for grades 1-4, $p<0.001$). Supplemental Figure E3 demonstrates that FEV_1 decline expressed as change in percent predicted follows similar trend to FEV_1 change in ml.

Clinical Predictors of FEV_1 change

The rate of FEV_1 change was strongly associated with a number of baseline demographic variables. Univariate and multivariable analyses for FEV_1 decline are presented in Supplemental Tables E1 and E2. In multivariable analysis, FEV_1 decline (ml/year) was greater in current

versus former smokers (6.91 ml/year greater decline; 95% CI 0.82, 13.01; p=0.01). Those with baseline bronchodilator reversibility had greater FEV_1 decline compared to those without bronchodilator reversibility (18.80 ml/year greater decline; 95% CI 12.60, 25.01; p<0.001). Greater rates of FEV_1 decline were also seen with higher baseline FEV_1 (14.45 ml/year decline per L; 95% CI 6.75, 22.14; p<0001), higher baseline FVC (14.74 ml/year decline per L; 95% CI 8.15, 21.32; p<0.001) and more smoking pack years (1.43 ml/year decline per 10 pack-years; 95% CI 0.82, 2.57; p=0.01). Exacerbations in the prior year demonstrated no significant association with FEV_1 decline in either the univariate (p=0.38) or multivariable model (p=0.55) and therefore was not retained in the final model. African American race was associated with more rapid decline compared to Non-Hispanic White participants (11.30 ml/year greater decline; 95% CI 4.34, 18.25; p=0.002) in multivariable analysis. Female sex was associated with more rapid FEV_1 decline than males (8.39 ml/year greater decline; 95% CI 0.94, 15.84; p=0.03), our analysis was not designed to assess sex difference.

Quantitative imaging and FEV_1 change

Results for the overall model are in Table E2. For all subjects, both PRM^{fSAD} and PRM^{emph} had a statistically significant association with lung function decline. In order to understand the impact of CT assessment of small airways disease and emphysema on FEV_1 decline based on presence or absence of baseline airflow obstruction, we also performed separate linear regression models for GOLD 0 and GOLD 1-4 subjects. Parameter estimates for the CT metrics for these stratified models are presented in Table 2.

Amongst GOLD 0 participants, PRM^{fSAD} but not PRM^{emph} was significantly associated with FEV_1 decline. For every additional 5% of lung affected by PRM^{fSAD}, a significant decline

in FEV_1 was seen (2.2 ml/year per 5% PRM^{fSAD}; p=0.04). Amongst GOLD 1-4 participants, for every additional 5% of lung affected by PRM^{fSAD} or PRM^{emph} a significant decline in FEV_1 was seen: (4.5 ml/year; 95% CI 6.3, 2.6; p<0.001 and 3.5 ml/year; 95% CI 5.6, 1.4; p=0.001, respectively).

We also sought to understand the contribution of CT metrics to FEV_1 decline relative to each other in milder versus more severe disease (Supplemental Figure E4). We therefore used the parameter estimates from the linear regression model and mean CT metric values corresponding to GOLD 1-2 and GOLD 3-4 groups to determine the relative contribution of PRM^{fSAD} and PRM^{emph} to FEV_1 decline. PRM^{fSAD} was associated with significantly greater FEV_1 decline than PRM^{emph} for both groups (p=0.001 for GOLD1-2; p=0.007 for GOLD 3-4), although this was even more pronounced for the GOLD 1-2 group (87% vs. 13% and 68% vs. 32% for PRM^{fSAD} and PRM^{emph} in GOLD 1-2 and 3-4, respectively).

Finally, in order to better understand the significance of PRM^{fSAD} in the GOLD 0 group, we also examined the mean rate of decline for varying levels of PRM^{fSAD}. As previously stated, the mean change in FEV_1 for GOLD 0 group was 41.8 (47.7) ml/year. For individuals at or above the median PRM^{fSAD} level for the GOLD 0 group (PRM^{fSAD} 11%), the mean decline in FEV_1 was 45.2 (47.8) ml/year vs. 38.6 (47.2) ml/year for those below the median (p=0.05). For individuals at or above the 75^{th} percentile of PRM^{fSAD} for GOLD 0 group (PRM^{fSAD} 16%) the mean decline in FEV_1 was 49.2 (50.2) ml/year compared to those below the 75^{th} percentile, 39.0 (46.4), p= 0.009. Supplemental Table E3 shows mean FEV_1 decline across quartiles of PRM^{fsad} for GOLD 0.

Discussion

We demonstrated that, in a cohort of current and former smokers, functional small airways disease as measured by chest CT is associated with subsequent FEV_1 decline. While we showed that emphysema is also associated with FEV_1 decline, its impact relative to small airway abnormality is weaker, particularly in mild-to-moderate disease stage. Finally we demonstrated that this association between functional small airways disease and FEV_1 decline is evident in GOLD 0 subjects even before the development of spirometrically detected airflow obstruction.

Our findings support prior pathologic investigations of COPD. The small airways < 2 mm in diameter are the major site of increased airflow resistance in COPD as established first in the 1960s through retrograde catheter studies in post-mortem lungs(3) and then later in living lungs.(4) Peripheral airway inflammation has been noted in young smokers even before COPD is established.(18) Further increases in this inflammatory response along with development of airway wall structural abnormalities have also been described in established COPD resulting in airway lumen narrowing.(6) Recent histologic and micro CT data also reveal that narrowing and disappearance of terminal bronchioles precedes the development of emphysema.(6)

Previously it has been demonstrated in individuals with moderate to severe COPD that emphysema on CT, defined as the percentage of voxels with density <-950 HU at full inspiration, is associated with a more rapid decline of FEV_1.(9, 19) However, a good way to assess the small airways in patients radiographically has been lacking. Gas trapping, measured as the percent of voxels <-856 HU using expiratory images alone, is limited by the inability to distinguish small airways disease from emphysema.(7) Unlike standard densitometric analyses using inspiratory or expiratory images in isolation, PRM digitally co-registers inspiratory and expiratory CT images which should help distinguish small airways disease from emphysema.(8)

Here we demonstrated, in a large cohort of current and former smokers with a broad spectrum of disease severity, that functional small airways disease on CT as measured by PRM is significantly associated with decline in FEV_1 particularly in mild-to-moderate stage disease, whereas the contributions of small airways disease and emphysema are relatively more equal in later stages (GOLD 3-4). This association between functional small airways disease and FEV_1 decline was evident even before the development of spirometrically detected airflow obstruction. We do note, however, that the effect size for PRM^{fSAD} was attenuated in GOLD 0 individuals as compared to those with established airflow obstruction. We postulate that airway disease if present in non-obstructed smokers may still be of a reversible nature and may represent bronchospasm or inflammation as opposed to fibrosis or airway loss. In prior work comparing paired CT scans in smokers with GOLD 0-4 disease performed at 30 days and one year apart, we demonstrated particularly in individuals with mild-to-moderate stage disease that PRM^{fSAD} may increase or decrease over these shorter time intervals suggesting a reversible component.(20) Here we demonstrated that in those with established airflow obstruction, PRM^{fSAD} is strongly associated with FEV_1 decline. While PRM^{emph} was also associated with FEV_1 decline, it's relative impact was weaker, particularly in mild-to-moderate disease. This is not to say, however, that emphysema as defined by PRM in mild-to-moderate stage disease is not important when present, but it is generally lesser in magnitude than small airways disease. We also demonstrated that high levels of CT defined small airway abnormality were present in individuals without airflow obstruction who subsequently experience more rapid declines in FEV_1. In fact, the rate of decline experienced by GOLD 0 participants with PRM^{fSAD} > median value (45.2 ml/year) was comparable to the rate of decline experienced by GOLD 2 individuals

(45.6 ml/year). These findings have potential implications for identifying individuals without airflow obstruction but at high risk for more rapid lung function decline.

Our study has several potential limitations. We had only two measurements of lung function separated by a median of approximately 5 years. However, within-person variability in our results was offset by the large number of individuals used to estimate average change. We also did not have data on lifelong FEV_1 trajectories;(21) however, our goal was primarily to examine the relative impact of structural lung disease on subsequent FEV_1 decline. Our analysis was based on subjects who had completed their second study visit by November 3, 2014. It is possible that patients who were first to follow-up differ from those who were either late for their second visit or lost to follow-up. Many of the patients with airflow obstruction were receiving therapy for their disease. Although no existing pharmacotherapy has been conclusively shown to affect the rate of FEV_1 decline, this still may have influenced our results. However, we chose not to include pharmacotherapy data in these analyses in order to reduce biases inherent to patient-reported pharmaco-epidemiologic data. (22) We also describe an imaging metric that measures "functional" small airways disease through the change in lung density seen between inspiration and expiration. It is not a direct measure of airway thickness or destruction. The lack of a normal increase in lung density between inspiration and expiration implies that air is trapped. We postulate that such air trapping is due to small airways disease, but the exact contribution of larger visible and smaller non-visible airways is actively being investigated with radiologic-pathologic correlation. In addition, this algorithm assigns every voxel to a specific disease category which likely represents the majority of abnormality, but in reality there may be a mix of histologic abnormalities in the tissue covered by one voxel. The goal for the expiratory

images was to obtain images at functional residual capacity. It is possible that this underestimates the amount of air trapping that might be seen at residual volume.

The current study also has a number of strengths. PRM is an advance over the traditional "gas trapping" metric defined by voxels <-856 HU on expiration which likely combines true emphysema and small airway abnormality.(7) Here we allow the relative contribution from each to be resolved. Analyses were performed within a well-characterized cohort that included subjects with all stages of disease severity represented proportionally and with stringent spirometry and CT quality control. PRM metrics provide a novel noninvasive CT biomarker for disease progression, particularly in mild to moderate COPD. Even though there are no established therapies to treat lung function decline, early identification of these subjects will allow prognostication and perhaps targeting novel therapies in these individuals using the detailed spatial information provided on disease distribution and relative contribution of small airways disease and emphysema.

Conclusions

Both CT assessed functional small airways disease and emphysema are associated with FEV_1 decline, but the association with functional small airways disease has greatest importance in mild-to-moderate stage COPD where the rate of FEV_1 decline is the greatest. These findings are consistent with prior pathologic studies and allow a non-invasive means to target at-risk patients at milder stages of the disease.

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Table 1. Baseline demographics

n=1,508	GOLD Spirometry Grade				
	0 n=751	1 n=150	2 n=356	3 n=192	4 n=59
Age (years)	58.2 (8.6)	63.8 (8.1)	63.3 (8.4)	64.1 (7.9)	62.8 (7.6)
Sex, n (% Female)	395 (52.6)	66 (44.0)	161 (45.2)	87 (45.3)	29 (49.2)
Race, n (% African American)	245 (32.6)	28 (18.7)	79 (22.2)	36 (18.8)	5 (8.5)
Height (cm)	169.5 (9.2)	169.7 (10.1)	170.9 (9.3)	169.9 (10.3)	169.6 (9.0)
FEV_1 (L)	2.8 (0.7)	2.6 (0.7)	1.9 (0.5)	1.2 (0.3)	0.68 (0.2)
FEV_1 % predicted	97.7 (11.4)	91.6 (8.6)	65.0 (8.3)	40.9 (5.9)	23.6 (4.1)
FVC (L)	3.6 (0.9)	4.1 (1.0)	3.3 (0.9)	2.7 (0.8)	2.3 (0.6)
FVC % predicted	96.2 (11.3)	108.5 (11.2)	87.4 (13.4)	72.4 (12.8)	59.1 (11.6)
FEV_1/FVC	0.79 (0.1)	0.64 (0.04)	0.47 (0.08)	0.44 (0.09)	0.31 (0.05)
Smoking pack years	37.2 (20.0)	40.0 (49.2)	37.9 (48.6)	55.4 (24.8)	57.8 (28.6)
Current smokers, n (%)	364 (48.5)	60 (40.0)	135 (37.9)	60 (31.3)	10 (16.9)
***Bronchodilator reversibility, n (%)**	68 (9.1)	42 (28.0)	136 (38.2)	80 (41.7)	19 (32.2)
Exacerbations in the prior year	0.13 (0.49)	0.13 (0.37)	0.43 (0.95)	0.71 (1.15)	1.14 (1.50)
Follow-up time (months)	63.9 (4.5)	63.7 (4.2)	64.1 (4.2)	64.0 (4.1)	65.0 (5.1)
Emphysema (%LAA<-950HU_{insp})	2.7 (3.0)	6.9 (6.4)	8.4 (8.4)	17.9 (12.6)	26.6 (13.6)
Gas Trapping (%LAA<-856HU_{exp})	11.8 (9.9)	23.4 (12.1)	29.9 (15.4)	48.7 (16.3)	60.9 (12.2)

PRM functional small airways disease (%)	12.4 (9.7)	22.2 (10.7)	26.6 (11.6)	36.3 (10.0)	39.2 (9.9)
PRM emphysema (%)	0.6 (1.4)	3.3 (4.4)	5.6 (7.4)	15.2 (12.9)	24.7 (14.7)

All values expressed as mean (SD) except categorical variables expressed as n (%). SD = standard deviation. GOLD = Global Initiative for Chronic Obstructive Lung Disease. FEV_1 = Forced expiratory volume in the first second. FVC = Forced vital capacity. $LAA<-950HU_{insp}$ = Low attenuation areas <-950 Hounsfield Units at end inspiration. $LAA<-856HU_{exp}$ = Low attenuation areas <-856 Hounsfield Units at end expiration. PRM = Parametric response mapping.

*Bronchodilator reversibility defined as 12% and 200 ml increase in FEV_1 and/or FVC

Table 2. Association between PRM emphysema and fSAD on change in FEV_1 ml/year by baseline GOLD grade (Estimate, 95% CI, p-value). Two separate models are shown in rows for the following groups (1) GOLD 0 and (2) GOLD 1-4 subjects. Parameter estimates and mean values for respective CT metrics are shown. All models adjusted for potential confounders as outlined below*.

	PRM^{fSAD}	PRM^{emph}
GOLD 0, n=751		
Parameter estimate per 5% (ml/yr)	-2.2 (95% CI -4.2, -0.1) p=0.04	5.5 (95% CI -8.0, 19.1) p=0.42
Mean value CT metric (%)	12.4 (9.7)	0.6 (1.4)
GOLD 1 – 4, n=757		
Parameter estimate per 5% (ml/yr)	-4.5 (95% CI -6.3, -2.6) p<0.001	-3.5 (95% CI -5.6, -1.4) p=0.001
Mean value CT metric (%)	29.2 (12.3)	9.1 (11.4)

PRM = Parametric response mapping. fSAD = functional small airways disease. GOLD = GOLD = Global Initiative for Chronic Obstructive Lung Disease. PRM^{emph} = emphysema on parametric response mapping. PRM^{fSAD} = functional small airways disease on parametric response mapping.

*All models adjusted for age, race, sex, height, current smoking, smoking history in pack years, baseline FEV_1, baseline FVC , bronchodilator reversibility and scanner type.

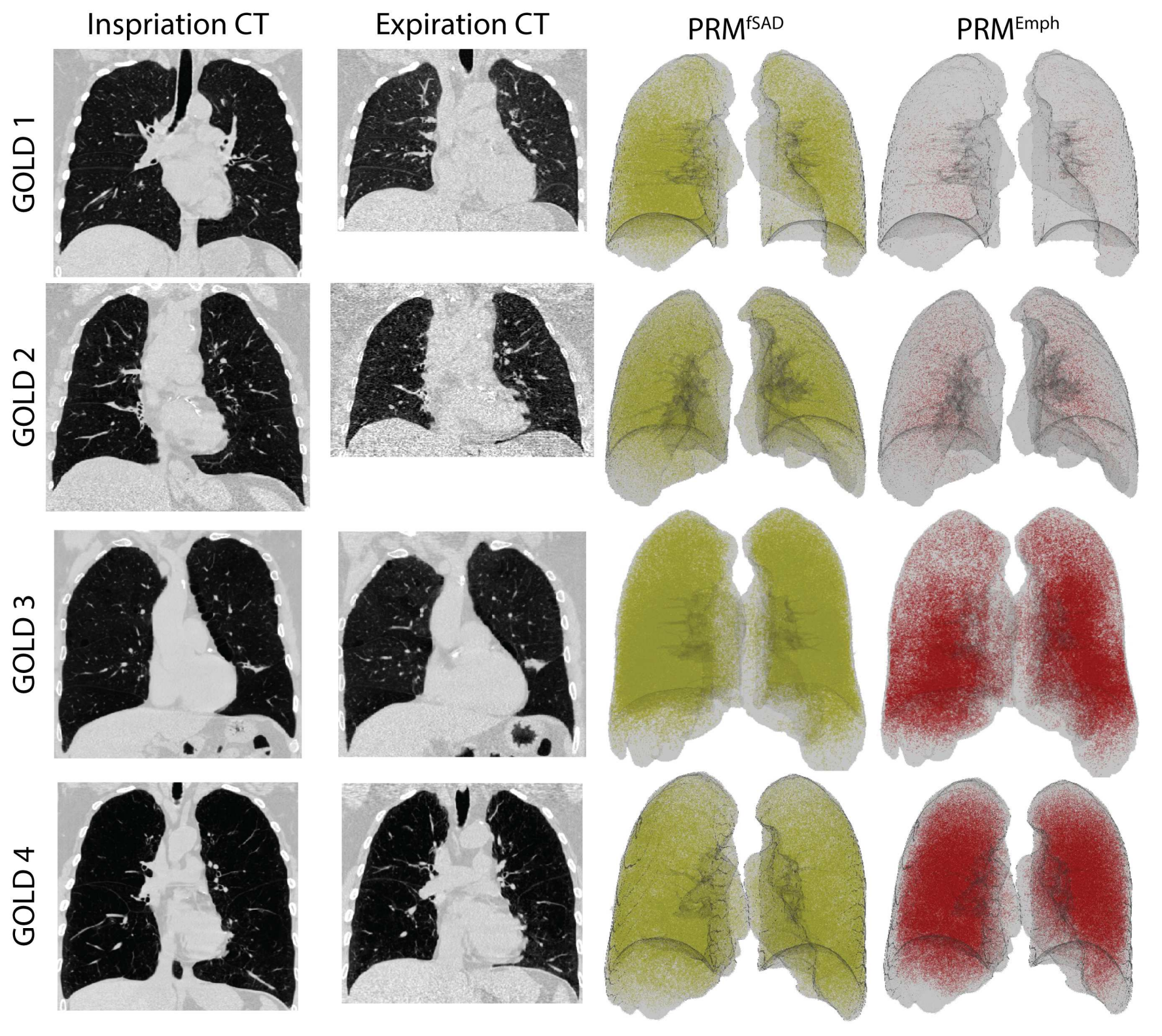
Figure 1: Graphic representation of the Parametric Response Mapping (PRM) methodology. COPD of GOLD grades 1-4 are shown in rows. In columns, inspiratory and expiratory CT images are shown on the left. PRM emphysema voxels in red and PRM functional small airways voxels in yellow are shown on the right. While every voxel receives an individual categorical assignment, in this example PRM^{Emph} and PRM^{fSAD} are distributed throughout the lung. Greater intensity of color indicates more voxels classified in each category.

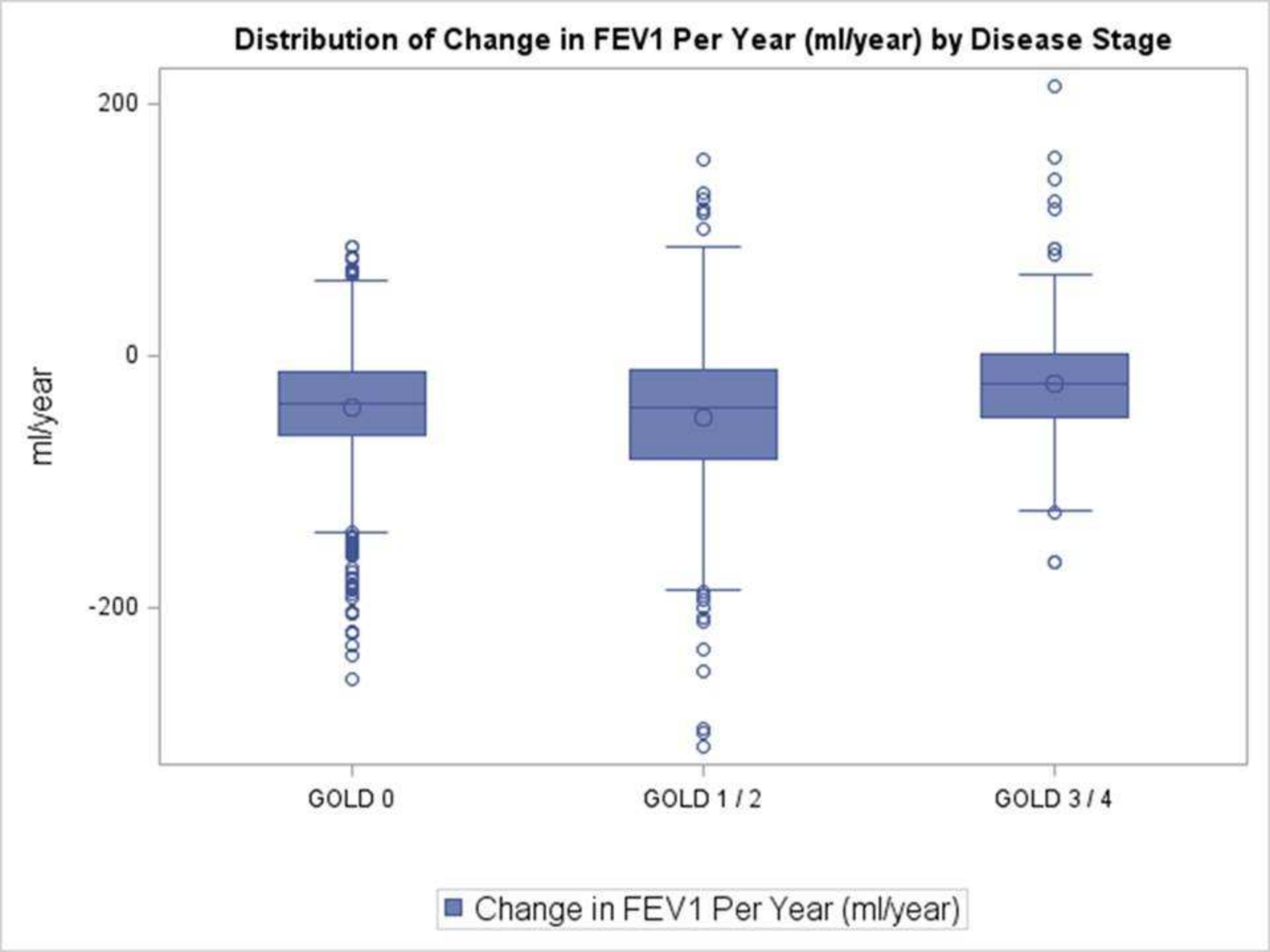
	PRM Normal (%)	PRM Functional small airways disease (%)	PRM Emphysema (%)
GOLD 1	78.8	18.5	0.8
GOLD 2	44.9	41.6	7.0
GOLD 3	28.8	40.8	25.1
GOLD 4	21.8	26.9	43.2

PRM = Parametric response mapping. PRM^{emph} = emphysema on parametric response mapping. PRM^{fSAD} = functional small airways disease on parametric response mapping. PRM^{norm} = neither emphysema nor functional airways disease on parametric response mapping. GOLD = Global Initiative for Chronic Obstructive Lung Disease.

Figure 2. Change in FEV_1 (ml/year) between Visit 1 and Visit 2 by disease stage. Figures show the proportion of subjects in each disease stage group with varying levels of change in FEV_1 (ml/year) over a 5-year period for (A) Global Initiative for Obstructive Lung Disease (GOLD) 0, mean -41.8 (47.7) ml/yr; (B) GOLD grades 1 and 2 combined, mean -48.0 (SD 60.0) ml/yr; and (C) GOLD grades 3 and 4 combined, mean -25.3 (SD 43.3) ml/yr.

FEV_1 = Forced Expiratory Volume in 1 second. GOLD = GOLD = Global Initiative for Chronic Obstructive Lung Disease.


Inspriation CT
Expiration CT
PRM^fSAD
PRM^Emph
GOLD 1
GOLD 2
GOLD 3
GOLD 4


Distribution of Change in FEV1 Per Year (ml/year) by Disease Stage
200
0
-200
ml/year
GOLD 0
GOLD 1 / 2
GOLD 3 / 4
Change in FEV1 Per Year (ml/year)

Supplemental Table E1. Univariate Analyses for predictors of FEV_1 decline in ml/year (n=1,508). Negative values indicate decrease in FEV_1 at Visit 2.

	Parameter Estimate	95% Confidence Interval	P-value
Age (per 10 years)	3.35	0.37, 6.33	0.03
Gender (female)	15.28	10.08, 20.47	<0.001
Race (African American)	-3.12	-9.09, 2.86	0.31
Height (cm)	-0.75	-1.01, -0.49	<0.001
Baseline FEV_1 (ml)	-12.38	-15.22, -9.54	<0.001
Baseline FVC (ml)	-15.17	-18.52, -13.52	<0.001
Smoking pack years (per 10 years)	-1.59	-2.68, -0.50	0.004
Current smoking	-7.96	-13.27, -2.65	0.003
Bronchodilator reversibility	-15.75	-21.94, -9.95	<0.001
Exacerbations in the prior year	1.43	-1.79, 4.66	0.38
PRM emphysema (per 5%)	0.26	-1.18, 1.69	0.72
PRM small airways disease (per 5%)	-0.82	-1.77, 0.12	0.09
% Emphysema (per 5%)	-0.31	-1.68, 1.05	0.65
% Gas trapping (per 5%)	-0.32	-1.00, 0.36	0.36

FEV_1 = Forced expiratory volume in the first second. FVC = Forced vital capacity. PRM = Parametric response mapping.

Supplemental Table E2. Multivariable linear regression on FEV_1 decline in ml/year. Negative values indicate decline in FEV_1 at Visit 2 compared to Visit 1, n=1508.

	Parameter Estimate	95% Confidence Interval	P-value
Age (per 10 years)	-2.64	-6.31, 1.03	0.16
Gender (female)	-8.39	-15.84, -0.94	0.03
Race (African American)	-11.30	-18.25, -4.34	0.002
Height (per cm)	0.62	0.21, 1.03	0.003
Baseline FEV_1 (per ml)	-14.45	-22.14, -6.75	<0.001
Baseline FVC (per ml)	-14.74	-21.32, -8.15	<0.001
Smoking pack years (per 10 years)	-1.43	-2.57, -0.30	0.01
Current smoking	-6.91	-13.01, -0.82	0.03
Bronchodilator reversibility	-18.80	-25.01, -12.60	<0.001
PRM small airways disease (per 5%)	-2.78	-4.05, -1.52	<0.001
PRM emphysema (per 5%)	-2.52	-4.35, -0.70	0.007

*additionally adjusted for scanner type

FEV_1 = Forced expiratory volume in the first second. FVC = Forced vital capacity. PRM = Parametric response mapping.

Supplemental Table E3: FEV_1 decline in GOLD 0 subjects stratified by PRM^{fSAD} quartiles

	PRM^{fSAD} quartile 1 <5%	**PRM^{fSAD} quartile 2 5-10%**	**PRM^{fSAD} quartile 3 11-15%**	**PRM^{fSAD} quartile 4 ≥16%**
FEV_1 decline (ml/yr)	35.4 (47.3)	40.5 (47.3)	40.3 (44.5)	49.2 (50.2)

FEV_1 = Forced expiratory volume in the first second. PRM^{fSAD} = functional small airways disease defined using parametric response mapping.

Supplemental Figure E1. Parametric Response Mapping Methodology. (1) Inspiratory and expiratory CT images are acquired; (2) image processing allows the two images to be spatially aligned and voxels matched between the two images; (3) joint registration allows voxels to be classified as "normal" lung, "functional small airways disease" or fSAD and "emphysema" based on Hounsfield Unit measures of density on both the inspiratory and expiratory images.

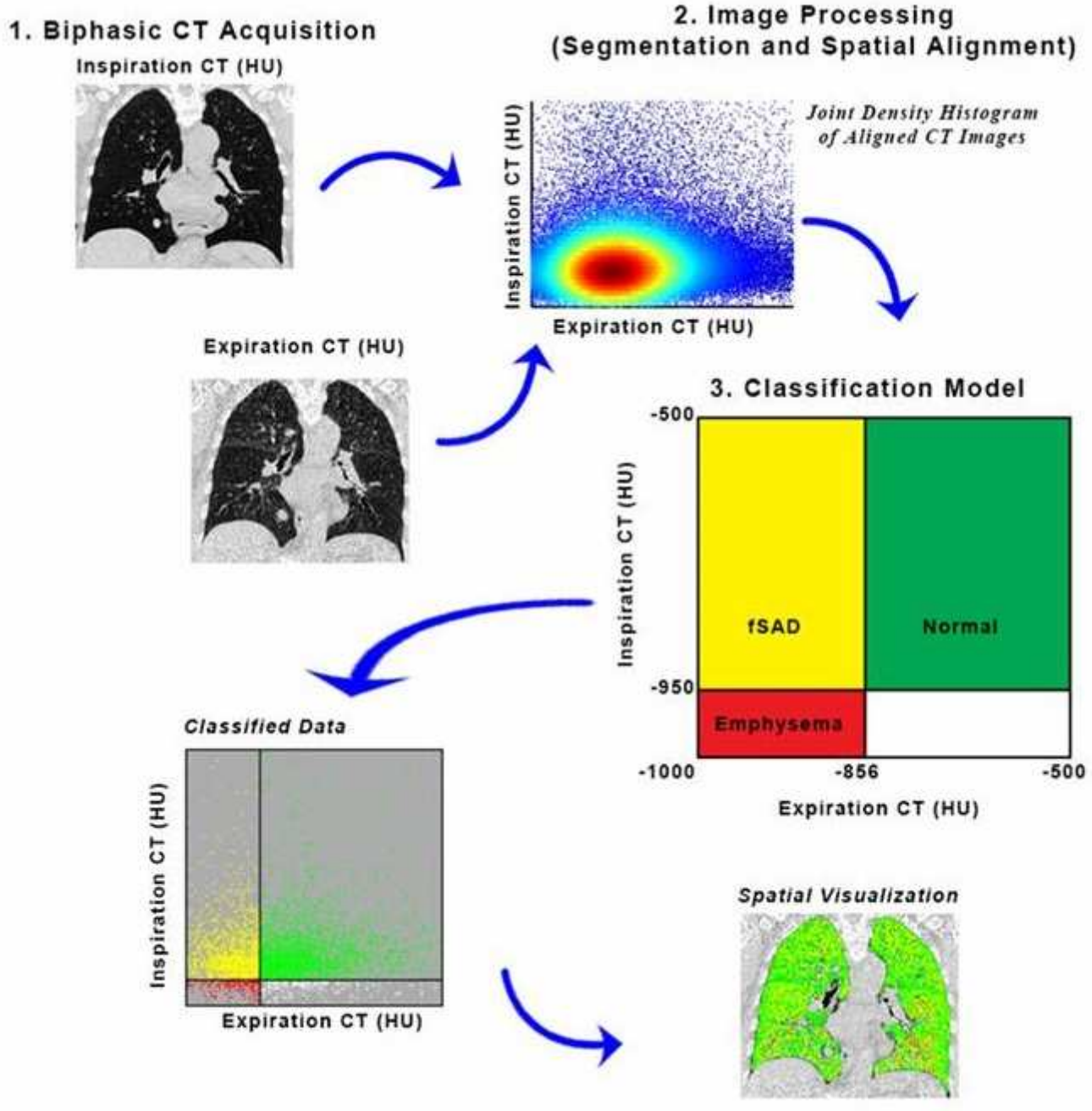
Supplemental Figure E2: Consort Diagram.

Supplemental Figure E3. FEV_1 decline expressed as percent change by disease stage.

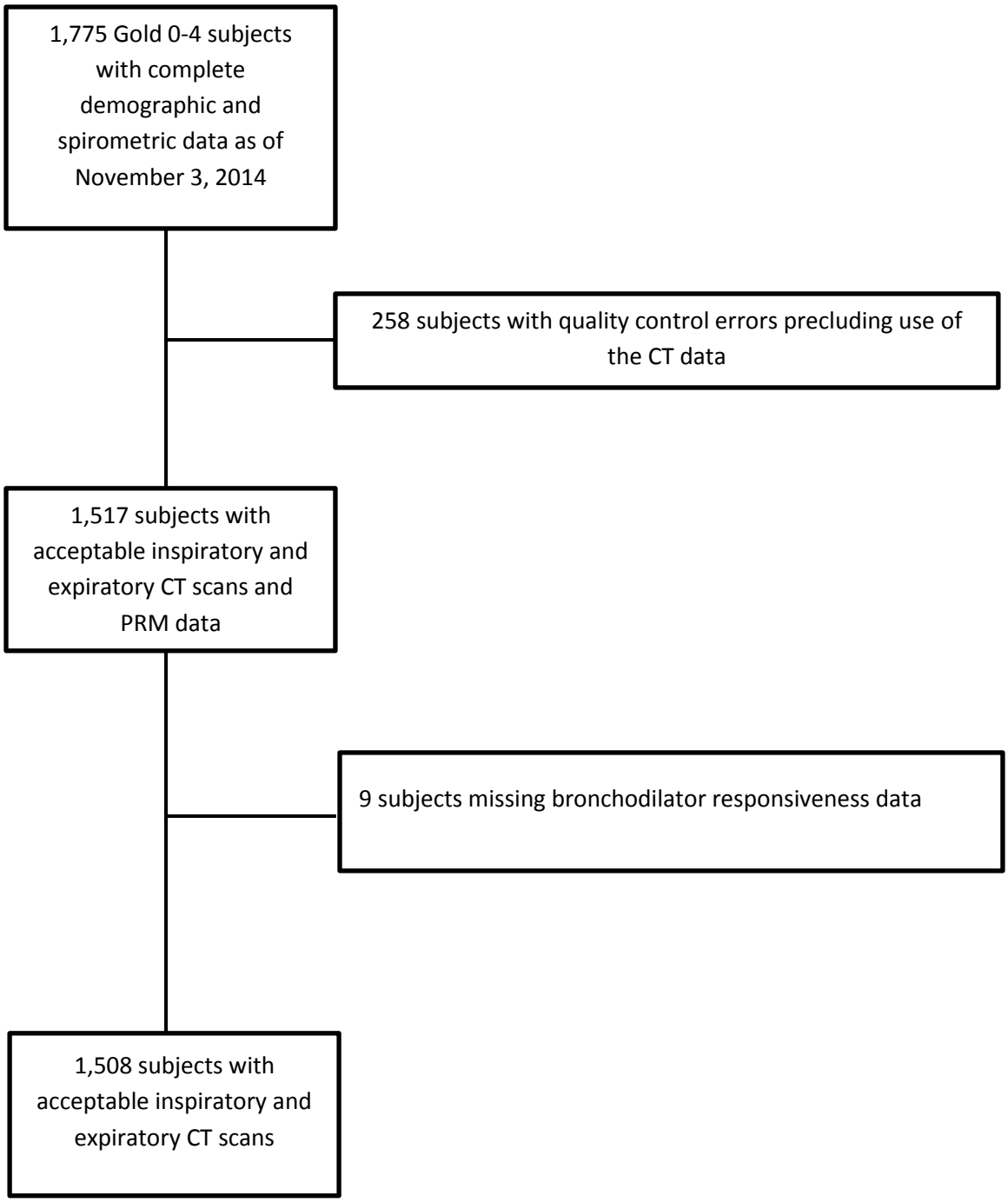
PRM = Parametric response mapping. GOLD = Global Initiative for Chronic Obstructive Lung Disease. PRM^{emph} = emphysema defined using parametric response mapping. PRM^{fSAD} = functional small airways disease defined using parametric response mapping. GOLD = Global Initiative for Obstructive Lung Disease.

Supplemental Figure E4: Distribution of PRM^{fSAD} and PRM^{emph} by disease stage.

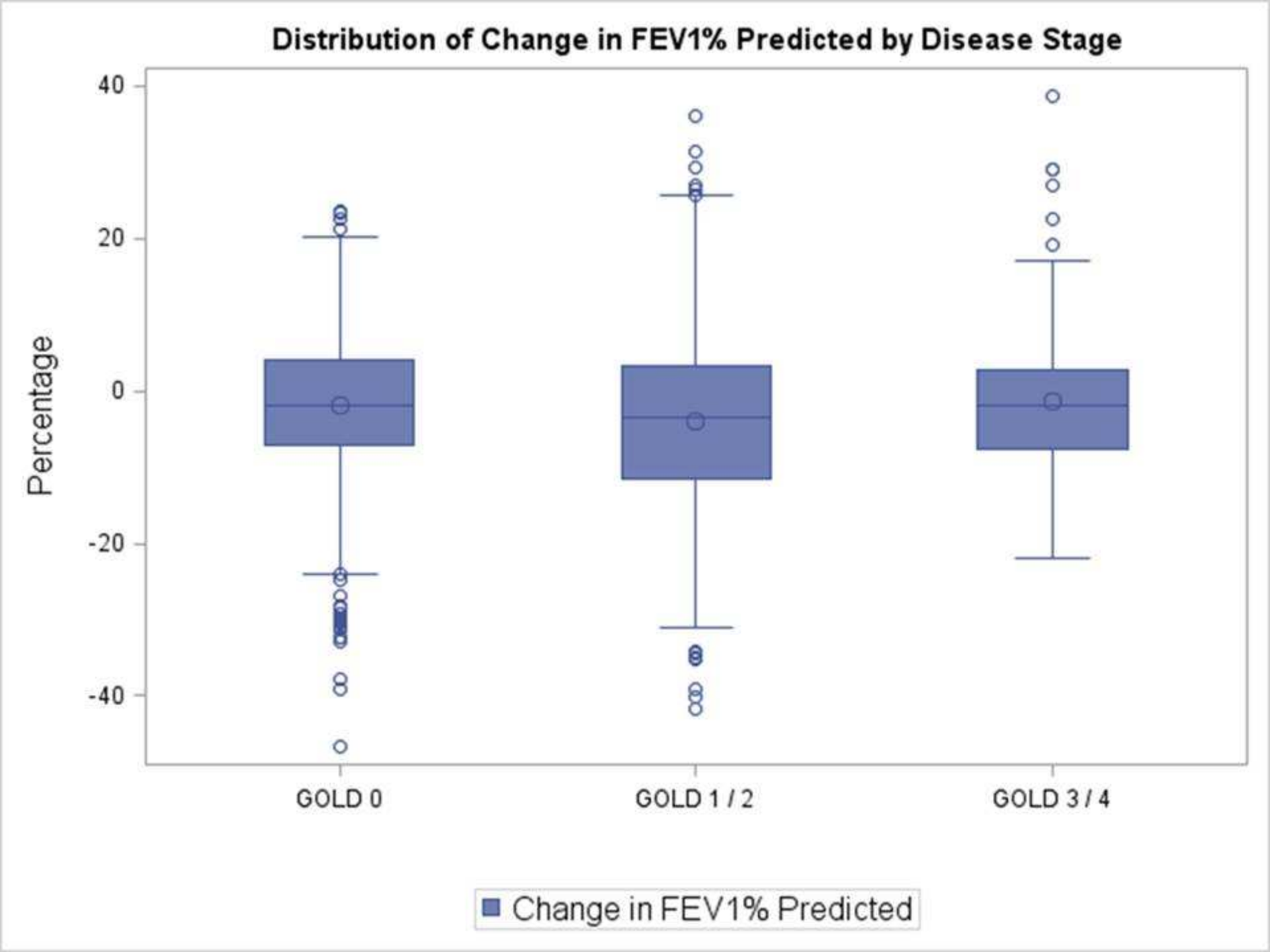
PRM = Parametric response mapping. GOLD = Global Initiative for Chronic Obstructive Lung Disease. PRM^{emph} = emphysema defined using parametric response mapping. PRM^{fSAD} = functional small airways disease defined using parametric response mapping.

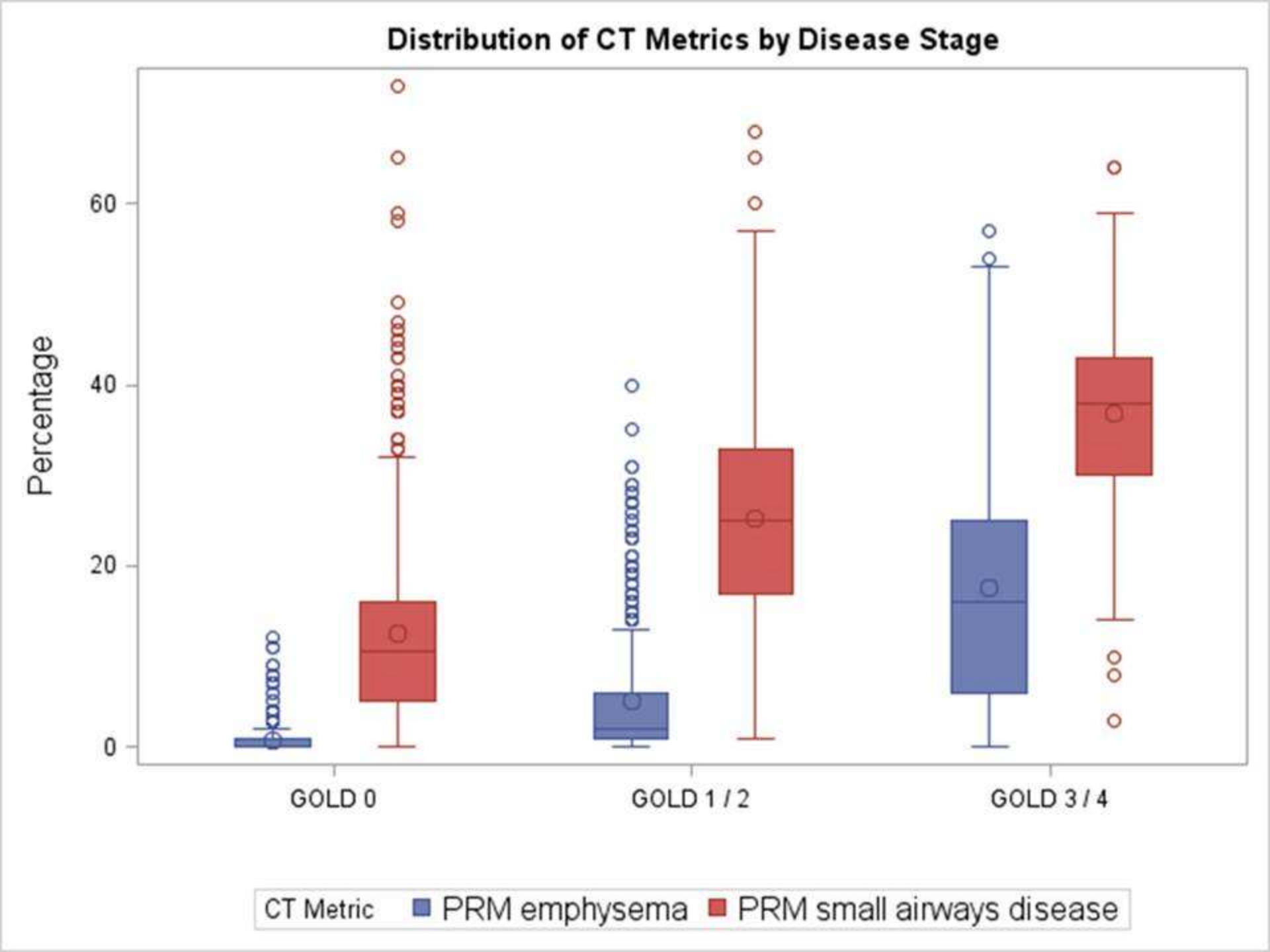

1. Biphasic CT Acquisition
Inspiration CT (HU)
Expiration CT (HU)
2. Image Processing
(Segmentation and Spatial Alignment)
Joint Density Histogram
of Aligned CT Images
Inspiration CT (HU)
Expiration CT (HU)
3. Classification Model
-500
-950
-1000
-856
-500
fSAD
Normal
Emphysema
Inspiration CT (HU)
Expiration CT (HU)
Classified Data
Inspiration CT (HU)
Expiration CT (HU)
Spatial Visualization

Supplemental Figure E2. Consort Diagram



CT = Computed Tomography. PRM = Parametric Response Mapping.


Distribution of Change in FEV1% Predicted by Disease Stage
Percentage
40
20
0
-20
-40
GOLD 0
GOLD 1 / 2
GOLD 3 / 4
Change in FEV1% Predicted


Distribution of CT Metrics by Disease Stage
Percentage
0
20
40
60
GOLD 0
GOLD 1 / 2
GOLD 3 / 4
CT Metric
PRM emphysema
PRM small airways disease