Accelerated Spirometric Decline in New York City Firefighters With $\alpha_1$-Antitrypsin Deficiency

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Background: On September 11, 2001, the World Trade Center (WTC) collapse caused massive air pollution, producing variable amounts of lung function reduction in the New York City Fire Department (FDNY) rescue workforce. $\alpha_1$-Antitrypsin (AAT) deficiency is a risk factor for obstructive airway disease.

Methods: This prospective, longitudinal cohort study of the first 4 years post-September 11, 2001, investigated the influence of AAT deficiency on adjusted longitudinal spirometric change (FEV$_1$) in 90 FDNY rescue workers with WTC exposure. Workers with protease inhibitor (Pi) Z heterozygosity were considered moderately AAT deficient. PiS homozygosity or PiS heterozygosity without concomitant PiZ heterozygosity was considered mild deficiency, and PiM homozygosity was considered normal. Alternately, workers had low AAT levels if serum AAT was $\leq$ 20 $\mu$mol/L.

Results: In addition to normal aging-related decline (37 mL/y), significant FEV$_1$ decline accelerations developed with increasing AAT deficiency severity (110 mL/y for moderate and 32 mL/y for mild) or with low AAT serum levels (49 mL/y). Spirometric rates pre-September 11, 2001, did not show accelerations with AAT deficiency. Among workers with low AAT levels, cough persisted in a significant number of participants at 4 years post-September 11, 2001.

Conclusions: FDNY rescue workers with AAT deficiency had significant spirometric decline accelerations and persistent airway symptoms during the first 4 years after WTC exposure, representing a novel gene-by-environment interaction. Clinically meaningful decline acceleration occurred even with the mild serum AAT level reductions associated with PiS heterozygosity (without concomitant PiZ heterozygosity).

Abbreviations: AAT = $\alpha_1$-antitrypsin; EMS = emergency medical services; FDNY = New York City Fire Department; MMP = Medical Monitoring Program; Pi = protease inhibitor; WTC = World Trade Center
(performed with protease inhibitor [Pi] typing).23,24 Given the variability of airflow obstruction and hyper-reactivity in FDNY workers with WTC exposure and the known link between AAT deficiency and airway disease, we analyzed the influence of AAT expression on longitudinal spirometric change in 90 FDNY workers with WTC exposure over the first 4 years post-September 11, 2001.

Materials and Methods

Study Design and Timeline

This prospective cohort study compared longitudinal spirometric decline during the first 4 years post-September 11, 2001, among three AAT phenotype combinations in FDNY workers with high and moderate WTC exposure. Spirometry was obtained at 1 to 3 and 6 months, and 1, 2, and 4 years post-September 11, 2001. AAT testing was offered only at 4 years post-September 11, 2001.

WTC Exposure Groups

Exposure intensity was self-reported (FDNY-WTC-MMP questionnaire, confirmatory interviews). Exposure intensity was categorized according to workers' first WTC site arrival time: high or moderate WTC exposure registering for the FDNY-WTC-MMP after referred to as the source population) were on medical leave. After one month post-September 11, 2001, every second worker with high or moderate exposure registering for the FDNY-WTC-MMP who met study eligibility criteria was approached for enrollment. Three months post-September 11, 2001, because of the strain on resources from larger numbers of workers registering for the MMP at that time, every 20th worker with high or moderate exposure who met study eligibility criteria was approached for enrollment. Exclusion criteria were current smoking, allergies, FEV1 < 65% predicted, or low-intensity WTC exposure.

Follow-up Visits

Study participation was voluntary. Each study visit required informed consent approved by the Montefiore Medical Center institutional review board (protocol # 01-12-299). Longitudinal participation is shown in Figure 1 and Table 1. At the final follow-up 4 years post-September 11, 2001, no participant reported new or recurrent tobacco use, and two refused AAT testing. Thus, the final cohort comprised 90 FDNY workers with WTC exposure (60% retention). All follow-ups included spirometry and a self-administered questionnaire assessing respiratory symptoms. All symptoms were recorded prior to disclosing AAT status.

Spirometry

Spirometry was performed according to American Thoracic Society guidelines.25 Spirometers were calibrated daily, and testing was performed while seated and wearing noseclips and with up to eight forced expiratory maneuvers per session to maximize quality. To allow calculation of separate spirometric rates for time periods pre- and post-September 11, 2001, as well as to allow for more precise modeling for post-September 11, 2001, spirometric measurements obtained from the FDNY-WTC-MMP pre-September 11, 2001 (Portascreen; S&M Instruments; Doylestown, PA) and post-September 11, 2001 (EasyOne; NDD Medical Technologies; Andover, MA) were included with those obtained on the study dates (KoKo Spirometers; PDS Instrumentation; Louisvile, CO). Each spiromgram was reviewed by a board-certified pulmonologist blinded to patient identifier, exposure status, AAT phenotype, and serum level to determine that adherence to strict quality assurance guidelines was met.26 Spiromgrams were accepted if they (1) did not show artifacts of cough or glottis closure during the first second of exhalation, early termination, variable effort, leak, and obstructed mouthpiece; (2) had good starts with back-extrapolated volume not exceeding 5% of FVC or 150 mL (whichever was larger); and (3) had satisfactory exhalation length (at least 6 s or a plateau in the volume-time curve). Spirometric measurements were considered reproducible if the best and second-best FVC or FEV1 measurements were within 200 mL of each other. The largest FVC and FEV1, from among all acceptable spiromgrams were selected for electronic archiving. Pre-September 11, 2001, 142 spiromgrams were accepted for inclusion in the database: the median number per study participant was two (range, 0-3), and 77 (56%) participants had at least one spiromgram. Post-September 11, 2001, 321 spiromgrams from the FDNY-WTC-MMP and 299 from the study visits were accepted for inclusion for a total of 520 spiromgrams; the median number per study participant was six (range, 2-8). Nine spirometric measurements were rejected.
AAT Deficiency Categories

Two different methods were used to categorize AAT deficiency severity. The main categorization used AAT Pi phenotype combinations; the alternate categorization used serum AAT level. For the main categorization, workers with PiZ heterozygosity were considered moderately deficient; workers with PiS homozygosity or PiS heterozygosity without concomitant PiZ heterozygosity were considered mildly deficient; and workers with PiM homozygosity were considered normal. For the alternate categorization, a serum AAT level ≤ 20 μmol/L was considered low.

Demographic, Clinical, and Spirometric Comparisons—Univariate Analyses

FDNY work assignment on September 11, 2001 (firefighter vs EMS worker), FDNY tenure, age, race, height, sex, and smoking status were extracted from the FDNY-WTC-MMP database. Sex, race, ex-smoking status, work assignment, WTC exposure intensity, and upper- or lower-respiratory symptoms were compared at enrollment among the following groups: source population and study cohort, AAT phenotype combination categories, and low vs normal serum AAT categories (χ², Fisher exact test).

Four years post-September 11, 2001, upper- or lower-respiratory symptoms were compared among AAT phenotype combinations and between low vs normal serum AAT levels (χ², Fisher exact test). Symptom persistence from enrollment to final visit was explored within each AAT phenotype combination, and within low vs normal serum levels (McNemar test). Percentages of AAT deficiency phenotypes were compared between low vs normal serum levels (Fisher exact test). Mean serum AAT levels were compared among AAT phenotype combinations (Mann-Whitney U, Kruskal-Wallis test). Spirometric measurements before September 11, 2001, at enrollment, and at 4 years post-September 11, 2001, as well as AAT levels, age, and FDNY tenure were compared between the same groups detailed previously (paired t-test, one-way analysis of variance, Mann-Whitney U, Kruskal-Wallis test).

Clinical and Spirometric Comparisons—Multivariate Analyses

Indicators for clinical symptoms 1 to 3 months post-September 11, 2001, were compared between the source population and study cohort, adjusting for the following factors: age, FDNY tenure, WTC exposure intensity, sex, work assignment, and ex-smoker percentage. Indicators for clinical symptoms 4 years post-September 11, 2001, were compared among AAT phenotype combinations and between workers with low vs normal serum AAT levels adjusted for the same factors using logistic regression. Spirometric measurements 1 to 3 months post-September 11, 2001 (adjusted for the same factors plus sex and height) were compared using linear regression between the source population and study cohort, among the different AAT phenotype combinations, and between workers with low vs normal serum AAT levels.

Spirometric Decline Rates—Mixed Linear Random Effects Models

Using mixed linear random effects modeling, we analyzed differences in average spirometric change rates (FVC or FEV₁) during 3 years pre-September 11, 2001, and during 4 years post-September 11, 2001, and whether AAT deficiency combinations influenced spirometric change rates during 4 years post-September 11, 2001. Separate models were run for FEV₁ and FVC as dependent variables. Workers contributed two to 10 observations. The primary predictor of interest was the interaction between spirometric change rate during the 4 years post-September 11, 2001, and AAT deficiency combinations (based on either phenotype combinations or serum levels). AAT deficiency severity was modeled both as nominal predictor and as ordinal predictor (to test for linear

### Table 1—Enrollment and Follow-up Data of Study Cohort

<table>
<thead>
<tr>
<th>AAT Deficiency Category</th>
<th>Enrollment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-3 mo Post-September 11, 2001</td>
<td>6 mo Post-September 11, 2001</td>
</tr>
<tr>
<td>Moderate</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Mild</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Normal AAT phenotype</td>
<td>79</td>
<td>65</td>
</tr>
<tr>
<td>Total No. tested each time period</td>
<td>90</td>
<td>75</td>
</tr>
<tr>
<td>AAT = α₁-antitrypsin.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
trend) in separate models. Separate spirometric change rates and separate interaction terms between spirometric change and AAT categories were included for 3 years pre-September 11, 2001, and for 4 years post-September 11, 2001. In addition, models allowed a spirometry decrement post-September 11, 2001, because this was previously observed in longitudinal spirometric analysis of this workforce. Additional predictors included were as the following confounders: age, sex, height, race, smoking status, work assignment (firefighter, EMS worker), FDNY tenure, WTC exposure intensity, and interaction between AAT deficiency and history of tobacco use. All predictors were fixed effects. A random intercept was used to reflect across-subject heterogeneity and correlation induced by having repeated same-subject observations. To eliminate nonlinear confounding because of the known interaction of smoking with AAT deficiency, we modeled spirometric change rates both in the study cohort that included ex- and never smokers (n = 90) and in the subcohort of never smokers (n = 75). SPSS version 12.0 (SPSS Inc; Chicago, IL) was used for all analyses.

### Results

#### Study Cohort and Source Population

The study cohort consisted of 90 source population members (FDNY workers with high to moderate WTC exposure, no allergies, ex- or never-smoking status, and an FEV$_1$ ≥65% predicted as measured during FDNY-WTC-MMP 1-3 months post-September 11, 2001) who agreed to participate in and completed this longitudinal 4-year study (Fig 1, Table 1). Demographic and symptom information of the source population and study cohort are shown in Table 2. No significant difference in sex, age, and ex-smoker percentage between study cohort and source population was found. The study cohort included significantly more workers with high WTC exposure and, to a lesser extent, significantly more nonwhite and EMS workers. Compared with the source population, study participants at enrollment (1-3 months post-September 11, 2001) were more symptomatic, with increased prevalence of nocturnal respiratory symptoms and nasal drip and congestion.

Source population and study cohort spirometric measurements are shown in Table 3. Pre-September 11, 2001, study participants had significantly lower mean spirometric measurements than the source population, but these differences were not significant when normalized as percent-predicted values. At enrollment 1 to 3 months post-September 11, 2001, lower spirometric measurements in study participants was consistent with the larger number of workers with high WTC exposure in the study cohort than in the source population.3,4

#### AAT Phenotype Distributions and AAT Deficiency Combinations

For analysis, workers were grouped according to AAT phenotype combination deficiency severity as follows: four workers with PiZ heterozygosity were considered moderately deficient (two with M1Z, one with M3Z, and one with SZ), seven workers with PiS homozygosity or PiS heterozygosity without concomitant PiZ heterozygosity were considered mildly deficient (three with M1S, two with M2S, one with M3S, and one with SS), and 79 workers with PiM homozygosity were considered normal (38 with M1M1, 28 with M1M2, 11 with M1M3, and two with M3M3). Significant differences in mean serum AAT levels were observed among the three AAT deficiency combinations (Table 4). Alternatively, 13 workers were categorized as having low AAT serum levels (≤20 µmol/L) (Table 5), and significant differences in percentages of AAT deficiency combinations were observed between workers with low vs normal serum AAT levels.
During routine occupational health surveillance at FDNY (available for 83% of source population and 56% of study cohort).

Pre-September 11, 2001, were compared with rates post-September 11, 2001, even though such deficiency did not affect spirometric declines pre-September 11, 2001. A gene-by-environment interaction exists when disease risk among individuals with both genotype and environmental exposure is greater than predicted from either genotype or exposure alone. The magnitude of AAT deficiency-related adjusted FEV₁ decline rate acceleration thus equaled nearly triple the cohort’s yearly adjusted aging-related decline rate for workers with moderate AAT deficiency and almost equaled the yearly adjusted aging-related decline rate for those with mild AAT deficiency (Fig 3). This finding was true regardless of whether smokers were included or whether the single individual with a PiSZ phenotype combination was included. Furthermore, after accounting for aging-related decline and the 370-mL immediate decrement, workers with low AAT serum levels had an additional 49-mL/y decline rate acceleration compared with those with normal levels during the 4 years post-September 11, 2001. For workers with low serum AAT levels, the magnitude of adjusted AAT deficiency-related decline rate acceleration thus exceeded the cohort’s yearly adjusted aging-related decline rate (Fig 3). This finding was true regardless of whether ex-smokers were included. Similar results were obtained for adjusted FVC decline rate accelerations (data not shown). When adjusted spirometric decline rates pre-September 11, 2001, were compared with rates post-September 11, 2001, no decline rate acceleration attributable to AAT deficiency was observed for the 3-year period preceding the WTC exposure (Fig 2).

**Discussion**

In this prospective longitudinal cohort study, we showed that FDNY rescue workers with AAT deficiency developed significant spirometric decline accelerations during the first 4 years post-September 11, 2001, even though such deficiency did not affect spirometric declines pre-September 11, 2001. A gene-by-environment interaction exists when disease risk among individuals with both genotype and environmental exposure is greater than predicted from either genotype or exposure alone. Accelerated lung function decline developed in workers with AAT deficiency after the intense inflammatory stimulus of WTC inhalation injury, representing a novel gene-by-environment interaction. Clinically meaningful and statistically significant lung function loss developed even with only the mild serum AAT level reduction associated with PiS heterozygosity without concomitant PiZ heterozygosity.

It is now well accepted that respirable pollutants after the WTC attack caused inhalation injury, Biochemical, physiologic, and clinical.
correlates of airway inflammation due to this exposure have been described in multiple cohorts, including FDNY rescue workers. Subacutely, during study initiation 1 to 3 months post-September 11, 2001, irritative respiratory symptoms and physiologic correlates (eg, decreased spirometric measurements) were associated with WTC exposure intensity. \(^2\)\(^-\)\(^5\) This association was no longer detectable at final follow-up 4 years post-September 11, 2001. Instead, AAT deficiency severity emerged as a determinant of both persistent symptoms and spirometric decline acceleration, highlighting its role in lung injury and repair. Although AAT deficiency has repeatedly been implicated in the development of chronic airflow obstruction, \(^42\)\(^-\)\(^43\) this study revealed development of AAT deficiency-related spirometric decline acceleration during a much shorter period (ie, 4 years), thus highlighting how quickly AAT deficiency can produce clinical disease and airflow obstruction. WTC-derived airborne pollution was a complex mixture of particulates and chemicals. \(^1\)\(^,\)\(^7\) To date, severe deteriorations in pulmonary function are well described for persons with AAT deficiency following bacterial infections \(^44\)\(^,\)\(^45\) but have not been described following exposures to particulates, chemicals, or mixtures. In addition, no such gene-by-environment interactions for pulmonary disease have been previously described for mild to moderate AAT deficiency due to PiS heterozygosity without concomitant PiZ heterozygosity. This interesting, novel finding might be due to the strength of the inhalational inflammatory stimulus sustained by FDNY rescue workers at the WTC site.

It is important to note our investigation’s limitations. First and most importantly, sample size was moderate, but this moderate-sized study cohort represented the FDNY source population quite well in key demographic and spirometric aspects. Second, FDNY rescuers sustained extremely high-intensity exposures, which might be qualitatively different compared with other rescue and recovery workers or for residents. For these reasons, caution is prudent when extrapolating our current findings. Third, the missing AAT characterization of the initially enrolled subjects who did not participate in the 4-year follow-up examination has the potential to bias our results. Specifically, study results would falsely favor an association between AAT deficiency and accelerated FEV\(_1\) decline if a disproportionate number of subjects with PiM homozygosity did not participate in the follow-up and at the same time did have accelerated airflow obstruction. The fact that the prevalence of deficiency phenotype carriers in our current cohort (12\%) is close to the prevalence of deficiency

Table 4—Clinical and Biochemical Characteristics of Study Cohort by AAT Deficiency Category

<table>
<thead>
<tr>
<th>AAT Phenotype Combination</th>
<th>Moderate Deficiency</th>
<th>Mild Deficiency</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number</td>
<td>4</td>
<td>7</td>
<td>79</td>
</tr>
<tr>
<td>AAT characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum AAT level, (\mu)mol/L</td>
<td>PiMZ, PiSZ</td>
<td>PiMS, PiSS</td>
<td>PiMM</td>
</tr>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>100</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td>White race</td>
<td>100</td>
<td>71</td>
<td>86</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>25</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>EMS work assignment on September 11, 2001</td>
<td>0</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>High WTC exposure intensity(^a)</td>
<td>75</td>
<td>71</td>
<td>65</td>
</tr>
<tr>
<td>FDNY tenure length on September 11, 2001, y</td>
<td>20.0 ± 6.4</td>
<td>11.5 ± 4.9</td>
<td>10.9 ± 8.4</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, unless otherwise indicated. See Table 1 and 2 legends for expansion of abbreviations.

\(^a\)Arrived at WTC site morning of September 11, 2001.

\(^b\)P < .001 comparing mean serum AAT levels among AAT phenotype categories, Kruskal-Wallis test.

\(^c\)P < .001 comparing AAT deficiency phenotype combinations among workers with low vs normal AAT serum levels, Mann-Whitney \(U\).

Table 5—AAT Values and AAT Phenotype Combinations of Study Cohort by AAT Deficiency Category and AAT Serum Level

<table>
<thead>
<tr>
<th>AAT Deficiency Category</th>
<th>Normal</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAT Serum Level, (\mu)mol/L</td>
<td>24.55 ± 2.81</td>
<td>18.60 ± 1.01</td>
</tr>
<tr>
<td>Phenotype combination</td>
<td>75 PiMM</td>
<td>4 PiMM</td>
</tr>
<tr>
<td>Mild deficiency</td>
<td>21.70 ± 0.28</td>
<td>17.34 ± 1.85</td>
</tr>
<tr>
<td>Phenotype combination</td>
<td>2 PiMS</td>
<td>4 PiMS, 1 PiSS</td>
</tr>
<tr>
<td>Moderate deficiency</td>
<td>14.18 ± 3.25 (^b)</td>
<td>14.18 ± 3.25 (^b)</td>
</tr>
<tr>
<td>Phenotype combination</td>
<td>3 PiMZ, 1 PiSZ</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, unless otherwise indicated. See Table 1 and 4 legends for expansion of abbreviations.

\(^b\)P < .001 comparing mean serum AAT levels among AAT phenotype categories, Kruskal-Wallis test.
FDNY workers with moderate AAT deficiency, 32-mL/y FEV$_1$ for September 11, 2001, for the three AAT deficiency phenotype combinations. B, Time course of average adjusted FEV$_1$ pre- and post-September 11, 2001, for low vs normal AAT serum levels. Significant acceleration in average adjusted spirometric declines according to AAT phenotype combination (110-mL/y FEV$_1$ for FDNY workers with moderate AAT deficiency, 32-mL/y FEV$_1$ for workers with mild AAT deficiency; $P$ for trend, .003) occurred during the 4 years post-September 11, 2001, but not during the 3 years pre-September 11, 2001. Spirometric measurements for a white male never-smoking FDNY firefighter with high WTC-exposure of mean age and height and with median length of FDNY tenure are depicted. A, Workers with protease inhibitor (Pi) Z heterozygosity were categorized as moderately AAT deficient ($n$ = 4), those with PiS homozygosity or PiS heterozygosity without concomitant PiZ heterozygosity were categorized as mildly AAT deficient ($n$ = 7), and those with PiM homozygosity were categorized as normal ($n$ = 79). B, Workers with serum AAT levels $\leq 20$ $\mu$mol/L were categorized as having low levels ($n$ = 13), and those with serum AAT levels $>20$ $\mu$mol/L were categorized as having normal levels ($n$ = 77). Spirometric decline rates were adjusted for sex, race, age, height, ex-smoking status, work assignment on September 11, 2001, length of FDNY tenure, WTC exposure intensity, and the interaction of smoking with AAT deficiency. The statistical models allowed for a decrement in spirometric measurements post-September 11 because this had previously been observed in the FDNY workforce.$^5$ See Figure 1 legend for expansion of other abbreviations.

Mild phenotype carriers in the general North American population (9%)$^{46}$ suggests that our results were likely not substantially affected by incomplete follow-up.

We partitioned participants into three AAT phenotype combinations, considering those with PiZ heterozygosity as moderately deficient, those with PiS homozygosity or with PiS heterozygosity without concomitant PiZ heterozygosity as mildly deficient, and those with PiM homozygosity as normal. Statistically significant differences in mean serum AAT levels among the three phenotype combinations supported this categorization. With this categorization, we demonstrated significant, clinically meaningful spirometric decline rate accelerations, even for mildly abnormal PiS carriers—to our knowledge, a unique finding in the literature.

Magnitude of AAT deficiency-related spirometric decline rate acceleration was both clinically and statistically significant, equaling almost triple this cohort’s aging-related spirometric decline rate for workers with moderate AAT-deficiency, despite allowing for a one-time decrement in spirometric measurements post-September 11, 2001. When we reported this one-time spirometric decrement 1 year post-September 11, 2001,$^3$ we speculated whether the acute inflammatory response and pulmonary function decrement would be transient and reversible. However, in our current...
study, which includes spirometric measurements obtained as long as 4 years post-September 11, 2001, we still observed a decrement of almost equal magnitude as that observed during the first year post-September 11, 2001 (370-mL FEV₁ decline). This one-time decrement persisted in addition to the AAT-related decline rate acceleration post-September 11, 2001, and persistence of this decrement has been reported in the entire FDNY workforce. These findings argue strongly against a transient, reversible adverse effect. 2

In conclusion, we demonstrated significant associations between spirometric decline rate acceleration and AAT deficiency severity in the FDNY workforce during the first 4 years after WTC-related inhalation injury. These decline rate accelerations represent a novel gene-by-environment interaction, are both clinically and statistically significant, and occur even in workers with PiS heterozygosity who had only mild reductions in serum AAT levels. This finding of accelerated pulmonary function decline despite modest sample size, milder degrees of AAT deficiency, and only 4 years of follow-up allows for inferences about the key antiinflammatory role of AAT in the lower airways and about the strength of the WTC-related inhalation injury in FDNY workers.

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Dr Brantly: contributed to the data acquisition, laboratory measurements, and revision of the manuscript.
Dr Izbicki: contributed to the data acquisition, revision of the manuscript, and preparation of the final version of the manuscript.
Dr Hall: contributed to the data analysis and interpretation, revision of the manuscript, and preparation of the final version of the manuscript.
Dr Shanske: contributed to the study design, revision of the manuscript, and preparation of the final version of the manuscript.
Dr Chavko: contributed to the data acquisition and revision of the manuscript.
Dr Santhyakula: contributed to the data acquisition and revision of the manuscript.
Li Christodoulou: contributed to the data acquisition and revision of the manuscript.
Dr Weiden: contributed to the revision of the manuscript.
Dr Prezant: contributed to the study design, drafting and revision of the manuscript, and preparation of the final version of the manuscript.

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