Relationships Among Health-Related Quality of Life, Pulmonary Health, and Newborn Screening for Cystic Fibrosis

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Background: The objective of this study was to examine relationships between pulmonary health and health-related quality of life (HRQOL) in patients with cystic fibrosis (CF) evaluated longitudinally in the Wisconsin Newborn Screening Project.

Methods: Patients aged 8 to 18 years (mean $\pm$ SD, 13.5 ± 2.8) in early diagnosis ($n = 45$) and control ($n = 50$) groups completed Cystic Fibrosis Questionnaires (CFQs) to measure HRQOL at three data points over a 2-year period. Pulmonary health was evaluated concurrently by the Wisconsin chest x-ray scoring system (WCXR) and pulmonary function tests (PFTs).

Results: WCXR showed significant group differences ($P \leq .023$), with the early diagnosis group showing more-severe lung disease. When adjusted for group differences in mucoid *Pseudomonas aeruginosa* status and pancreatic status, however, WCXR differences and PFT data were not significant. Most patients (74%) had FEV₁ values $\geq 80\%$ predicted (within normal range). For patients aged < 14 years, as WCXR scores worsened CFQ respiratory and physical domain scores decreased (both $P \leq .007$). FEV₁/FVC showed a positive relationship with the respiratory and physical domains (both $P \leq .006$). WCXR scores for patients aged ≥ 14 years were associated with CFQ weight, respiratory, and health domains (all $P \leq .011$). FEV₁ was associated with CFQ weight, respiratory, health, and physical domains (all $P \leq .003$). Changes in pulmonary health were not associated with changes in CFQ over time. Significant group differences on the CFQ-Child social functioning domain favored the control group.

Conclusions: To our knowledge, this study is the first to compare pulmonary outcomes with HRQOL indicators assessed by serial, standardized, patient-reported outcome measures for patients with CF identified either through newborn screening or diagnosed by use of traditional methods. This study found no benefits of newborn screening for pulmonary health or HRQOL after controlling for risk factors. Using WCXR and PFT data collectively helped to identify associations between pulmonary health and HRQOL.

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Abbreviations: CF = cystic fibrosis; CFQ = Cystic Fibrosis Questionnaire; HRQOL = health-related quality of life; NBS = newborn screen; PFT = pulmonary function test; RCT = randomized clinical trial; WCXR = Wisconsin chest x-ray scoring system

Medical advances have significantly improved the longevity of patients with cystic fibrosis (CF). The median survival age is approximately 37 years, and many patients live well into middle age.¹ Newborn screening (NBS) is an innovation that provides early intervention for affected infants. Although neonatal diagnosis offers nutritional advantages, over time, patients experience complications that require increasingly complex treatments²⁻⁴ for which they and their families typically shoulder most of the burden. The

progressive nature of CF and treatment side effects can adversely affect every aspect of life. Thus, there has been a growing interest in understanding how this chronic illness and related life-long care affect health-related quality of life (HRQOL) for persons with CF.

This study examined relationships between pulmonary health and HRQOL in patients with CF who participated in the Wisconsin CF Neonatal Screening randomized clinical trial (RCT).² Although HRQOL

has been measured in short-term CF-related intervention studies⁵⁻⁹ and cross-sectional psychosocial research,¹⁰⁻¹³ the relationship between NBS and HRQOL in children and adolescents has not been thoroughly evaluated. Thus far, the RCT has consistently revealed better nutritional status among pre-symptomatic patients with CF diagnosed through NBS (early diagnosis group) compared with those with CF diagnosed traditionally by symptom identification (control group).²⁻⁴ Mixed results and confounding factors have been observed in pulmonary outcomes.^{14,15} Random chance led to more risk factors (genotype, pancreatic status) in the early diagnosis group. Furthermore, the RCT was implemented before the risk of *Pseudomonas* transmission through patient-to-patient contact was known. Consequently, a subsample of the early diagnosis group was exposed to and contracted *Pseudomonas aeruginosa*, adding to the risk factors in that group associated with greater pulmonary disease progression than in the control group.¹⁶ The current study further evaluates NBS for CF by examining the effects of pulmonary health on patient-reported HRQOL. Given known group differences in risk factors, we expected the following: (1) After controlling for risk factors, there would be no significant differences in pulmonary health between the early diagnosis and control groups, and (2) changes in pulmonary health over 2 years would be positively associated with HRQOL.

MATERIALS AND METHODS

Design

This study (descriptor No. 102 [Cystic Fibrosis in Children]) was one of many investigations conducted within the Wisconsin NBS Project, a longitudinal evaluation of the benefits and risks of

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NBS for CF.^{4,17} The original study, conducted from 1985 to 1994, involved random assignment of newborns into an early diagnosis or control group. Infants within the early diagnosis group were identified through NBS at a median age of 6.9 weeks (range, 0.43 weeks to 5.4 years, including five false-negatives). The condition of those in the control group was diagnosed by traditional methods or when the child's screening results were unblinded at age 4 years per study protocol (median age at diagnosis, 24 weeks; range, 4 days to 15.7 years, including six false-negatives). Parents of 145 children with CF (confirmed by sweat chloride levels of ≥ 60 mmol/L) provided written informed consent to enroll their children in the RCT. Six children were excluded as not meeting the criteria of having an NBS specimen collected and analyzed within 28 days after birth. Patients received regular evaluations and treatment through a study protocol based on standard practices for CF care. Details about the RCT can be found elsewhere.²

In the current HRQOL study, previously enrolled children with CF aged 8 to 18 years were invited to participate. Parents of minors and adult patients provided written informed consent. Children aged 14 to 17 years provided assent. From 2002 to 2006, we collected data for each patient yearly during three regularly scheduled clinical evaluations at one of two CF centers. Mean $\pm$ SD time between first and second evaluations was 1.1 ± 0.3 years and between second and third, 1.0 ± 0.3 years. These differences were not significant. The Institutional Review Boards at the University of Wisconsin, Madison, and the Medical College of Wisconsin, Milwaukee, approved both studies (UW protocol #1983-270 and #1998-105; MCW protocol #CHW 85/02, #HRR 9-85, #CHW 98/12, and #HRR 76-98).

HRQOL Sample

The current study included 95 patients aged 13.5 ± 2.8 years who participated in the original RCT (early diagnosis group, $n = 45$; control group, $n = 50$). Table 1 shows demographic and clinical characteristics of each group. Figure 1 illustrates the relationship between the original RCT sample and the HRQOL subsample. A comparison of demographic and clinical variables revealed no significant differences. With the exception of known risk factors, the early diagnosis and control groups of the current sample were comparable.

Patients were predominately white with a slight male majority; their parents were well educated, and most were married. As expected,^{4,16} the percentage of risk factors (genotype, pancreatic status, and *P aeruginosa*) was higher in the early diagnosis group, although only differences in mucoid *Pseudomonas* status coded as absent, intermittent (present in $< 75\%$ of cultures taken in the previous 2 years), or persistent (present in $\geq 75\%$ of cultures taken in the previous 2 years) reached statistical significance. The clinical characteristics of patients in this study were typical of patients with CF throughout the United States.¹⁸

Measures

Pulmonary Health: Pediatric pulmonologists and radiologists blinded to patient study groups independently scored chest radiographs using the Wisconsin Chest Radiograph System.¹⁹ Total Wisconsin chest x-ray scoring system (WCXR) scores were composite ratings of hyperinflation, peribronchial thickening, bronchiectasis, nodule/branching opacities, large round/ill-defined opacities, and atelectasis. Pulmonary function tests (PFTs) were routinely performed every 6 months. The Pediatric Alternate Spirometry System¹⁴ provided quality assurance by filtering out poor-quality data. This analysis included FEV₁ and FEV₁/FVC data collected closest to the dates of completed HRQOL measures. We used data representing patients' baseline pulmonary

status not associated with pulmonary exacerbations. All outcome measures were subject to rigorous quality control.^{4,17}

Health-Related Quality of Life: The Cystic Fibrosis Questionnaire (CFQ) measures HRQOL within eight domains for ages 6 to 11 years (interview) and 12 to 13 years (self-report) and 12 domains for ages ≥ 14 years (self-report).^{20,21} Four-point Likert scales rate the difficulty, frequency, or applicability of items. Higher standardized scores (0-100 scale) indicate better HRQOL. Ceiling effects have been noted for the eating, diges-

tive, and body image domains.²² Similar ceiling effects are apparent for both child versions.²⁰

In the current study, except for treatment (0.49) and social (0.52), reliability coefficients on CFQ-Child domains were good (0.73-0.82). Most CFQ-Adolescent/Adult domains had favorable reliability (0.70-0.93). Social (0.54), eating (0.60), and digestion (0.57) were marginal. Role (0.15) was dropped from the analysis because of poor reliability. These results were similar to previous reports.²⁰⁻²²

Statistical Analyses

CFQ-Child data for ages 6 to 11 and 12 to 13 years were combined because they contain the same questions. Internal consistency within CFQ domains was measured using Cronbach α . Mixed-effects linear regression analysis measured cross-sectional relationships between pulmonary health (WCXR, $n = 91$; FEV₁ and FEV₁/FVC, $n = 90$) and early vs late diagnosis and changes between two time points. To compensate for known sample bias, we controlled for mucoid *Pseudomonas*, pancreatic status, and different CFQ versions. Mixed-effects tobit regression models, including a random intercept for correlation between multiple observations for each patient, compensated for ceiling effects on all but the CFQ vitality domain and floor effects on the weight domain. CFQ scores were treated as left censored at the value of 0 and right censored at 100. We analyzed each pulmonary health measure separately. WCXR scores were included as their natural log.

Relationships between changes in CFQ scores and changes in pulmonary health over time were examined using mixed-effects linear regression analysis. Data from all three time points were used to produce two observations reflecting changes between times 1 and 2 and between times 2 and 3. Observations were defined as changes in CFQ scores between consecutive times (dependent variable) and changes in pulmonary health. We grouped patients into those with a decline of 5 or 10 points, an increase of 5 or 10 points, or no change in WCXR and PFT scores between time points.^{14,23,24} Then we examined changes in CFQ scores by group. We used mixed-effects tobit analysis to examine relationships between HRQOL and NBS status. All models evaluating group differences controlled for mucoid *Pseudomonas* and pancreatic status. All 95 patients provided data for at least one CFQ. Each CFQ analysis was conducted separately for 12 CFQ domains.

To address multiple comparisons and preserve an overall statistical significance level of .05, we selected a P value of $< .012$ for statistical significance. This value was determined by assessing the average correlation among the 11 CFQ domains and using this to modify a standard Bonferroni adjustment.²⁵ Reported P values are unadjusted; those considered statistically significant after adjustment are highlighted. See e-Appendix 1 for details about the statistical analyses.

RESULTS

HRQOL Sample

All patients completed the first CFQ. Most (96%) completed at least two CFQs, with 83% completing all three; 9.4% potential WCXR scores and 15.8% potential PFT scores were missing. Ninety-one patients had valid WCXR data, and 90 had valid PFT data for at least one of the three time points. CFQ data were missing because of participant attrition. Pulmonary health data were missing for lack of a valid WCXR score to match CFQ (40%) or vice versa (60%),

Table 1—Demographic and Clinical Characteristics of Early and Control Groups

Characteristic	Early Diagnosis	Control	Fisher P Value
No. patients	45	50	...
Sex			
Male	25 (55.6)	29 (58.0)	.8382
Female	20 (44.4)	21 (42.0)	...
Parent education			
Mother			
< High school	6 (14.6)	4 (8.9)	.5860
High school degree	15 (36.6)	18 (40.0)	...
Some college/tech	13 (31.7)	11 (24.4)	...
College degree	7 (17.1)	12 (26.7)	...
Missing	4	5	...
Father			
< High school	8 (19.5)	3 (6.8)	.1990
High school degree	15 (36.6)	14 (31.8)	...
Some college/tech	13 (31.7)	16 (36.4)	...
College degree	5 (12.2)	11 (25.0)	...
Missing	4	6	...
Parent marital status (at baseline)			
Single	7 (15.6)	7 (14.0)	.3920
Married	38 (84.4)	40 (80.0)	...
Divorced/separated	0 (0.0)	3 (6.0)	...
Race/ethnicity			
White	43 (95.6)	50 (100.0)	.2217
Black	0 (0.0)	0 (0.0)	...
Hispanic	2 (4.4)	0 (0.0)	...
American Indian	0 (0.0)	0 (0.0)	...
Missing	0	0	...
Meconium ileus			
Absent	38 (84.4)	36 (72.0)	.2154
Present	7 (15.6)	14 (28.0)	...
Center			
Madison	21 (46.7)	28 (56.0)	.4143
Milwaukee	24 (53.3)	22 (44.0)	...
Genotype			
DF508/DF	26 (57.8)	27 (54.0)	.1840
DF508/OT	19 (42.2)	19 (38.0)	...
Other	0 (0.0)	4 (8.0)	...
Pancreatic status			
Insufficient	41 (91.1)	38 (77.6)	.0938
Sufficient	4 (8.9)	11 (22.4)	...
Missing	0	1	...
Mucoid <i>Pseudomonas</i> at CFQ1			.0170
Absent	18 (40.0)	34 (75.6)	...
Intermittent	11 (24.4)	8 (17.8)	...
Present	16 (35.6)	8 (17.8)	...

Data are presented as No. and No. (%). CFQ = Cystic Fibrosis Questionnaire.

FIGURE 1. Enrollment and data collection time frames for the original RCT and current HRQOL study. HRQOL = health-related quality of life; RCT = randomized clinical trial.

lack of adequate PFTs (70%) to match CFQ or vice versa (30%), PFTs not meeting quality control standards, or data falling outside the time criteria relative to CFQ completion.

Participants included in the longitudinal analysis of WCXR tended to be about 1.5 years younger than those not included. Those included in the longitudinal analysis of PFT scores were about 2.2 years older. Only the latter reached statistical significance ($P = .001$). Patients in both longitudinal analyses were healthier than those not included, but the differences in pulmonary health and the presence of risk factors were not statistically significant. Quantitative chest imaging results at the first CFQ showed 4.6% with mild (1-4.9), 23.0% with moderate (5-12), 21.8% with moderately severe (12.1-20), and 50.6% with severe (>20) lung disease, whereas the corresponding FEV₁ data showed 74.2% with normal functioning and 13.5% with mild (70%-79%), 7.9% with moderate (60%-69%), 3.4% with moderately severe (50%-59%), and 1.1% with severe ($<49\%$) lung disease; greater sensitivity of the WCXR score compared with spirometry data has been published previously.¹

Pulmonary Health and NBS

PFT measures were not significantly different between the two groups ($z \geq -1.20$, $P \geq .229$) over the 2-year time frame. WCXR scores were statistically different ($z \geq 2.27$, $P \leq .023$). The early diagnosis group showed higher scores, indicative of more severe lung disease. This finding was partly due to higher bronchiectasis subscores in the early diagnosis group ($z = 2.27$, $P = .023$). However, group difference in bronchiectasis subscores was 3.4, but group differ-

ence in WCXR scores was 6.1. Thus, bronchiectasis explained about half the difference.

After adjusting for *Pseudomonas* and pancreatic status, the early diagnosis group was not significantly different from the control group in WCXR scores or PFT data (Fig 2). Most patients (74%) had FEV₁ values $\geq 80\%$ predicted (within normal range) at the first time point. Group differences in risk factors accounted for nearly one-third of the difference in WCXR scores and more than one-half of the difference in PFT scores. All patients were combined in the statistical comparisons of CFQ and pulmonary health data.

Pulmonary Health and HRQOL

Table 2 shows the strong negative relationship between total WCXR score and CFQ-Child respiratory and physical domains ($z \leq -2.71$, $P \leq .007$). As

FIGURE 2. Group comparison of objective measures of pulmonary health. PFT = pulmonary function test; WCXR = Wisconsin chest x-ray scoring system.

Table 2—Relationship Between Self-Reported HRQOL and Objective Measures of Pulmonary Health

CFQ Domain	Total WCXR Score			FEV ₁ /FVC			FEV ₁		
	Coeff	SE	P Value	Coeff	SE	P Value	Coeff	SE	P Value
CFQ-Child^a									
Physical functioning	−9.00	3.32	.007	0.24	0.09	.006	0.32	0.15	.036
Respiratory symptoms	−7.00	2.21	.002	0.17	0.06	.005	0.11	0.11	.311
Social functioning	−4.70	2.30	.041	0.14	0.06	.023	0.26	0.11	.018
Emotional functioning	−4.44	2.49	.074	0.05	0.06	.393	−0.12	0.11	.290
Digestive symptoms	−4.23	5.24	.420	0.08	0.15	.584	0.25	0.28	.378
Treatment burden	−3.33	2.71	.220	0.02	0.08	.799	0.00	0.14	.980
Body image	1.27	5.59	.820	0.34	0.14	.017	0.57	0.27	.036
Eating disturbances	1.58	5.36	.769	0.20	0.14	.159	0.15	0.25	.565
CFQ-Adolescent/Adult^b									
Weight	−55.95	13.89	.000	−0.03	0.33	.929	1.96	0.59	.001
Respiratory symptoms	−7.32	2.29	.001	0.08	0.05	.110	0.27	0.09	.003
Health perceptions	−9.99	3.93	.011	0.22	0.09	.020	0.54	0.17	.002
Treatment burden	−6.92	2.88	.016	0.17	0.07	.014	0.20	0.11	.067
Body image	−12.13	5.55	.029	0.01	0.12	.956	0.36	0.26	.158
Physical functioning	−7.69	3.70	.038	0.26	0.11	.013	0.91	0.17	.000
Social functioning	−4.16	2.34	.076	−0.02	0.05	.756	0.18	0.11	.088
Vitality	−2.95	2.00	.141	0.03	0.05	.525	0.06	0.08	.497
Eating disturbances	−6.71	5.81	.248	0.14	0.18	.451	0.62	0.28	.025
Digestive symptoms	−1.74	5.02	.729	−0.06	0.13	.643	0.07	0.23	.766
Emotional functioning	−0.68	2.47	.784	0.01	0.05	.789	0.02	0.09	.800

Coeff = coefficient; HRQOL = health-related quality of life; WCXR = Wisconsin chest x-ray scoring system. See Table 1 legend for expansion of other abbreviation.

^aTime 1, n = 53; time 2, n = 41; time 3, n = 25.

^bTime 1, n = 41; time 2, n = 50; time 3, n = 55.

pulmonary health declined, HRQOL declined. Relationships between CFQ scores and bronchiectasis subscores were similar. There was also a positive relationship between FEV₁/FVC and CFQ respiratory and physical domains ($z \geq 2.75$, $P \leq .006$). As FEV₁/FVC scores decreased, CFQ scores decreased. Although the effect sizes for relationships between FEV₁/FVC and CFQ social, eating, and body image were similar, none reached statistical significance. No HRQOL domains were significantly related to FEV₁.

Significant relationships were found between WCXR and CFQ-Adolescent/Adult weight, health perceptions, and respiratory symptoms ($z \leq -2.54$, $P \leq .011$) and between FEV₁ and these and physical functioning ($z \geq 2.95$, $P \leq .003$). FEV₁/FVC was not significantly related to any CFQ domain. The weight domain uses a single item that violates the assumptions underlying the tobit model. We conducted an ordered probit analysis for confirmation but report tobit results because conclusions are similar.

Change in pulmonary health over the 2-year time frame was not significantly associated with change in HRQOL. Based on the American Thoracic Society and European Respiratory Society standards for interpreting PFT results²⁴ and on our research in developing and applying the WCXR scoring system,^{14,23} we examined changes in HRQOL among patients who

had a 5- or 10-point increase or decrease in WCXR and PFT scores. There were no associated changes in their HRQOL. These results confirmed those found in linear analyses.

HRQOL and NBS

HRQOL CIs for group differences were adjusted for *Pseudomonas* and pancreatic status. As shown in Figure 3, few differences were found. Only the −9.7 (± 3.6)-point difference on the social domain

FIGURE 3. Group differences on CFQ-Child and CFQ-Adolescent/Adult scores. CFQ = Cystic Fibrosis Questionnaire.

reached statistical significance ($z = -2.66$, $P = .008$), suggesting lower social functioning for the early diagnosis group.

DISCUSSION

To our knowledge, this project was the first to investigate HRQOL at multiple data points for patients with CF identified through NBS compared with those with CF diagnosed by traditional means. PFT and WCXR results were consistent with previous observations for the full RCT sample when patients were aged about 10 years.¹⁶ At diagnosis, patients in the early diagnosis group showed significantly better WCXR scores but later demonstrated worse lung disease than the control group. In the current study, after adjustment for confounding risk factors to control for sample bias, the two groups were not significantly different on WCXR or PFT outcomes. FEV₁ scores remained generally within normal limits for both groups. FEV₁ has been considered the gold standard for measuring disease progression and severity. Our results also suggest that addition of WCXR scores can increase sensitivity in detecting relationships between pulmonary health and HRQOL.

These findings should be interpreted within the historical context of the larger RCT. By protocol design, the original RCT control group was unblinded at age 4 years, and families were invited to enroll their children in the treatment protocol, regardless of whether the children were symptomatic. If not for the RCT, some control group patients might have received a diagnosis much later after developing more serious complications. Patients in the control group undoubtedly benefited from the rigorous evaluation and treatment protocol, thereby explaining the relatively good pulmonary health of patients in both groups and the lack of significant group differences. We could statistically control for group differences in risk factors, but it is impossible to calculate how ill some control group patients might have become had they not entered the RCT by 4 years. Thus, the lack of significant group differences does not rule out potential pulmonary benefits of NBS for CF.

Our findings are similar to previous intervention studies⁵⁻⁹ that found significant associations between HRQOL and objective pulmonary measures. However, in this study, changes in pulmonary health were not associated with changes in HRQOL over 2 years. One likely explanation is the relatively good health of participants in this study. Modi and Quittner²² observed that a restricted range of disease severity can limit the predictive validity of the CFQ. The CFQ might be more sensitive to acute changes associated with pulmonary exacerbation than more-subtle physi-

cal deterioration that occurs over years. Additionally, patients might adjust their perceptions of HRQOL in adaptation to their progressive decline in health. The CFQ requires participants to consider how they have been feeling over the previous 2 weeks. Language encourages subjective interpretations (eg, “as you wanted,” “that you enjoy,” “a lot”). Although it is unlikely that perceptions of these concepts would change over 2 weeks, they could change over 2 years as children mature. Additionally, patients’ impressions of fatigue, wellness, and being bothered by treatments also could shift as they acclimate to new baselines of lower functioning. Such perceptual shifts could partially account for response shifts leading to minimal long-term changes on self-reported HRQOL.

Only the CFQ-Adolescent social domain showed a significant difference favoring the control group. Given the marginal reliability of this domain, we exercise caution in interpreting the results. That said, we speculate that parents in the early diagnosis group might have restricted their children’s social encounters early in life. As these children matured, they most likely wanted fewer restrictions and greater autonomy, as reflected in their lower social domain scores. This premise is supported by another study²⁶ in which young adults with CF described their reliance on their parents for health-related issues and efforts to attain independence and lead active social lives. With the recent national implementation of CF NBS, significantly more children will receive a diagnosis of CF as neonates. The group differences on the CFQ social domain highlight the importance of assessing family dynamics for evidence of parental overprotectiveness that might interfere with their children’s social development.

Despite the lack of statistical significance, many of the group differences were >5.0 points. To our knowledge, a minimal clinically important difference of 4.0 points has been established only for the respiratory domain.²⁷ Establishment of a minimal clinically important difference for other domains would enhance our understanding of group differences found in this and future studies.

The current study has several limitations. The age range of patients necessitated the use of different versions of the CFQ, which contained different items and domains. The restricted age range of this sample and homogeneity of patients’ relatively good health could have limited our ability to detect long-term changes in HRQOL. When we initiated the current study, the original CFQ was the only valid CF-specific instrument available. This early version appears to have limited sensitivity in detecting changes in HRQOL over a long period of time. The CFQ-Revised version might be more sensitive to modest changes in pulmonary health over time.

CONCLUSIONS

To our knowledge, this study is the first to compare pulmonary outcomes with HRQOL for patients with CF identified either through NBS or diagnosed by traditional methods. After controlling for risk factors, there were no significant group differences in pulmonary health. NBS did not offer benefits for HRQOL. Using WCXR and PFT data collectively strengthened our ability to identify associations between pulmonary health and HRQOL.

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Dr Becker: contributed to the data analysis, interpretation of results, writing the manuscript, and approving the final draft.

Ms Laxova: contributed to study coordination, data management, writing the manuscript, and approving the final draft.

Mr Grieve: contributed to data management, writing the manuscript, and approving the final draft.

Dr Racine Gilles: contributed to data management, writing the manuscript, and approving the final draft.

Dr Rock: contributed to study conception, design, writing the manuscript, and approving the final draft.

Dr Gershman: contributed to study conception, design, writing the manuscript, and approving the final draft.

Dr Green: contributed to interpretation of results, writing the manuscript, and approving the final draft.

Dr Farrell: contributed to study conception, design, data analysis, interpretation of results, writing the manuscript, and approving the final draft.

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Additional information: The e-Appendix can be found in the Online Supplement at <http://chestjournal.chestpubs.org/content/140/1/170/suppl/DC1>.

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