Original Research
Impact of Bronchiectasis on COPD Severity and Alpha-1 Antitrypsin Deficiency as a Risk Factor in Individuals with a Heavy Smoking History

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**Running Head:** Impact of Bronchiectasis on COPD and Alpha-1 as a Risk Factor

**Key Words:** bronchiectasis; alpha-1 antitrypsin; lung function; COPD

**Abbreviations:**

**Funding Support:** SPIROMICS was supported by contracts from the NIH/NHLBI (HHSN268200900013C, HHSN268200900014C, HHSN268200900015C, HHSN268200900016C, HHSN268200900017C, HHSN268200900018C, HHSN268200900019C, HHSN268200900020C), grants from the NIH/NHLBI (U01 HL137880 and U24 HL141762), and supplemented by contributions made through the Foundation for the NIH and the COPD Foundation from AstraZeneca/MedImmune; Bayer; Bellerophon Therapeutics; Boehringer-Ingelheim Pharmaceuticals, Inc.; Chiesi Farmaceutici S.p.A.; Forest Research Institute, Inc.; GlaxoSmithKline; Grifols Therapeutics, Inc.; Ikaria, Inc.; Novartis Pharmaceuticals Corporation; Nycomed GmbH; ProterixBio; Regeneron Pharmaceuticals, Inc.; Sanofi; Sunovion; Takeda Pharmaceutical Company; and Theravance Biopharma and Mylan. Genetic studies of \( SERPINA1 \) were supported by NHLBI grants R01 HL142992 and R01 HL111527 and resequencing services provided through the RS&G Service by the Northwest Genomics Center at the University of Washington, Department of Genome Sciences, under U.S. Federal Government contract number HHSN268201100037C from the National Heart, Lung, and Blood Institute.

**Date of Acceptance:** May 3, 2023  **Published Online Date:** May 16, 2023
Citation: Izquierdo M, Marion CR, Genese F, et al; for the National Heart, Lung and Blood Institute’s SubPopulations and InteRmediate Outcome Measures In COPD Study (SPIROMICS) investigators. Impact of bronchiectasis on COPD severity and alpha-1 antitrypsin deficiency as a risk factor in individuals with a heavy smoking history. *Chronic Obstr Pulm Dis.* 2023; Published online May 16, 2023. doi: [https://doi.org/10.15326/jcopdf.2022.0388](https://doi.org/10.15326/jcopdf.2022.0388)
Abstract

**Rationale:** Bronchiectasis is common among those with heavy smoking histories, but risk factors for bronchiectasis, including α1-antitrypsin deficiency and its implications for COPD severity are uncharacterized in such individuals.

**Objectives:** To characterize the impact of bronchiectasis on COPD and explore α1-antitrypsin as a risk factor for bronchiectasis.

**Methods:** SPIROMICS participants (N=914; ages 40-80 years; ≥20 pack-years smoking) had HRCT scans interpreted visually for bronchiectasis, based on airway dilation without fibrosis or cicatrization. We performed regression-based models of bronchiectasis with clinical outcomes and quantitative CT measures. We deeply sequenced the gene encoding α1-antitrypsin, *SERPINA1*, in 835 participants to test for rare variants, focusing on PiZ (Glu^{366}Lys, rs28929474).

**Measurements and Main Results:** We identified bronchiectasis in 365 (40%), more frequently in women (45% versus 36%, p=0.0045), older participants (mean age=66[SD=8.3] versus 64[SD=9.1] years, p=0.0083), and those with lower lung function (FEV₁%predicted=66 %[SD=27] versus 77%[SD=25], p<0.0001; FEV₁/FVC=0.54[0.17] versus 0.63[SD=0.16], p<0.0001). Participants with bronchiectasis had greater emphysema (%voxels ≤950HFU, 11%[SD=12] versus 6.3%[SD=9], p<0.0001) and PRM^{SAD} (26[SD=15] versus 19[SD=15], p<0.0001). Bronchiectasis was more frequent in the combined PiZZ and PiMZ genotype groups compared to those without PiZ, PiS, or other rare pathogenic variants (N=21 of 40[52%] versus N=283 of 707[40%], OR=1.97; 95%CI=1.002, 3.90, p=0.049), an association attributed to whites (OR=1.98; 95%CI = 0.9956, 3.9; p=0.051).
Conclusions: Bronchiectasis was common in those with heavy smoking histories and was associated with detrimental clinical and radiographic outcomes. Our findings support α1-antitrypsin guideline recommendations to screen for α1-antitrypsin deficiency in an appropriate bronchiectasis subgroup with a significant smoking history.
INTRODUCTION

Chest CT scans have become commonplace in both clinical practice and research, resulting in the demonstration by epidemiologic studies of the high prevalence of bronchiectasis in older individuals with Chronic Obstructive Pulmonary Disease (COPD) and a history of cigarette smoking (1, 2). Estimates of bronchiectasis prevalence in COPD range between 4-72%, likely related to the differing ages and tobacco smoke-exposure among cohorts (3). The largest meta-analysis of six observational studies totaling 881 participants with COPD noted a mean prevalence of 54.3% with bronchiectasis (1). This frequent association motivated the GOLD guidelines to acknowledge bronchiectasis as a comorbid factor in COPD (4).

Clinical associations of bronchiectasis in COPD include lower lung function (1) and more frequent exacerbations (5, 6). Among bronchiectasis patients, those with COPD were more likely to be colonized with *Pseudomonas* species, a risk factor for increased mortality, compared to those without COPD (7-9). The etiologic factors underlying the pathogenesis of bronchiectasis are unclear but are likely an overlap of features related to the development of an infective phenotype overlapping with COPD characterized by the mucus hypersecretion, mucin dysregulation, and impaired mucociliary clearance characteristic of genetic causes of bronchiectasis and chronic bronchitis.

In individuals with a smoking history, α1-antitrypsin deficiency is the strongest genetic risk factor for COPD. α1-antitrypsin deficiency has been implicated in concomitant bronchiectasis development, due to loss of inhibition of neutrophil elastase and the resulting inflammatory and proteolytic destruction of the large airways (10). Besides biologic plausibility, the relationship between α1-antitrypsin deficiency and bronchiectasis is based on case reports and α1-antitrypsin deficiency registry-based epidemiologic studies, irrespective of smoking history.
Bronchiectasis was found in the majority of those in a registry-based study enriched for α1-antitrypsin deficiency, and was associated with CT scan-based emphysema but not with reduced lung function (15). In contrast, in a general population with CT scan-based bronchiectasis, α1-antitrypsin deficiency was rarely found (16). Gene-by-environment interactions with variation at the locus encoding α1-antitrypsin, SERPINA1, likely determines the relationship between α1-antitrypsin deficiency and bronchiectasis development in individuals with smoking histories. However, both the full extent of the clinical implications of bronchiectasis on COPD severity and the impact of SERPINA1 variation on development of bronchiectasis in those with heavy smoking histories have to be determined (17).

We hypothesized that the presence of bronchiectasis will adversely impact COPD risk and severity and that SERPINA1 variation is a risk factor for bronchiectasis in individuals with a significant smoking history. To test these hypotheses, we evaluated clinical and genetic risk factors for CT scan-based bronchiectasis and its effect on COPD severity in a subgroup of the SPIROMICS cohort with visually read CT scan data.

METHODS

Study population

The Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS) is an NHLBI-sponsored multicenter observational study of COPD designed to further explore COPD and potential therapeutics. Here, we analyzed 914 current or ex-smoking participants with ≥20 pack-years smoking history, with or without spirometrically defined COPD (post-bronchodilator FEV1/FVC ratio<0.7) based on previously described strata 2-4 (SPIROMICS strata 2 [N=287], 3
Participants were 40-80 years old at enrollment; all had coached inspiratory (total lung capacity) and coached expiratory (residual volume) baseline thoracic high-resolution computed tomography (HRCT) scans. This analysis examines those with radiologist visual reads. All SPIROMICS participants were characterized with post-bronchodilator spirometry and standardized questionnaires. Consent for the clinical and genetic studies has been described. Protocols and ethics criteria were reviewed and approved by institutional review boards at each participating site.

**Statistical analysis**

**Definition of Bronchiectasis and Clinical Outcomes**

Bronchiectasis was determined using a lack of tapering over 2 cm and airway size greater than adjacent pulmonary artery size as bronchial/arterial ratios alone has the potential to misclassify the presence of bronchiectasis. These determinations were made by a single chest radiologist visually identifying radiographic evidence of bronchiectasis on standard SPIROMICS CT scans without the presence of concomitant pulmonary fibrosis or cicatrization in the area of bronchiectasis. Linear regression models for continuous outcomes tested for the association between bronchiectasis and our co-primary lung function measures of post-bronchodilator FEV1 and FVC as a percentage of predicted and the FEV1/FVC ratio. Secondary COPD-related outcomes included quantitative CT scan measures of air trapping based on the percentage of bilateral lung voxels ≤-856 Hounsfield units (HFU) at full exhalation, quantitative CT scan measures of emphysema based on the percentage of bilateral lung voxels ≤-950HFU at full inspiration, six-minute walk distance, and COPD Assessment Test (CAT) score (dichotomized at ≥10) which were evaluated with linear regression models for continuous outcomes and logistic regression for dichotomous outcomes (Figure 1). Regression-based model
included age, sex, BMI, race, pack-years smoking history, current smoking status, and clinical site with height included for radiographic measures. Analyses were performed in all patients with ≥20 pack-years smoking history and stratified by the presence and absence of COPD based on GOLD criteria. A p-value <0.05 was used to determine significance. Analyses were performed using JMP Pro (version 15.2.1 SAS Institute Inc., NC, USA).

**SERPINA1 DNA Resequencing and Genetic Studies**

To identify less common and low frequency-to-rare SERPINA1 variants, n=835 participants (n=668 whites) underwent deep DNA resequencing of a 16.9kB genomic region of containing SERPINA1 with sequencing coverage at an average read depth of 61.8 reads (×; median=60.5×) through the NHLBI Resequencing and Genotyping Service (RS&G) as previously described (Figure 1)(20). This same subset had concentrations of α1-antitrypsin and C-reactive protein (CRP) measured on their baseline samples using the RBM-Myriad platform (Austin, TX).

As described above for analyses of COPD-related outcomes, we evaluated associations of bronchiectasis with genotype groups, using regression-based allelic association tests and burden tests (20). Groups were defined based on the presence or absence of PiZ (Glu366Lys, alleles C/T, rs28929474), PiS, and other non-PiS or PiZ low frequency-to-rare variants (allele frequency<0.05, VR). Thus, these burden-based regression models compared individuals without a PiZ allele (“No Z” genotype), those with only one copy of PiZ without background PiS or other rare variants (“PiMZ” genotype), and Pi Z homozygotes (“PiZZ” genotype). In both allelic association and burden models, covariates consisted of age, sex, BMI, pack-years smoking history, five principal components of genetic ancestry using EIGENSOFT (22). These models
were performed for the multi-racial (white vs other) cohort and stratified by race to identify ancestry-specific effects.

RESULTS

Baseline Characteristics Based on Bronchiectasis

Overall, bronchiectasis was common (40%) among these participants with at least 20 pack-years smoking history. Bronchiectasis was more frequently found in women than men (45% versus 36%, p=0.0045) (Table 1). Those with bronchiectasis were on average slightly older (mean age=66 [SD=8.3] versus 64 [9.1] years, p<0.0001) and as a group were more likely to have spirometrically-defined COPD (79% versus 61% of participants, p<0.0001). Participants with bronchiectasis had a significantly reduced lung function (FEV1 % predicted=66% [SD=27] versus 77% [SD=25], p<0.0001 [Figure 2]; FVC% predicted=89% [SD=19] versus 92% [SD=17], p=0.0083; FEV1/FVC ratio=0.54 [SD=0.17] versus 0.63 [SD=0.16], p<0.0001 [Table 1]). Their exercise capacity was worse: six-minute walk distance=392 [SD=116] versus 423 [SD=116], p=0.014), and they had a greater symptom burden, as evidenced by both CAT scores ≥10, (69% versus 59% of participants; OR=1.75, 95%CI=1.25-2.45, p=0.00093) and the St. Georges Respiratory Questionnaire which was statistically but not clinically significant (SGRQ, p=0.00027) (23). However, they did not have significantly greater smoking histories or prospective exacerbations.

Individuals with bronchiectasis also had greater quantitative CT-based evidence of other lung anatomic abnormalities, including greater air trapping %voxels ≤-856HU=33% [SD=22] versus 22% [19], p<0.0001), emphysema (%voxels ≤-950HU=11% [SD=12] versus 6.3% [SD=9], p<0.0001), and functional small airways disease (PRMBSAD=26 [SD=15] versus 19...
[SD=15], p<0.0001, Table 1). Of note, PRM$^{\text{RSAD}}$ represents regions of air trapping on expiration not associated with regional emphysema on inspiration.

**COPD-stratified analysis**

Among all those with bronchiectasis, a spirometrically-defined diagnosis of COPD was more commonly appreciated (46% versus 26%, p<0.0001, Figure 3). In the COPD subgroup, the presence of bronchiectasis was associated with worse lung function (FEV$_1$=57% [SD=22.8] vs 65% [SD=22.7] predicted, p=0.0009; FVC=87% [SD=20.3] vs 90% [SD=18.7] predicted, p=0.076; FEV$_1$/FVC=0.49 [SD=0.14] versus 0.53 [SD=0.12], p=0.0024) than in its absence. COPD participants with bronchiectasis showed higher CT-based air trapping (39% [SD=20.8] versus 31% [SD=19.4], p=0.02). They also experienced worse quality of life, based on higher SGRQ scores (38 [SD=18.2] vs 35 [SD=20], p=0.033] and greater symptom burden (CAT score≥10: 76% versus 65% of participants, p=0.0057) compared to COPD participants without bronchiectasis (Table 2).

**α1-antitrypsin, SERPINA1, and the PiZ Variant**

In the subgroup of n=835 participants (n=668 whites) with plasma measurements, concentrations of α1-antitrypsin and CRP were not significantly associated with the presence of bronchiectasis (Table 1). With respect to the PiZ variant (rs28929474, alleles C/T, Glu$^{366}$Lys), bronchiectasis was found in 3 (75%) of 4 minor allele homozygotes for rs28929474, 18 (46%) of 39 CT heterozygotes and 309 (39%) of 792 CC homozygotes. In a dominant model, (where the assumption is made that having one or more allele of interest will cause the phenotype being investigated) the combined TT homozygote and CT heterozygote groups had a numerically
higher frequency of bronchiectasis compared to CC homozygotes (OR=1.7, 95%CI=0.89-3.26, p=0.11, Table 3). Genotype associations between CC homozygotes versus TT homozygotes (OR=8.79, 95%CI=0.88-87.6, p=0.063) and CC homozygotes versus CT heterozygotes (OR=1.45, 95%CI=0.74-2.88, p=0.28, Table 3) were not significant.

The PiS SNP was not significantly associated with increased bronchiectasis (21 of 57 [37%] versus 309 of 778 [40%] for PiS heterozygotes versus common allele homozygotes (OR=0.85, 95%CI=0.47-1.5, p=0.58). The cumulative burden of non-S or Z variation was not significantly associated with the increased presence of bronchiectasis, but showed an opposite association (5 of 29 [17%] with at least one rare variant versus 283 of 707 [40%] without variants, OR=0.31, 95%CI=0.11-0.85, p=0.013). Accordingly, we focused our burden-based studies on the presence or absence of PiZ.

Burden-based regression models limited to whites demonstrated bronchiectasis in 18 of 34 (53%) PiMZ heterozygotes without background rare SERPINA1 variation and 3 of 4 (75%) PiZZ homozygotes, compared to 220 of 554 (40%) without a PiZ allele. A dominant model showed near significant associations when comparing the combined PiMZ and PiZZ genotype groups to those without a PiZ allele (OR=1.98, 95%CI=0.996-3.9, p=0.051, Figure 4a). These findings were driven by PiZZ homozygotes, who showed near significant associations versus those without a PiZ allele (OR=8.02, 95%CI=0.79-80.73, p=0.052). The association for PiMZ heterozygotes was weaker but in the same direction and not significant (OR=1.72, 95%CI=0.84-3.55, p=0.13, Figure 4a).

These PiZ-based associations with bronchiectasis were similar for the combined racial groups, where bronchiectasis was detected in 18 of 36 (50%) PiMZ heterozygotes (OR=1.71, 95%CI=0.84-3.48, p=0.13) and 3 of 4 (75%) PiZZ homozygotes (OR=8.38, 95%CI=0.84-83.8,
p=0.070) compared to 283 of 707 (40%) without a PiZ allele (Figure 4b). When all racial groups were combined, the dominant model showed significant associations for bronchiectasis in the combined PiMZ and PiZZ genotype groups compared to those without PiZ alleles (OR=1.97, 95%CI=1.00-3.90, p=0.049, Figure 4b).

DISCUSSION

Results of this large (N=914) multi-center cohort study define two inter-related features of bronchiectasis in individuals with heavy smoking histories. First, we show that bronchiectasis detected by CT visual reads was common (40%) in such individuals, and that they had significantly worse lung function and a greater symptom burden, especially among those with airflow obstruction, than those without bronchiectasis. Second, we demonstrate that the PiZ locus is a genetic risk factor for co-morbid bronchiectasis in COPD, and that the cumulative frequency of PiZZ and PiMZ genotypes in patients with COPD is not uncommon as shown in ours and other studies (20, 24). The ability to detect these novel associations was facilitated by the design of the SPIROMICS cohort, which required a heavier smoking history than many studies to date, and which spans COPD severities. This is the largest and most diverse cohort of individuals with heavy smoking histories characterized for CT scan evidence of bronchiectasis. An important strength is its prospective collection of physiologic, clinical, and quantitative CT outcomes plus both proteomic and genetic data specific to α1-antitrypsin biology. Our results have important implications for the care of those with significant smoking histories regardless of the presence of airflow obstruction, and should be investigated in COPD resulting from other injurious inhalational exposures.
Our findings extend multiple studies showing a correlation between COPD and bronchiectasis (1, 2). The 46% frequency of bronchiectasis we observed among SPIROMICS participants with COPD approximates results of a large meta-analysis, in which its prevalence was 54% among all with COPD and 57% in moderate-to-severe disease (1). In a bronchiectasis registry, the prevalence of COPD was found to be approximately 20% which is considerably lower than our findings, but the SPIROMICS cohort was enriched for a heavier smoking history and COPD of varying severities (18, 25). Identifying comorbid bronchiectasis is crucial, as it is associated with worse outcomes, such as more frequent exacerbations, greater airway colonization by potentially pathogenic microbes, and in those with moderate-to-severe COPD, higher two-year mortality (3, 8). Those same studies and one from Spain (26) noted that those with bronchiectasis had higher rates of colonization with *Pseudomonas aeruginosa*, which has been associated in COPD with longer hospitalization, greater rates of readmission and death (7, 27). It is likely that the recurring chronic bacterial infection common in bronchiectasis accelerates COPD progression (28). Hence, CT detection of bronchiectasis identifies a high-risk subset of COPD patients who could be targeted for interventions to improve outcome and survival, an important topic for future research. Similarly, a key future direction for the SPIROMICS cohort (29) will be to investigate the lower respiratory tract bacterial microbiome in relationship to anatomic bronchiectasis, using existing samples.

There are two plausible reasons that α1-antitrypsin concentrations were not significantly associated with bronchiectasis in our cohort. First, radiographic evidence of bronchiectasis has been highly variable (27-95%) in cohorts ascertained for α1-antitrypsin deficiency (14, 15, 30). This broad range likely reflects small sample sizes and the inclusion of younger individuals with less significant smoking histories. For *SERPINA1* genotypes previously strongly associated with
α1-antitrypsin deficiency (20), bronchiectasis frequency in SPIROMICS was within this range: 75% of PiZZ homozygotes and 51% of PiMZ heterozygotes. Conversely, a previous large screening cohort study ascertained for bronchiectasis alone rarely found individuals with α1-antitrypsin deficiency; however, it was based on α1-antitrypsin concentrations, not SERPINA1 or PiZ variation, and did not consider age or smoking history (11, 12, 16). These important risk factors interact with pathogenic SERPINA1 variation to cause bronchiectasis, as we and others have demonstrated.

Second, α1-antitrypsin is an acute phase reactant, upregulated by systemic inflammation as in both bronchiectasis and COPD, which might mask relative deficiency. Using SERPINA1 genetic markers to identify deficiency-associated genotypes could circumvent this issue. We demonstrated that having at least one PiZ allele was associated with bronchiectasis. Interestingly, the PiS locus was not significantly associated with bronchiectasis in our study which is a finding that merits exploration in future studies. We were underpowered to assess non-PI S or Z variants (Vr). In non-white racial groups where PiZ is much less frequent, we cannot exclude pathogenic compound heterozygote genotypes or ancestry-specific variation as risk factors for bronchiectasis (20). By suggesting that bronchiectasis is more frequent in those with PiZ genotypes, our findings support considering SERPINA1 risk variation, rather than evidence for α1-antitrypsin concentrations below the protective threshold, as a risk factor when a significant smoking history exists.

Limitations of our study include the non-population-based design of SPIROMICS, which preclude extrapolation to the general population. The associations we show are solely cross-sectional from the baseline visit. Moreover, SPIROMICS evaluated history of environmental respiratory exposures, and in a later clinical visit collected measures of social determinants of
health (including area deprivation index). Hence, evaluating longitudinal outcomes and additional factors for contribution to bronchiectasis development will be key future directions. Additional limitations include the fact that bronchiectasis was determined by a single radiologist rather than multiple as has been done in previous studies (13, 15). Furthermore, clinical and radiographic measures of severity were not taken into account, both of which necessitate exploration in future studies. Chronic bronchitis based on questions one and two of the SGRQ as surrogate for sputum production showed no significant differences in between those with and without bronchiectasis however this has its limitations as a marker of severity and merits further exploration (31).

This study highlights early recognition of radiographic bronchiectasis as a means to identify a group at-risk for adverse outcomes among those currently or previously exposed directly to tobacco products. Our results should also motivate investigating, in this group, therapies not traditionally recommended in patients with emphysema or COPD without frequent exacerbations. Specific examples could include long-term efforts to improve airway clearance and to reduce microbial burden. By demonstrating that the PiZ locus is a risk factor for bronchiectasis in this group, our findings support α1-antitrypsin guideline recommendations to screen for α1-antitrypsin deficiency in an appropriate subgroup, but provide evidence that screening might be most appropriate for those with a significant smoking history and at risk SERPINA1 genotypes.
Acknowledgments

Author Contributions: Manuel E. Izquierdo: Writing-original draft: writing-review and editing; formal analysis. Chad R. Marion: Conceptualization; methodology; writing—review & editing; writing—original draft. Frank Genese: Conceptualization; formal analysis. John D. Newell: Investigation; resources. Wanda K. O'Neal: Investigation; resources. Xingnan Li: Investigation; resources. Gregory A. Hawkins: Investigation; resources. Igor Barjaktarevic: Investigation; resources. R. Graham Barr: Investigation; resources. Christopher B. Cooper: Investigation; resources. David Couper: Investigation; resources. Jeffrey Curtis: Investigation; resources. Meilan K. Han: Investigation; resources. Nadia N. Hansel: Investigation; resources. Richard E. Kanner: Investigation; resources. Fernando J. Martinez: Investigation; resources. Robert Paine: Investigation; resources. Vickram Tejwani: Investigation; formal analysis. Prescott Woodruff: Investigation; resources. Joe Zein: resources; formal analysis. Eric A. Hoffman: Investigation; resources. Stephen P. Peters: Investigation; resources. Deborah A. Meyers: Supervision; resources; formal analysis; methodology; writing—review & editing; writing—original draft; investigation; conceptualization. Eugene R. Bleecker: Supervision; resources; formal analysis; methodology; writing—review & editing; writing—original draft; investigation; conceptualization. Victor E. Ortega: Conceptualization; investigation; funding acquisition; writing—original draft; methodology; validation; visualization; writing—review & editing; formal analysis; project administration; software; supervision; resources.
The authors thank the SPIROMICS participants and participating physicians, investigators and staff for making this research possible. More information about the study and how to access SPIROMICS data is available at www.spiromics.org. The authors would like to acknowledge the University of North Carolina at Chapel Hill BioSpecimen Processing Facility for sample processing, storage, and sample disbursements (http://bsp.web.unc.edu/). We would like to acknowledge the following current and former investigators of the SPIROMICS sites and reading centers: Neil E Alexis, MD; Wayne H Anderson, PhD; Mehrdad Arjomandi, MD; Igor Barjaktarevic, MD, PhD; R Graham Barr, MD, DrPH; Patricia Basta, PhD; Lori A Bateman, MSc; Surya P Bhatt, MD; Eugene R Bleecker, MD; Richard C Boucher, MD; Russell P Bowler, MD, PhD; Stephanie A Christenson, MD; Alejandro P Comellas, MD; Christopher B Cooper, MD, PhD; David J Couper, PhD; Gerard J Criner, MD; Ronald G Crystal, MD; Jeffrey L Curtis, MD; Claire M Doerschuk, MD; Mark T Dransfield, MD; Brad Drummond, MD; Christine M Freeman, PhD; Craig Galban, PhD; MeiLan K Han, MD, MS; Nadia N Hansel, MD, MPH; Annette T Hastie, PhD; Eric A Hoffman, PhD; Yvonne Huang, MD; Robert J Kaner, MD; Richard E Kanner, MD; Eric C Kleerup, MD; Jerry A Krishnan, MD, PhD; Lisa M LaVange, PhD; Stephen C Lazarus, MD; Fernando J Martinez, MD, MS; Deborah A Meyers, PhD; Wendy C Moore, MD; John D Newell Jr, MD; Robert Paine, III, MD; Laura Paulin, MD, MHS; Stephen P Peters, MD, PhD; Cheryl Pirozzi, MD; Nirupama Putcha, MD, MHS; Elizabeth C Oelsner, MD, MPH; Wanda K O’Neal, PhD; Victor E Ortega, MD, PhD; Sanjeev Raman, MBBS, MD; Stephen I. Rennard, MD; Donald P Tashkin, MD; J Michael Wells, MD; Robert A Wise, MD; and Prescott G Woodruff, MD, MPH. The project officers from the Lung Division of the National Heart, Lung, and Blood Institute were Lisa Postow, PhD, and Lisa Viviano, BSN;

Declaration of Interest
Dr. Izquierdo has nothing to disclose.

Dr. Marion has nothing to disclose.

Dr. Genese has nothing to disclose.

Dr. Newell reports grants from NIH, Medical Advisor with consulting income, patents and stock options with VIDA, book royalties from Elsevier.

Dr. O'Neal has nothing to disclose.

Dr. Li has nothing to disclose.

Dr. Hawkins has nothing to disclose.

Dr. Barjaktarevic reports personal fees from Astra Zeneca, personal fees from Boehringer Ingelheim, grants from AMGEN, grants and personal fees from GE Healthcare, personal fees from Grifols, personal fees from Verona Pharma, personal fees from GSK, grants and personal fees from Mylan/Theravance, outside the submitted work.

Dr. Barr reports grants from NIH, grants from Foundation for the NIH, grants from COPD Foundation, during the conduct of the study; grants from Alpha1 Foundation, personal fees from UpToDate, outside the submitted work.

Dr. Cooper reports grants from NIH/NHLBI, grants from Foundation NIH, during the conduct of the study; personal fees from PulmonX, other from GlaxoSmithKline, personal fees from NUVAIRA, personal fees from MGC Diagnostics, outside the submitted work.

Dr. Couper reports grants from NHLBI, grants from COPD Foundation, during the conduct of the study.
Dr. Curtis reports consulting fees paid to his institution from AstraZeneca PLC, Novartis AG, and CSL Behring LLC, outside this work; and personal travel support from AstraZeneca PLC, outside this work.

Dr. Han reports personal fees from GSK, personal fees from BI, personal fees from AZ, personal fees from Merck, personal fees from Mylan, non-financial support from Novartis, non-financial support from Sunovion, outside the submitted work.

Dr. Hansel reports grants and personal fees from AstraZeneca, grants and personal fees from GSK, grants from Boehringer Ingelheim, grants from NIH, grants from COPD Foundation, personal fees from Mylan, outside the submitted work.

Dr. Kanner has nothing to disclose.

Dr. Martinez reports grants from Department of Defense, during the conduct of the study; personal fees, non-financial support and other from AstraZeneca, personal fees, non-financial support and other from Boehringer Ingelheim, non-financial support and other from ProterrixBio, personal fees from Columbia University, personal fees and non-financial support from Genentech, personal fees and non-financial support from GlaxoSmithKline, personal fees and non-financial support from Inova Fairfax Health System, personal fees from MD Magazine, personal fees from Methodist Hospital Brooklyn, personal fees and non-financial support from Miller Communicatinos, personal fees and non-financial support from National Association for Continuing Education, personal fees and non-financial support from Novartis, personal fees from New York University, personal fees and non-financial support from Pearl Pharmaceuticals, personal fees and nonfinancial support from PeerView Communications, personal fees and non-financial support from Prime Communications, personal fees and non-financial support from Puerto Rican Respiratory Society,
personal fees and non-financial support from Chiesi, personal fees and non-financial support from Sunovion, personal fees and non-financial support from Theravance, personal fees from UpToDate, personal fees from WebMD/Medscape, other from Afferent/Merck, non-financial support from Gilead, non-financial support from Nitto, personal fees and other from Patara/Respivant, personal fees and non-financial support from Potomac, other from Biogen, personal fees and non-financial support from University of Alabama Birmingham, other from Veracyte, non-financial support from Zambon, personal fees from American Thoracic Society, grants from NIH, personal fees and non-financial support from Physicians Education Resource, personal fees from Rockpointe, other from Prometic, personal fees from Rare Disease Healthcare Communications, other from Bayer, other from Bridge Biotherapeutics, personal fees and non-financial support from Canadian Respiratory Network, other from ProMedior, personal fees and non-financial support from Teva, personal fees from France Foundation, personal fees and non-financial support from Dartmouth, other from Gala, personal fees from Physicians Education Resource, outside the submitted work.

Dr. Paine reports grants from NHLBI, grants from COPD Foundation, during the conduct of the study; grants from Department of Veterans Affairs, outside the submitted work.

Dr. Tejwani has nothing to disclose.

Dr. Woodruff is a consultant for Astra Zeneca, Theravance, Glenmark pharmaceuticals, Sanofi and Regeneron and has received funding from Genetech and the COPD Foundation.

Dr. Zein has nothing to disclose.

Dr. Hoffman is a founder and shareholder of VIDA Diagnostics, a company commercializing lung image analysis software developed, in part, at the University of Iowa.
Dr. Peters, MD, PhD reports grants from NIH, NHLBI, during the conduct of the study; personal fees from Array Biopharma, personal fees from Integrity CE, personal fees from AstraZeneca, personal fees from Aerocrine, personal fees from Boehringer-Ingelheim, personal fees from Experts in Asthma, personal fees from Gilead, personal fees from GlaxoSmithKline, personal fees from Merck, personal fees from Novartis, personal fees from Ono Pharmaceuticals, personal fees from Pfizer, personal fees from PPD Development, personal fees from Quintiles, personal fees from Sunovion, personal fees from Saatchi & Saatchi, personal fees from Targacept, personal fees from TEVA, personal fees from Theron, personal fees from AstraZeneca, personal fees from Sanofi and Regeneron, grants from NIH, NHLBI, outside the submitted work.

Dr. Meyers has nothing to disclose.

Dr. Bleeker reports other from NIH grant, clinical trials through his employer, Wake Forest School of Medicine and University of Arizona for AstraZeneca, MedImmune, Boehringer Ingelheim, Genentech, Johnson and Johnson (Janssen), Novartis, Regeneron, and Sanofi Genzyme, personal fees also serving as a paid consultant for AstraZeneca, MedImmune, Boehringer Ingelheim, Glaxo Smith Kline, Novartis, Regeneron, and Sanofi Genzyme outside the submitted work.

Dr. Ortega reports grants from NIH, personal fees from CSL Behring, and personal fees from Regeneron and Sanofi for Independent Data and Monitoring Committee participation outside the submitted work.
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29. Opron K, Begley LA, Erb-Downward JR, Freeman C, Madapoosi S, Alexis NE, Barjaktarevic I, Graham Barr R, Bleecker ER, Bowler RP, Christenson SA, Comellas AP, Cooper CB, Couper DJ, Doerschuk CM, Dransfield MT, Han MK, Hansel NN, Hastie...


### Table 1. Demographics and Clinical Characteristics of all Participants with and without Bronchiectasis.

<table>
<thead>
<tr>
<th></th>
<th>BOE+ (N=365, 40%)</th>
<th>BOE- (N=549, 60%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, Female (%)</td>
<td>185 (51)</td>
<td>223(41)</td>
<td>0.0045</td>
</tr>
<tr>
<td>Age, year (SD)</td>
<td>66 (8.3)</td>
<td>64 (9.1)</td>
<td>0.0083</td>
</tr>
<tr>
<td>Ethnic Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-Hispanic whites (%)</td>
<td>288(79)</td>
<td>441(80)</td>
<td>0.07</td>
</tr>
<tr>
<td>African Americans (%)</td>
<td>60(16)</td>
<td>84(15)</td>
<td></td>
</tr>
<tr>
<td>Other (%)</td>
<td>17(4.5)</td>
<td>24(4.5)</td>
<td></td>
</tr>
<tr>
<td>Smoking pack-years, mean (SD)</td>
<td>50(25)</td>
<td>49 (22)</td>
<td>0.68</td>
</tr>
<tr>
<td>BMI (SD)</td>
<td>27(5.3)</td>
<td>28(5.1)</td>
<td>0.057</td>
</tr>
<tr>
<td>Post-BD % predicted FEV1 (SD)</td>
<td>66(27)</td>
<td>77(25)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Post-BD% predicted FVC (SD)</td>
<td>89(19)</td>
<td>92(17)</td>
<td>0.0083</td>
</tr>
<tr>
<td>Post-BD FEV1/FVC (SD)</td>
<td>0.54(0.17)</td>
<td>0.63(0.16)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>289(79)</td>
<td>339(61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6-minute walk distance (SD)</td>
<td>392(116)</td>
<td>423(116)</td>
<td>0.014</td>
</tr>
<tr>
<td>SGRQ score (SD)</td>
<td>35(19)</td>
<td>31(20)</td>
<td>0.00027</td>
</tr>
<tr>
<td>CAT score≥10 (%)</td>
<td>222(69)</td>
<td>285(59)</td>
<td>0.00093</td>
</tr>
<tr>
<td>Chronic Bronchitis n (%)</td>
<td>148(42)</td>
<td>213(41)</td>
<td>0.06</td>
</tr>
<tr>
<td>COPD exacerbation first year (%)</td>
<td>84(24)</td>
<td>108 (20)</td>
<td>0.58</td>
</tr>
<tr>
<td>PRM ISAD (SD)</td>
<td>26(15)</td>
<td>19(15)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CT scan emphysema (SD)</td>
<td>11(12)</td>
<td>6.3(9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CT scan air trapping (SD)</td>
<td>33(22)</td>
<td>22(19)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$\alpha_1$-antitrypsin (mg/ml, SD)</td>
<td>1.96(0.47)</td>
<td>1.94(0.48)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

P-values for each comparison are from linear and logistic regression models adjusted for age, sex, race, BMI, pack-years smoking, site, and current smoking status. Data presented as means with standard deviation (SD) or numbers (N) with percentages for proportions. Computed Tomography Scan measures of emphysema, air trapping, and PRM ISAD were log-transformed for analysis and also adjusted for height. BOE=Bronchiectasis, BMI=Body Mass Index, Post-BD=Post-bronchodilator, %pred=percentage predicted, SGRQ=St. Georges Respiratory Questionnaire, chronic bronchitis was based on questions 1 and 2 of the SGRQ, CT scan air trapping=percent lung voxels<-856 Hounsfield units, CAT=COPD Assessment Test.
PRM\textsuperscript{fSAD}=parametric response mapping functional small airways disease, CT scan emphysema-percent lung voxels<-950 Hounsfield Units.
### Table 2: Clinical Characteristics of Participants with COPD

<table>
<thead>
<tr>
<th></th>
<th>BOE+ (289, 46%)</th>
<th>BOE- (339, 54%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI (SD)</strong></td>
<td>27(5.3)</td>
<td>28(5.0)</td>
<td>0.057</td>
</tr>
<tr>
<td>Post-BD % pred FEV1 (SD)</td>
<td>57(22.8)</td>
<td>65(22.7)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Post-BD% pred FVC (SD)</td>
<td>87(20.3)</td>
<td>90(18.7)</td>
<td>0.076</td>
</tr>
<tr>
<td>Post-BD FEV1/FVC (SD)</td>
<td>0.49(0.14)</td>
<td>0.53(0.12)</td>
<td>0.0024</td>
</tr>
<tr>
<td>6-minute walk distance (SD)</td>
<td>379(119.7)</td>
<td>408(125)</td>
<td>0.195</td>
</tr>
<tr>
<td>SGRQ score (SD)</td>
<td>38(18.2)</td>
<td>35(20)</td>
<td>0.033</td>
</tr>
<tr>
<td>CAT score ≥ 10 (%)</td>
<td>193(76)</td>
<td>195(65)</td>
<td>0.0057</td>
</tr>
<tr>
<td>Chronic Bronchitis (%)</td>
<td>121(44)</td>
<td>148(46)</td>
<td>0.24</td>
</tr>
<tr>
<td>COPD exacerbation first year (%)</td>
<td>80(28)</td>
<td>86(26)</td>
<td>0.6</td>
</tr>
<tr>
<td>PRM&lt;sub&gt;fSAD&lt;/sub&gt; (SD)</td>
<td>30(13.5)</td>
<td>26(13.8)</td>
<td>0.047</td>
</tr>
<tr>
<td>CT scan emphysema (SD)</td>
<td>13(11.9)</td>
<td>9(10.1)</td>
<td>0.0024</td>
</tr>
<tr>
<td>CT scan air trapping (SD)</td>
<td>39(20.8)</td>
<td>31(19.4)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

p-values for each comparison are from linear and logistic regression models adjusted for age, sex, race, BMI, pack-years smoking, site, and current smoking status. Data presented as means with standard deviation (SD) or numbers (N) with percentages for proportions. Computed Tomography Scan measures of emphysema, air trapping, and PRM<sub>fSAD</sub> were log-transformed for analysis and also adjusted for height. BOE=Bronchiectasis, BMI=Body Mass Index, Post-BD=Post-bronchodilator, %pred=percentage predicted, SGRQ=St. Georges Respiratory Questionnaire, chronic bronchitis was based on questions 1 and 2 of the SGRQ, CT scan air trapping=percent lung voxels<-856 Hounsfield units, CAT=COPD Assessment Test, PRM<sub>fSAD</sub>=parametric response mapping functional small airways disease, CT scan emphysema-percent lung voxels<-950 Hounsfield Units.
Table 3: Frequency of Bronchiectasis by PiZ SNP Genotype (C/T)

<table>
<thead>
<tr>
<th>PiZ Genotype (rs28929474, C/T)</th>
<th>BOE+</th>
<th>BOE-</th>
<th>Odds Ratio (95% Confidence interval)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>3 (75%)</td>
<td>1 (25%)</td>
<td>8.79(0.88-87.6)</td>
<td>0.063</td>
</tr>
<tr>
<td>CT</td>
<td>18 (46%)</td>
<td>21 (54%)</td>
<td>1.45(0.74-2.88)</td>
<td>0.28</td>
</tr>
<tr>
<td>TT/CT</td>
<td>21 (49%)</td>
<td>22 (51%)</td>
<td>1.7(0.89-3.26)</td>
<td>0.11</td>
</tr>
<tr>
<td>CC (reference)</td>
<td>309 (39%)</td>
<td>483 (61%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Regression-based models compared the frequency of bronchiectasis in TT, CT, or CT/TT genotype groups with the common allele homozygote genotype, CC. Logistic regression models adjusted for age, sex, race, BMI, pack-years smoking history, and current smoking status.
Figure Titles and Legends:

Figure 1: Flow Diagram of Analytical Methods for the Clinical and α1-Antitrypsin-based Studies of Bronchiectasis Study in SPIROMICS.

914 patients from the SPIROMICS cohort with (N=365) and without (548) bronchiectasis were evaluated for different clinical outcomes, including a subgroup analysis of individuals with COPD. Deep sequencing of the gene encoding α1-antitrypsin (SERPINA1) was performed in a subgroup of 835 patients from which we derived the frequency of PI type Z and S genotypes and evaluated plasma α1-antitrypsin concentrations for associations with bronchiectasis.

Figure 2: Mean post-bronchodilator FEV1 percent predicted in SPIROMICS participants with and without bronchiectasis (BOE).

Linear regression models adjusted for age, sex, race, BMI, pack-years smoking history, clinical site, and current smoking status.

Figure 3: Frequency of bronchiectasis in SPIROMICS participants with and without COPD.

COPD was defined by post-bronchodilator FEV1/FVC ratio<0.7. Logistic regression models adjusted for age, sex, race, BMI, pack-years smoking history, clinical site, and current smoking status.

Figures 4a and 4b: Frequency of bronchiectasis by PiZ-containing genotypes in (a) non-Hispanic whites and (b) the multi-ethnic SPIROMICS cohort.

Genotypes grouped by presence or absence of a PiZ genotype. The “No Z” group represents a PI MM wild type alleles with no additional background rare SERPINA1 variants, including PiS-containing genotypes and non-PiS-containing genotypes who were excluded. Logistic regression models adjusted for age, sex, race, BMI, pack-years smoking history, and current smoking status.
SPIROMICS Cohort with Visually Read CT Scans for Bronchiectasis (N=914 total):
- N with Bronchiectasis = 365
- N without Bronchiectasis = 548

Bronchiectasis Clinical Outcomes Study (N=914):
- Lung function
- COPD
- Chronic bronchitis
- Symptom/Quality of Life Measures
  - SGRQ, CAT, 6-minute walk distance
  - CT scan lung structure measures
  - Emphysema
  - Air trapping

α1-antitrypsin Bronchiectasis Study (N=835):
- N with Bronchiectasis = 330
- N without Bronchiectasis = 505

α1-antitrypsin gene (SERPINA1) resequencing analyses
- Pi type Z, Pi type S
- Pi type Z-based
  (No Z, MZ, ZZ)
Figure 2: Mean post-bronchodilator FEV1 percent predicted in SPIROMICS participants with and without bronchiectasis (BOE).
Figure 3: Frequency of bronchiectasis in SPIROMICS participants with and without COPD.
Figures 4a and 4b: Frequency of bronchiectasis by PiZ-containing genotypes in (a) non-Hispanic whites and (b) the multi-ethnic SPIROMICS cohort.