Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Pulmonary Arterial Enlargement and Acute Exacerbations of COPD Supplementary Appendix

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METHODS

Patient Populations:

The COPDGene® study includes self-reported non-Hispanic White and African American smokers with 10 pack-years or more of cigarette smoking, age 45-80 years from twenty-one U.S. clinical centers who after written informed consent underwent pre and post-bronchodilator spirometry and whole lung chest CT scanning in an effort to identify genetic factors associated with COPD[1]. Enrolment began in November 2007 and ended in April 2011. The COPDGene® study enrolled a total of 10,300 subjects and we included the 3,464 participants with Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage II-IV COPD and verified data including quantitative CT analysis. Of these patients, 2,985 (86%) participated in a longitudinal follow-up study (2.1 year median length of follow-up) to prospectively track their clinical course including the development of exacerbations using an automated system. Longitudinal follow-up participants were required to have a minimum of one follow up contact at least 6 months after initial enrollment and longitudinal follow-up surveys were conducted every 3 or 6 months by automated telephone, web based data entry, or direct contact by a research coordinator. The ECLIPSE study was a three year longitudinal study with the overall objective of identifying the factors that predict disease progression and exacerbations in individuals with different COPD subtypes, as well as biomarkers (including CT scan parameters) that may serve as surrogate end-points. Details regarding the ECLIPSE study cohort and protocol have been previously published[2,3].

Physiological and Symptom Assessments

For COPDGene® participants, demographics, smoking, and medical history were collected via self-administered questionnaires. Patients underwent spirometry using the

EasyOne™ system (ndd Inc., Zurich) before and after the administration of short-acting bronchodilating medication (albuterol)[1]. 6 minute walk test (6MWT) was performed according to ATS criteria[4]. Quality of life was assessed with the St. George's Respiratory Questionnaire (SGRQ)[5] and dyspnea with the Modified Medical Research Council questionnaire (MMRC)[6].

Exacerbation Determination

Exacerbations of COPD were self-reported in both the COPDGene® and ECLIPSE studies. These episodes were defined and quantified in both trials by answers from respiratory epidemiology questionnaires modified from the ATS Chronic Respiratory Disease Questionnaire (ATS-DLD-78)[7]. In both studies, participants were recorded as suffering a severe exacerbation if they developed increased dyspnea, cough and/or sputum production and required admission to the hospital for treatment. Mild-to-moderate exacerbations were defined by similar symptoms which were treated with antibiotics and/or systemic corticosteroids in the outpatient setting or during an emergency room visit. The occurrence and frequency of all exacerbations (mild-to-moderate plus severe) was also determined. The following series of questions was used at baseline in COPDGene®: "Have you had a flare-up of your chest trouble in the last 12 months?" If the answer was "No", then zero exacerbations were recorded. If the answer was "Yes", then the subject was directed to answer, "How was the flare-up treated?" Participants were recorded as suffering a severe exacerbation if the respondent answered affirmatively to: "Admitted to hospital." The total number of episodes to which the respondent answered affirmatively to any of the following was also recorded as the overall exacerbation frequency: "Took additional antibiotic or steroid medication which you keep at home"; "Consulted your doctor who prescribed additional antibiotic and/or steroid treatment, but did not admit you to the hospital";

or "Admitted to hospital." Respondents were allowed to report at most six such episodes as described previously[8]. Exacerbations during longitudinal follow-up were ascertained by asking "Since we last spoke, have you had an episode of increased cough and phlegm or shortness of breath, which lasted 48 hours or more." If patients answered yes, they were further asked whether they received antibiotics or steroids. If they answered yes to either of these questions, they were considered to have an exacerbation. In both studies, participants were recorded as suffering a mild to moderate exacerbation if they received a course of antibiotics and/or corticosteroid treatment, either in the outpatient setting or during an emergency room visit. Severe exacerbations were defined by admission to the hospital for treatment.

Imaging

For COPDGene® participants objective analysis of the lung parenchyma and airways was performed on volumetric CT scans of the chest obtained without contrast. Parenchymal analysis was performed using Slicer (www.Slicer.org), and airway analysis was performed using VIDA Pulmonary Workstation 2 (VIDA Diagnostics, Coralville, Iowa, www.vidadiagnostics.com). All lung volume with a CT attenuation value of less than -950 Hounsfield Units (HU) on the inspiratory scan was considered to be emphysematous tissue and CT attenuation of less than -856 HU on expiratory scans was considered gas trapping. Airway disease was measured by airway wall area percent (WA% = wall area/total cross sectional area) using the average of six 4th generation airways as reported previously[8,9].

Vascular measurements were made using baseline CT scans from COPDGene® and ECLIPSE by an investigator blinded to clinical characteristics. Using digital imaging and communications in medicine software (Osirix DICOM Viewer, Version 4.0, 32-bit, www.osirix-viewer.com), the interpreter would scroll the length of the pulmonary trunk from the level of the

right ventricle-PA junction to visually locate an image having both the bifurcation of the left and right PA present as well as the widest diameter of the main PA present. The interpreter measured the diameter of the main PA and the diameter of the ascending aorta (A) in its maximum dimension using the same images as demonstrated in Figure 1 (Original manuscript). In some instances, the widest diameter of the main PA is not uniform due to its variable oblique course as well as anatomic variability between the locations of the left and right PA. In these cases, the same method for measurement was employed. Since the aortic shape ranges between a near perfect circle and an ellipse, bi-dimensional measurements of the aortic diameter were averaged to give a final ascending aortic diameter for use in all analyses.

Statistical Analysis:

Baseline data from the COPDGene® cohort are expressed as means with standard deviations for normally distributed values. Bivariate analyses were conducted with two-tailed Fisher's exact test for categorical data and two tailed t-tests or Wilcoxon rank-sum test for continuous data where appropriate. Cohen's kappa (k) was calculated to identify the intra- and inter-observer agreement for measurements of PA/A > 1. Linear regression was used to calculate the association between echocardiographic estimates of PA pressure as well as inflammatory biomarkers and CT measured PA/A. Univariate logistic regression was used to determine the associations between patient characteristics (including the PA/A ratio) and the occurrence of a severe exacerbation of COPD in the year prior to enrolment in COPDGene®. Independent variables studied included age, gender, race, body mass index (BMI), smoking status (current versus former), pack-year smoking history, a prior diagnosis of chronic bronchitis, asthma, coronary artery disease, congestive heart failure, thromboembolic disease,

gastroesophageal reflux disease, sleep apnea, use of long-term supplemental oxygen, history of working in a hazardous environment (defined as exposure to dust or fumes), systolic blood pressure, forced expiratory volume in 1-second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, bronchodilator response, 6-minute walk test (6MWT), MMRC score, SGRQ score and the following CT metrics: percent emphysema, percent gas trapping, fourth-generation wall area percent, main PA diameter, ascending aorta diameter, and PA/A. Variables demonstrating a univariate association with severe exacerbation ($p<0.10$) were included in stepwise backward multivariate logistic models to adjust for confounders. In an effort to prospectively validate the association of PA/A with future severe exacerbations, we then examined the relationship between PA/A>1 and these events as reported in the COPDGene® longitudinal follow-up dataset and the ECLIPSE cohort using separate multivariate logistic regression and zero-inflated negative binomial models. These models included variables previously reported to be independently associated with AECOPD in the ECLIPSE study[2]: gastroesophageal reflux disease (GERD), FEV_1, history of AECOPD within the previous year, white blood cell (WBC) count, and quality of life as measured by the St George's Respiratory Questionnaire (SGRQ) score. Similar models for its association with all exacerbations were also developed. All analyses were performed with SPSS software (version 20.0) and p-values less than 0.05 were designated as statistically significant.

Correlation Between Echocardiogram Derived Pulmonary Artery Systolic Pressure and PA/A >1 in COPDGene®:

A subset (n=33) of subjects at one institution underwent trans-thoracic echocardiography in addition to CT scan. Estimates of pulmonary artery systolic pressure were calculated using standard techniques[10]. When stratified according to PA/A >1, both groups were similar in terms of demographics, smoking history, co-morbid illnesses, oxygen use, lung function and echocardiographic derived right atrial pressure and aortic diameter (32.2mm versus 31.4mm, p=0.61) as outlined in Table 1s. The PA/A >1 group had larger PA diameters (33.7mm versus 27.7mm, p=0.01), more self-reported exacerbations (11 versus 3, p=0.01), lower resting oxygen saturation (86% versus 92%, p=<0.001), shorter 6MWT (721 feet versus 1098 feet, p=0.03), higher tricuspid regurgitant velocity (2.96 m/s versus 2.42 m/s, p=0.03) and higher PA systolic pressure (38mmHg versus 31mmHg, p=0.04). Using linear regression between PA/A values and PA systolic pressure, a Pearson's correlation coefficient of r = 0.61 (0.33-0.79, p<0.001) was calculated. This was analyzed in order to determine a best-fit equation to determine estimated PA systolic pressure from CT measurements as seen in Figure 1s.

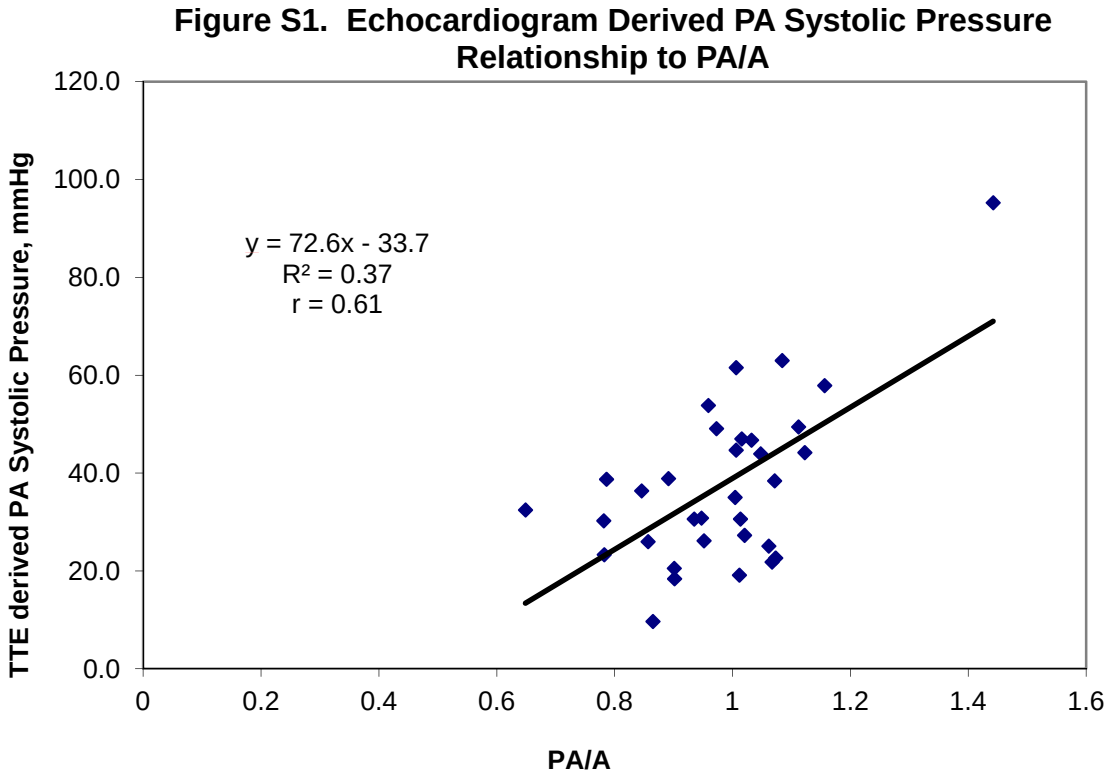

Figure S1. Correlation between Echocardiogram derived PA systolic pressure and PA/A. The best-fit equation of $y = 72.635x - 33.713$ (r^2=0.37) was derived using linear regression. Application of this equation yields a Pearson's correlation coefficient of r = 0.61 (p<0.001, 0.33-0.79) between estimated PA systolic pressure and PA/A values. Abbreviations: PA = pulmonary artery, A = aorta.

Table S1. Characteristics of Subjects with Echocardiogram Data in COPDGene®

	PA/A <1 (n=15)	PA/A >1 (n=18)	p-value
Age, years	65	63	0.57
Gender (Percent Male)	40%	28%	0.48
Race (Percent Non-Hispanic White)	100%	94%	0.37
GOLD Stage, Mean	3	3	0.73
BODE Index, Mean	4	5	0.35
Asthma	53%	39%	0.28
Pack Years Smoked	53	48	0.53
Current Smoker	7%	22%	0.23
Coronary Artery Disease	13%	6%	0.45
Heart Failure	7%	11%	0.67
Thromboembolism	7%	17%	0.40
Supplemental Oxygen Use	73%	89%	0.26
Resting Oxygen Saturation	92%	86%	<0.001
SGRQ	50	46	0.47
MMRC	2	3	0.19
FEV_1 (Percent Predicted)	38%	38%	0.98
FVC (Percent Predicted)	72%	70%	0.76
FEV_1/FVC	39%	41%	0.55
Right Atrial Pressure, mmHg	6.33	6.18	0.85
Tricuspid Regurgitant Velocity, m/s	2.42	2.96	0.03

Pulmonary Artery Systolic Pressure, mmHg	31	43	0.04
Echocardiogram Detected PH, mmHg	7%	28%	0.12
CT Detected PA Size, mm	2.77	3.37	<0.001
CT Detected Aorta Size, mm	3.22	3.14	0.59
6-minute walk distance, ft	1098	721	0.03
Self-reported COPD exacerbation, number	3	11	0.01

Data are presented as mean or percentages. Definition of abbreviations: GOLD = Global Initiative for Obstructive Lung Disease, BODE = body mass index, airflow obstruction, dyspnea, and exercise capacity index, SGRQ = St. George's Respiratory Questionnaire, MMRC = modified Medical Research Council questionnaire, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, PA = pulmonary artery, A = aorta.

Table S2. Patient Characteristics at Enrollment in COPDGene®

	PA/A <1 (n=2645)	PA/A>1 (n=819)	p-value
Age, years	64 (9)	63 (9)	0.003
Gender (Percent Male)	60%	42%	<0.001
Race (Percent Non-Hispanic White)	81%	67%	<0.001
GOLD stage II	56%	43%	<0.001
GOLD stage III	30%	36%	0.004
GOLD stage IV	14%	21%	<0.001
BMI, kg/m^2	28 (6)	29 (7)	<0.001
Hypertension	50%	53%	0.08
Chronic Bronchitis	28%	28%	0.76
Asthma	25%	34%	<0.001
Pack Years Smoked	54 (28)	50 (25)	0.001
Current Smoker	43%	36%	<0.001
Coronary Artery Disease	16%	17%	0.88
Heart Failure	4%	9%	<0.001
Thromboembolism	5%	9%	<0.001
Sleep apnea	16%	22%	<0.001
GERD	30%	34%	0.03
Peripheral Vascular Disease	4%	3%	0.24
Cerebrovascular Disease	6%	6%	0.58

Hazardous Job	64%	64%	0.96
Supplemental oxygen use	22%	44%	<0.001
6 minute walk distance, ft	1204 (415)	983 (450)	<0.001
SGRQ, total	38 (22)	48 (21)	<0.001
MMRC	2 (1.4)	3 (1.3)	<0.001
FEV_1 (Percent Predicted)	52 (18)	46 (18)	<0.001
FVC (Percent Predicted)	78 (17)	73 (18)	<0.001
FEV_1/FVC	0.5 (0.13)	0.48 (0.13)	<0.001
Aorta Diameter, cm	3.27 (0.38)	3.09 (0.35)	<0.001
PA Diameter, cm	2.75 (0.37)	3.33 (0.42)	<0.001
Percent CT Emphysema	12.6 (12.5)	14.0 (13.1)	0.01
Percent CT Gas Trapping	38.7 (20.7)	40 (20.6)	0.14
4^{th} Generation Wall Area Percentage	65.5 (2.4)	66.2 (2.2)	<0.001
Exacerbation Frequency in prior year	0.59 (1.09)	1.21 (1.48)	<0.001

Data are presented as mean (standard deviation). A hazardous job is defined as exposure to dusts or volatile chemicals at work. Definition of abbreviations: GOLD = Global Initiative for Obstructive Lung Disease, BMI = body mass index, SBP = systolic blood pressure, GERD = gastroesophageal reflux disease, SGRQ = St. George's Respiratory Questionnaire [range 0-100; higher scores denote worse quality of life with minimal important difference of 4], MMRC = modified Medical Research Council questionnaire [range 0-4; higher scores denote greater dyspnea], FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, PA = pulmonary artery, A = aorta, AECOPD = acute exacerbation of COPD

Table S3. Clinical Characteristics Associated with PA/A>1 in COPDGene® by Multivariate Logistic Regression

	OR	95% CI	p-value
Female Gender	2.16	1.62-2.88	<0.001
African American Race	1.95	1.34-2.84	0.001
BMI, per 1 kg/m^2 increase	1.03	1.004-1.05	0.02
Pack Years, per increase of 1	0.99	0.99-1.00	0.04
Former Smoker Status	1.43	1.04-1.98	0.03
Congestive Heart Failure	2.16	1.21-3.84	0.009
Sleep Apnea	1.41	0.98-2.04	0.07
Supplemental oxygen use	1.65	1.17-2.32	0.04
6 minute walk distance, per ft decrease	1.00	1.00-1.01	<0.001
FEV_1 (% Predicted), per 1% decrease	1.01	1.001-1.02	0.03
4^{th} Generation WA%, per 1% increase	1.10	1.03-1.17	0.003

Multivariate logistic regression model identifying factors independently associated with PA/A>1. Factors included in the model: age, gender, race, BMI, hypertension, asthma, pack-year history of smoking, smoking status, heart failure, thromboembolism, sleep apnea, gastroesophageal reflux disease, supplemental oxygen use, 6-minute walk distance, SGRQ, MMRC, FEV_1, CT detected percent emphysema, and CT measured 4^{th} generation WA%. Definition of abbreviations: GOLD = Global Initiative for Obstructive Lung Disease, BMI = body mass index, SGRQ = St. George's Respiratory Questionnaire, MMRC = modified Medical Research Council questionnaire, FEV_1 = forced expiratory volume in 1 second, PA = pulmonary artery, A = aorta, WA% = Wall Area Percent

Table S4. Univariate Associations with Severe COPD Exacerbations in COPDGene®

	OR	95% CI	p-value
Age, year	0.97	0.96-0.98	<0.001
Male Gender	0.91	0.77-1.07	0.24
Non-Hispanic White Race	0.52	0.44-0.63	<0.001
BMI, per increase of 1 kg/m^2	1.001	0.99-1.01	0.91
Hypertension	1.01	0.88-1.21	0.74
Peripheral Vascular Disease	1.05	0.69-1.62	0.81
Cerebrovascular Disease	1.25	0.90-1.72	0.18
Chronic Bronchitis	1.34	1.12-1.59	0.001
Asthma	2.03	1.71-2.40	<0.001
Pack Years Smoked	1.00	0.99-1.002	0.66
Current Smoker	0.89	0.76-1.05	0.18
Coronary Artery Disease	1.10	0.89-1.37	0.36
Heart Failure	1.87	1.36-2.57	<0.001
Thromboembolism	1.57	1.14-2.15	0.006
Gastroesophageal Reflux Disease	1.21	1.02-1.43	0.03
Sleep apnea	1.24	1.01-1.52	0.04
Hazardous Job	1.38	1.16-1.64	<0.001
Supplemental oxygen use	2.35	1.98-2.78	<0.001
6MWT, per foot decrease	0.99	0.99-0.99	<0.001
MMRC, per point increase	1.65	1.55-1.77	<0.001

SGRQ, per 1 point increase	1.04	1.04-1.05	<0.001
FEV_1, per percent decrease	1.03	1.02-1.03	<0.001
Bronchodilator Response	1.04	0.88-1.22	0.70
PA diameter, per cm increase	2.47	2.07-2.94	<0.001
Aortic diameter, per cm increase	0.43	0.34-0.53	<0.001
PA/A>1 present	7.44	6.23-8.89	<0.001
PA >2.8 cm	2.23	1.88-2.64	<0.001
Percent CT Emphysema	1.02	1.01-1.02	<0.001
Percent CT Gas Trapping	1.01	1.01-1.02	<0.001
4^{th} Generation Wall Area Percentage	1.14	1.08-1.21	<0.001

Definition of abbreviations: BMI = body mass index, 6MWT = six-minute walk test, SGRQ = St. George's Respiratory Questionnaire[range 0-100; higher scores denote worse quality of life with minimal important difference of 4] , MMRC = modified Medical Research Council questionnaire [range 0-4; higher scores denote greater dyspnea], FEV_1 = forced expiratory volume in 1 second, PA = pulmonary artery, A = aorta

References:

1. Regan EA, Hokanson JE, Murphy JR, et al. Genetic epidemiology of COPD (COPDGene) study design. COPD 2010;7:32-43.
2. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 2010;363:1128-38.
3. Vestbo J, Anderson W, Coxson HO, et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). Eur Respir J 2008;31:869-73.
4. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-7.
5. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis 1992;145:1321-7.
6. Brooks S. Surveillance for respiratory hazards. ATS News 1982:12-6.
7. Ferris BG. Epidemiology Standardization Project (American Thoracic Society). Am Rev Respir Dis 1978;118:1-120.
8. Han MK, Kazerooni EA, Lynch DA, et al. Chronic Obstructive Pulmonary Disease Exacerbations in the COPDGene Study: Associated Radiologic Phenotypes. Radiology 2011.
9. Nakano Y, Muro S, Sakai H, et al. Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. Am J Respir Crit Care Med 2000;162:1102-8.
10. Pepi M, Tamborini G, Galli C, et al. A new formula for echo-Doppler estimation of right ventricular systolic pressure. J Am Soc Echocardiogr 1994;7:20-6.

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