Family History Is a Risk Factor for COPD

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Background: Studies have shown that family history is a risk factor for COPD, but have not accounted for family history of smoking. Therefore, we sought to identify the effects of family history of smoking and family history of COPD on COPD susceptibility.

Methods: We compared 821 patients with COPD to 776 control smokers from the Genetic Epidemiology of COPD (COPD Gene) Study. Questionnaires captured parental histories of smoking and COPD, as well as childhood environmental tobacco smoke (ETS) exposure. Socioeconomic status was defined by educational achievement.

Results: Parental history of smoking (85.5% case patients, 82.9% control subjects) was more common than parental history of COPD (43.0% case patients, 30.8% control subjects). In a logistic regression model, parental history of COPD (OR, 1.73; $P < .0001$) and educational level (OR, 0.48 for some college vs no college; $P < .0001$) were significant predictors of COPD, but parental history of smoking and childhood ETS exposure were not significant. The population-attributable risk from COPD family history was 18.6%. Patients with COPD with a parental history had more severe disease, with lower lung function, worse quality of life, and more frequent exacerbations. There were nonsignificant trends for more severe emphysema and airway disease on quantitative chest CT scans.

Conclusions: Family history of COPD is a strong risk factor for COPD, independent of family history of smoking, personal lifetime smoking, or childhood ETS exposure. Although further studies are required to identify genetic variants that influence COPD susceptibility, clinicians should question all smokers, especially those with known or suspected COPD, regarding COPD family history.

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Abbreviations: 6MWT = 6-min walk test; BODE = BMI, airflow obstruction, dyspnea, and exercise capacity; COPD Gene = Genetic Epidemiology of COPD; ETS = environmental tobacco smoke; GOLD = Global Initiative for Chronic Obstructive Lung Disease; PAR = population-attributable risk; RR = relative risk; SES = socioeconomic status; SGRQ = St. George Respiratory Questionnaire

Previous studies have demonstrated familial aggregation of COPD.¹ Radiologic measures of emphysema and airways disease have also been shown to cluster in families.² However, cigarette smoking also clusters in families,¹ leading to several possible explanations for the apparent familial risk

of COPD: (1) genetic factors influence COPD susceptibility; (2) genetic factors influence cigarette smoking behavior; (3) children learn cigarette smoking behaviors from their parents; and/or (4) exposure of the developing lung to cigarette smoke, either in utero or during childhood, predisposes to adult lung

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disease. A combination of these factors likely influences COPD susceptibility.

Most prior COPD genetics studies have considered familial smoking as a shared environmental factor, and have attempted to adjust away the potential effects of personal smoking history. Family history of smoking as a COPD risk factor has not been assessed previously. However, it is important to quantify the genetic risk of COPD independent of the genetic susceptibility to cigarette smoking. A recent genome-wide association study of COPD found significant association with a locus on chromosome 15 (α -nicotinic acetylcholine receptor 3/5),³ which has previously been associated with lung cancer,^{4,6} peripheral arterial disease,⁶ and cigarette smoking,⁷ highlighting the potential genetic overlap between disease and risk factor. In a family study, the independent heritabilities of COPD and smoking can be calculated directly, although previous family-based studies have not attempted to disentangle the genetic effects on disease vs risk factor. In a case-control study, the effect sizes of family history of COPD and familial smoking behaviors on COPD risk provide an indirect assessment of heritability.

Therefore, in a large case-control study, the Genetic Epidemiology of COPD (COPDGene) Study, we tested the hypothesis that family history of COPD is associated with COPD risk, independent of family history of smoking and of prenatal or childhood smoke exposure. The secondary hypothesis was that patients with COPD with a family history of COPD would have more severe disease, as determined by physiology, imaging, and symptoms.

MATERIALS AND METHODS

Study Subjects and Procedures

Study enrollment criteria and phenotype assessment, including chest CT scan protocols, have been described previously (www.copdgene.org).⁸ Briefly, the COPDGene Study enrolled self-identified non-Hispanic white and non-Hispanic black subjects aged 45 to 80 years with at least 10 pack-years of lifetime smoking history. Subjects were enrolled at 21 US clinical centers. Subjects with other diagnosed lung diseases except asthma and subjects with a first or second degree relative enrolled in the study were excluded. The COPDGene Study was approved by the institutional review boards at Partners Healthcare (protocol #2007p000554) and other participating centers.

After providing written informed consent, subjects completed questionnaires on medical history, medications, and respiratory symptoms.⁹ The St. George Respiratory Questionnaire (SGRQ) was used to assess disease-related quality of life.¹⁰ Spirometry measured lung function before and after the inhalation of 180 μ g (two puffs) of albuterol, according to American Thoracic Society criteria.¹¹ Exercise capacity was assessed on a 6-min walk test (6MWT).¹² Computerized image analysis (3D Slicer; www.slicer.org)^{13,14} quantified the percent of emphysema on inspiratory chest CT scan (% of lung < -950 Hounsfield units) and gas trapping on

expiratory CT scan (% of lung < -856 Hounsfield units). The square root wall area of a hypothetical airway of 10 mm internal perimeter (Pi10) was used as a measure of airway wall thickness (VIDA Diagnostics; Iowa City, Iowa).¹⁵

Statistical Analysis

COPD was defined by GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage II or greater (postbronchodilator $FEV_1 < 80\%$ predicted with $FEV_1/FVC < 0.7$).¹⁶ Control subjects had normal spirometry ($FEV_1 \geq 80\%$ predicted with $FEV_1/FVC \geq 0.7$). Family history of COPD was represented by parental history and was considered present if either the subject's father or mother had a history of COPD, emphysema, or chronic bronchitis, determined by the subject's questionnaire. Parental history of smoking was positive if the subject's father or mother was reported to have ever been a cigarette smoker. Childhood environmental tobacco smoke (ETS) exposure was considered present if a subject lived with someone who smoked for at least 1 year while the subject was under the age of 18 y. School completed (dichotomized as some college vs no college) was used as a marker of socioeconomic status (SES).¹⁷

Contingency table analysis and Student *t* test were used for univariate comparisons. Logistic regression was used for analysis of COPD status, adjusted for age, sex, race, and significant predictors from the univariate analysis. Quantitative outcomes were analyzed with linear regression, adjusted for clinically relevant covariates. Covariates for FEV_1 and 6MWT distance were selected from prediction equations.^{18,19} Health-related quality of life and COPD exacerbations outcomes were adjusted for FEV_1 because of the known associations between lung function and these measures.^{20,21} Chest CT measurements were not adjusted for lung function.² Negative binomial regression was used to model the number of COPD exacerbations in the year prior to study enrollment. Statistical significance was determined by $P < .05$. Population-attributable risk (PAR) was calculated by the following equation²²: $PAR = P(\text{exposure}|\text{disease}) \times (\text{relative risk (RR)} - 1) / \text{RR} \times 100$. In the case-control study, the OR was used as an estimator of the RR.

RESULTS

Among the first 2,500 subjects enrolled in the COPDGene Study, 821 COPD cases and 776 control smokers were included in the analysis. Subjects with GOLD stage I COPD ($n = 212$) or with unclassified patterns on spirometry ($FEV_1 < 80\%$ with $FEV_1/FVC \geq 0.7$; $n = 227$) were excluded, because the clinical significance of these phenotypes was unclear.²³ Subjects with unknown parental history of COPD were excluded ($n = 464$). Among both subjects with COPD and control subjects, subjects with unknown parental history were more commonly black and had a greater frequency of parental history of smoking (e-Table 1).

Patients with COPD were older and had a greater lifetime smoking history (Table 1). There were more non-Hispanic white subjects than black subjects among patients with COPD. There was no difference in gender distribution between patients with COPD and control subjects. Patients with COPD had lower educational achievement and more commonly had a

Table 1—Characteristics of Patients With COPD (GOLD stage $\geq$ II) and Control Subjects With Normal Spirometry

Characteristic	Case Subjects	Control Subjects	P Value
No.	821	776	
Age, y	64.2 $\pm$ 8.4	58.1 $\pm$ 9.0	< .0001
Male sex	425 (51.8)	372 (47.9)	.13
Race			< .0001
Non-Hispanic white	682 (83.1)	544 (70.1)	
Black	139 (16.9)	232 (29.9)	
Attended college or technical school	488 (59.4)	557 (71.8)	< .0001
Pack-y of smoking	53.2 $\pm$ 26.3	37.1 $\pm$ 20.1	< .0001
GOLD stage			
II	405	...	
III	267	...	
IV	149	...	
Maternal history of COPD ^a	192 (24.6)	134 (17.6)	.0009
Paternal history of COPD ^a	225 (29.5)	136 (18.3)	< .0001
Any parental history of COPD ^a	353 (43.0)	239 (30.8)	< .0001
Maternal smoking history	417 (51.4)	388 (50.7)	.80
Paternal smoking history	621 (78.7)	551 (74.6)	.055
Any parental history of smoking	693 (85.5)	636 (82.9)	.17
Childhood ETS exposure	684 (83.3)	623 (80.3)	.12
Mother smoked while pregnant	194 (29.1)	170 (27.8)	.60

Data are presented as mean $\pm$ SD or No. (%). Subjects with unknown parental history of COPD were excluded. ETS = environmental tobacco smoke; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

^aCOPD, emphysema, or chronic bronchitis.

parental history of COPD. Although there was a trend toward increased paternal history of smoking in patients with COPD, there was no difference in maternal or total parental history of smoking, nor were there differences in childhood ETS exposure or in utero smoke exposure (Fig 1).

Along with demographic covariates, parental history of COPD, parental history of smoking, and childhood ETS exposure were entered into a logistic regression model to identify their independent effects on COPD status (Table 2). In this full model, parental history of COPD remained a significant risk factor (OR, 1.73; 95% CI, 1.36-2.20), but parental history of smoking and childhood ETS exposure were not significant. The effect of parental history of COPD was similar in a parsimonious model that excluded parental history of smoking and childhood ETS exposure, to simplify the model. The nonsignificant effects of parental history of smoking and childhood ETS exposure are unlikely to be due to colinearity between these variables; when each factor was entered separately into the parsimonious model, neither was significant (data not shown). Based on the OR from the parsimonious model, the PAR due to parental history of COPD was 18.6%. When each parent's smoking history was entered separately into the parsimonious

model, both paternal (OR, 1.66; 95% CI, 1.24-2.22; $P = .0006$) and maternal (OR, 1.51; 95% CI, 1.10-2.09; $P = .011$) smoking history were independent COPD risk factors. The effect of COPD parental history was attenuated when the parsimonious model was additionally adjusted for the clinical centers (OR, 1.43; 95% CI, 1.11-1.83; $P = .005$).

To further control for the effects of SES, we included a covariate for occupational exposure to dust, gas, smoke, chemicals, or fumes (Table 2). This composite variable for occupational exposure was a significant risk factor for COPD, but the effect estimate for educational level was not changed. When separate covariates for occupational dust exposure and exposure to gas, smoke, chemicals, or fumes were entered into the model instead of the composite occupational exposure variable, both were significant predictors (dust: OR, 1.29; 95% CI, 1.07-1.56; $P = .0075$; fumes: OR, 1.20; 95% CI, 1.02-1.42; $P = .026$). The age at which a subject started smoking regularly was not significant when added to the parsimonious model; however, the age of smoking initiation became significant when lifetime pack-years was removed (OR, 0.96 per year; 95% CI, 0.94-0.99; $P = .002$).

Because of the racial differences in subjects with known and unknown COPD parental history (e-Table 1), we limited the regression analysis to non-Hispanic white subjects to assess for potential bias. The effect of parental history was similar in the stratified analysis (OR, 1.87; 95% CI, 1.44-2.44; $P < .0001$). Parental history of smoking was not included in the parsimonious model, so there is no potential bias due to imbalances in this variable between subjects with known and unknown COPD parental history.

Among COPD cases, subjects with a parental history of COPD were younger and more common among non-Hispanic whites (Table 3). There was no difference in gender, education, or smoking history

FIGURE 1. Parental history and early life smoke exposures in patients with COPD and control smokers with normal spirometry. ETS = environmental tobacco smoke.

Table 2—Logistic Regression for COPD Status, Defined as GOLD Stage $\geq$ II

	Full Model ^a		Parsimonious Model ^a		Parsimonious Model + Occupational Exposure	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Age, per 10 y	2.01 (1.75-2.31)	<.0001	1.98 (1.73-2.26)	<.0001	2.02 (1.76-2.33)	<.0001
Female sex	0.87 (0.69-1.09)	.22	0.88 (0.70-1.10)	.25	0.99 (0.78-1.26)	.95
Black race	0.79 (0.59-1.05)	.11	0.78 (0.58-1.04)	.09	0.75 (0.56-1.01)	.06
Lifetime smoking, per 10 pack-years	1.25 (1.18-1.32)	<.0001	1.26 (1.19-1.33)	<.0001	1.24 (1.18-1.32)	<.0001
Attended college or technical school	0.48 (0.37-0.61)	<.0001	0.48 (0.37-0.61)	<.0001	0.49 (0.38-0.63)	<.0001
Parental history of COPD ^b	1.73 (1.36-2.20)	<.0001	1.76 (1.40-2.23)	<.0001	1.68 (1.32-2.13)	<.0001
Parental history of smoking	1.22 (0.82-1.83)	.32	...	...	...	...
Childhood ETS exposure	0.98 (0.67-1.44)	.91	...	...	...	...
Occupational exposure to dust, gas, smoke, chemicals, or fumes	...	...	...	...	1.52 (1.19-1.94)	.0008

See Table 1 legend for expansion of abbreviations.

^aThe full model includes demographic covariates as well as parental history of COPD, parental history of smoking, and childhood ETS exposure. The nonsignificant effects of parental smoking and childhood ETS exposure were dropped from the parsimonious model to simplify the model.

^bCOPD, emphysema, or chronic bronchitis.

comparing subjects with COPD with and without a parental history, although more subjects with a positive COPD parental history had a parental history of smoking or were exposed to childhood ETS. Subjects with a COPD parental history had more severe disease, measured by lower lung function, greater dyspnea, worse quality of life (higher SGRQ scores), and a greater number and more severe COPD exacerbations in the year prior to enrollment. Subjects with a COPD parental history had higher scores on the multidimensional BMI, airflow obstruction, dyspnea, and exercise capacity (BODE) index, which is a marker of poor long-term prognosis.²⁴ There were trends for increased quantitative measures of emphysema and gas trapping on chest CT scans in subjects with a COPD parental history.

We performed regression analyses for physiologic, symptomatic, and CT markers of COPD severity, adjusted for age, sex, race, pack-years of smoking, and additional clinically relevant covariates (Table 4). In the adjusted models, subjects with COPD with a positive parental history had lower lung function, reduced exercise capacity, worse quality of life, and more severe and more frequent COPD exacerbations. Patients with a COPD parental history tended to have increased emphysema, gas trapping, and airways disease on chest CT scans, although none of these associations met statistical significance.

To further investigate the effects of SES, we compared patients with COPD who had attended at least some college with those who had completed high school or less. Subjects with greater educational achievement were older, more commonly white, and had a lower lifetime smoking intensity (e-Table 2). In multivariate analyses, subjects with greater education had better FEV₁, 6MWD, BODE scores, and

quality of life (lower SGRQ scores) (e-Table 3). More highly educated subjects had a trend toward reduced emphysema on chest CT scans and had significantly less gas trapping and airway wall thickening. The results were consistent using wall area percent as a measure of airway disease ($P = .009$ for segmental airways; $P = .02$ for subsegmental airways).

DISCUSSION

In the COPDGene Study, a large, US, multicenter study of smokers with and without COPD, we found that subjects with a parental history of COPD had an increased risk of COPD, which was independent of parental history of smoking, personal lifetime smoking intensity, childhood ETS exposure, and in utero smoke exposure. Parental history of COPD may contribute to nearly 20% of the risk of COPD in the population. Subjects with a parental history of COPD had more severe disease, with lower lung function, exercise capacity, and quality of life, and increased dyspnea and COPD exacerbations. There were trends for greater severity of CT scan measures of emphysema and airway disease, although these did not reach statistical significance. In addition, we found that lower SES, measured by lower educational achievement, was a risk factor for both COPD status and COPD severity. SES appeared to affect airway disease, but not emphysema.

Previous studies have demonstrated familial risk of COPD.^{1,25-31} Although most of these studies have recorded and adjusted for individual smoking status, none has examined family history of smoking as an independent COPD risk factor. Several family studies of lung function in the general population have

Table 3—Characteristics of Patients With COPD (GOLD Stage $\geq$ II) With and Without a Parental History of COPD, Emphysema, or Chronic Bronchitis

Characteristic	Positive Parental History of COPD ^a	No Parental History of COPD ^a	P Value
No.	353	468	
Age, y	63.1 $\pm$ 8.4	64.9 $\pm$ 8.3	.002
Male sex	174 (49.3)	251 (53.6)	.22
Race			.0008
Non-Hispanic white	311 (88.1)	371 (79.3)	
Black	42 (11.9)	97 (20.7)	
Attended college or technical school	212 (60.1)	276 (59.0)	.75
Pack-y of smoking	54.7 $\pm$ 27.6	52.0 $\pm$ 25.3	.14
Parental history of smoking	341 (96.6)	352 (76.9)	< .0001
Childhood ETS exposure	338 (95.8)	346 (73.9)	< .0001
FEV ₁ % predicted	46.7 $\pm$ 18.4	50.5 $\pm$ 18.3	.004
FEV ₁ /FVC	0.46 $\pm$ 0.13	0.49 $\pm$ 0.13	.0037
GOLD stage			.015
II	157 (44.5)	248 (53.0)	
III	118 (33.4)	149 (31.8)	
IV	78 (22.1)	71 (15.2)	
BMI, kg/m ²	27.8 $\pm$ 6.8	28.0 $\pm$ 6.0	.69
MMRC dyspnea score	2.4 $\pm$ 1.3	2.0 $\pm$ 1.5	.0001
6MWT, ft	1,129 $\pm$ 404	1,157 $\pm$ 452	.34
BODE score	3.4 $\pm$ 2.1	2.9 $\pm$ 2.1	.0003
Number of COPD exacerbations in the past year			< .0001
0	179 (50.7)	304 (65.0)	
1	83 (23.5)	92 (19.7)	
$\geq$ 2	91 (25.8)	72 (15.4)	
Severe exacerbation in past year	95 (26.9)	88 (18.8)	.0057
SGRQ score	43.4 $\pm$ 20.5	36.2 $\pm$ 21.2	< .0001
% Emphysema, -950 HU	16.8 $\pm$ 13.8	15.0 $\pm$ 13.1	.073
% Gas trapping, -856 HU	43.5 $\pm$ 20.6	41.2 $\pm$ 20.4	.12
Airway wall thickness, Pi10	3.80 $\pm$ 0.12	3.79 $\pm$ 0.12	.49

Values are presented as mean $\pm$ SD or No. (%). 6MWT = 6-min walk test; BODE = BMI, airflow obstruction, dyspnea, and exercise capacity; HU = Hounsfield unit; MMRC = modified Medical Research Council; Pi10 = square root wall area of a hypothetical airway of 10 mm internal perimeter; SGRQ = St. George Respiratory Questionnaire. See Table 1 legend for expansion of other abbreviations.

^aCOPD, emphysema, or chronic bronchitis.

considered the effects of familial smoking, but the authors treated it as a shared environmental factor and not a separate genetic effect.³²⁻³⁴ We demonstrated that family history of COPD was a risk factor for COPD, independent of family history of smoking or personal smoking habits, and that family history affected COPD severity. These findings have not been demonstrated previously. Our results point to genetic effects on both COPD risk and disease severity.

Low SES has been long recognized as a risk factor for chronic respiratory illness,³⁵⁻³⁷ and we confirmed this relationship in a modern US COPD population. Low SES may be associated with reduced lung growth

due to fetal smoke exposure, poor nutrition, childhood respiratory illnesses, and childhood exposures, including ETS. In the COPDGene Study, we found no significant effects of either in utero or childhood ETS exposure. Low SES may influence smoking behaviors, such as age of smoking initiation and lifetime smoking intensity, but we found the effects of SES to be similar when these factors were included in the regression models. SES is highly correlated with occupation, and harmful occupational exposures may accelerate lung function decline. In our study, low SES remained a significant COPD risk factor, even when adjusting for crude measures of occupational exposures. We found low SES to be associated with airway disease, but not emphysema, on chest CT scans. This may point to the importance of adult exposures causing airway inflammation, and not childhood exposures causing reduced lung growth, as a potential mechanism for the influence of SES on COPD risk.

In this study, we used educational achievement as a marker of SES. SES can also be measured by other individual level factors, such as occupation or income.^{17,38} Educational achievement is usually completed in early adulthood and therefore may be better correlated with early life events, such as smoking initiation. In addition, patients with COPD may change occupation or stop working because of disability, so current occupation or income may not accurately reflect a summary of lifetime SES.³⁶

Our study has several limitations. We relied on subjects' questionnaires to determine parental history of COPD and smoking. Because COPD is underdiagnosed,³⁹ this may underestimate the true prevalence of family history of COPD. Subjects with COPD may be more aware of the terms COPD, emphysema, and chronic bronchitis, and therefore may be more likely to recall these diagnoses in their parents. Childhood ETS exposure is also subject to recall; therefore, we used a liberal definition of at least 1-year exposure.⁴⁰ In addition, the COPDGene Study questionnaires captured family history data on parents only, and not on siblings, children, or other relatives; in our analysis, parental history was used as a surrogate for family history. Assessment of family history in parents, who are older first-degree relatives, may be more relevant to COPD and other diseases of older adults than a family history in siblings or children.

Enrollment in the COPDGene Study was limited to non-Hispanic whites and non-Hispanic black subjects so we cannot generalize our results to other racial or ethnic groups. Although we performed a secondary stratified analysis in non-Hispanic whites, there were too few black subjects for a parallel analysis in black subjects only.

Table 4—Adjusted Models for Effects of Parental History of COPD (Includes COPD, Emphysema, and Chronic Bronchitis) on Severity Measures in Patients With COPD

Outcome	Additional Covariates ^a	Parental History Effect	
		β (SD) or OR (95% CI)	P Value
FEV ₁ , L	Height	−0.10 (0.04)	.0092
6MWT, ft	Height, weight	−55.1 (29.3)	.061
BODE score	...	0.52 (0.15)	.0006
SGRQ score	FEV ₁ % predicted	4.5 (1.2)	.0004
Number of COPD exacerbations in the past year	FEV ₁ % predicted, current smoking	1.49 (1.20–1.86) ^b	.0004
Severe exacerbation in past year	FEV ₁ % predicted, current smoking	1.42 (1.00–2.04)	.053
% Emphysema, −950 HU	Current smoking, BMI, CT scanner model ^c	1.22 (0.83)	.14
% Gas trapping, −856 HU	Current smoking, BMI, CT scanner model ^c	1.98 (1.30)	.13
Airways wall thickness, Pi10	Current smoking, BMI, CT scanner model ^c	0.015 (0.009)	.12

See Table 1 and 3 legends for expansion of abbreviations.

^aAll models are adjusted for age, sex, race, and pack-years of smoking.

^bRelative risk from negative binomial model.

^cCT scans performed on Siemens 64 Sensation scanners (Munich, Germany) gave aberrant lung density measurements; this scanner type was adjusted as a covariate in the models.

CONCLUSIONS

Despite these limitations, our data suggest that although there is some previously reported overlap in the genetic determinants of COPD and smoking behavior, there remain genetic influences on COPD that are independent of genetic effects on smoking. Genetic factors are also likely to affect COPD severity in terms of physiology, symptoms, and exacerbations. Plausible candidate genes for COPD and COPD-severity phenotypes have already been identified,^{3,41,42} and future work should focus on the identification of additional genes for COPD and COPD-related traits. However, the identification of genes for COPD will not necessarily improve prediction of COPD diagnosis or severity. Studies in cardiovascular disease have shown that inclusion of genetic variation data did not necessarily improve prediction over traditional risk factors, which include family history of myocardial infarction.^{43,44} Unlike COPD, physicians often assess family history of cardiovascular disease and other common diseases such as cancers and diabetes.^{45,46} Asking about COPD family history is a straightforward intervention. Therefore, clinicians should question all current or former smokers, especially those with known or suspected COPD, about their family history of COPD to aid in the diagnosis of COPD or to assist in the evaluation of disease severity.

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Dr Hersh: contributed to the study concept and design, data collection and analysis, statistical support, and writing and editing of the manuscript.

Dr Hokanson: contributed to data collection and analysis, statistical support, and writing and editing of the manuscript.

Dr Lynch: contributed to data collection and writing and editing of the manuscript.

Dr Washko: contributed to data collection and writing and editing of the manuscript.

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Dr Crapo: contributed to data collection and writing and editing of the manuscript.

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