Rate of Lung Function Decline in People with Cystic Fibrosis Having a Residual Function Gene Mutation

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Received: September 12, 2022 / Accepted: October 7, 2022 / Published online: November 1, 2022
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ABSTRACT

Introduction: Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the CF transmembrane conductance regulator (CFTR) gene. Approximately 5% of people with CF have residual function (RF) CFTR mutations that result in partially retained CFTR activity. Published literature on disease trajectory among those with RF mutations is limited. In this retrospective study, we characterized lung function decline across different age groups in CFTR modulator-untreated people with CF heterozygous for F508del and an RF mutation (F/RF).

Methods: Rate of decline in percent predicted forced expiratory volume in 1 s (ppFEV1) was analyzed using data from the US CF Foundation Patient Registry (2006–2014) in F/RF (all), F/RF (excluding R117H), and F508del homozygous (F/F) cohorts. Annual rates of ppFEV1 decline were estimated over 2-year periods based on

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s41030-022-00202-y.

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calendar year. Subgroup analyses by age [6–12 (children), 13–17 (adolescents), 18–24 (young adults), and ≥ 25 years (adults)] were performed.

**Results:** The estimated annualized rate of ppFEV1 decline was −0.70 percentage points per year (95% CI −1.09, −0.30) in the F/RF (all) cohort (N = 1242) versus −1.91 percentage points per year (95% CI −2.01, −1.80) in the F/F cohort (N = 11,916) [difference, 1.29 percentage points per year (95% CI 0.88, 1.70); P < 0.001]. In the F/RF (all) cohort, all age groups demonstrated lung function decline ranging from −0.30 to −1.38. In the F/RF (excluding R117H) cohort, the rate of decline was −1.05 percentage points per year (95% CI −1.51, −0.60) [difference versus F/F cohort, 0.95 percentage points per year (95% CI 0.48, 1.41; P < 0.001); not statistically significant in children and young adults].

**Conclusion:** Progressive lung function decline was observed in people with F/RF genotypes across all assessed age groups, reinforcing the importance of early intervention and clinical monitoring to preserve lung function in all people with CF.

**Keywords:** Cystic fibrosis; F508del; Lung function; Lung function decline; R117H; Residual function

**Key Summary Points**

Although approximately 5% of people with cystic fibrosis (CF) have residual function (RF) CFTR mutations, published data on disease trajectory in this population is limited

This retrospective study characterized lung function decline in CFTR modulator-untreated patients who were heterozygous for F508del-CFTR and an RF mutation (F/RF genotypes) compared with patients who were homozygous for F508del-CFTR (F/F genotype)

Lung function decline was observed in all age groups of patients with F/RF genotypes

Findings reinforce the importance of early intervention to preserve lung function in all people with CF, including those with F/RF genotypes

**INTRODUCTION**

Cystic fibrosis (CF) is a progressive, life-shortening, multisystem, autosomal recessive disease affecting > 80,000 people worldwide [1]. CF is caused by mutations in the CF transmembrane

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conductance regulator (CFTR) gene that result in reduced quantity and/or function of CFTR protein [1, 2]. Loss of chloride transport activity can lead to various clinical manifestations, including mucus accumulation in the airways, pulmonary exacerbations, reduced lung function, exocrine pancreatic insufficiency, intestinal malabsorption, reproductive dysfunction, and elevated sweat chloride concentration [1]. Disease severity and rate of progression vary in people with CF and may be determined in part by the extent of chloride transport loss associated with each mutation [3–6]. Lung function and its rate of decline are important clinical outcomes in CF [5, 7].

Approximately 5% of people with CF have residual function (RF) CFTR mutations that exhibit residual CFTR-mediated ion transport due to partially retained CFTR activity [6, 8]. Those with RF mutations are most frequently heterozygous with an F508del-CFTR mutation (F/RF genotypes) [9], although RF mutations may be found in combination with other mutations. F/RF genotypes can result in a range of molecular defects, including reduced or variable synthesis of CFTR channels, moderate defects in CFTR processing and trafficking, impaired channel gating, and altered channel conductance [10–12]. These defects result in a reduced quantity of normal CFTR channels at the cell surface or a normal quantity of CFTR channels at the cell surface that exhibit reduced chloride ion transport ability [8, 13–15]. Compared with people with CF who are homozygous for F508del-CFTR (F/F genotype), those with F/RF genotypes—including those with the most common RF mutation, R117H—may have slower disease progression and are more likely to be pancreatic sufficient and have lower sweat chloride concentrations, indicative of partially maintained CFTR activity [10, 16, 17]. Nevertheless, people with CF who have F/RF genotypes have been shown to develop progressive lung disease with age and die prematurely [6].

As published literature on the disease trajectory in people with CF with RF mutations is limited, we sought to characterize lung function decline in a CFTR modulator-untreated cohort of people with CF with F/RF genotypes compared with that in people with the F/F genotype. Here, we report the findings from a retrospective study of longitudinal registry data evaluating the rate of percent predicted forced expiratory volume in 1 s (ppFEV1) decline in people with CF with F/RF and F/F genotypes.

METHODS

Analysis Population

Data from participants in the US Cystic Fibrosis Foundation Patient Registry (CFFPR) [18] from 2006 to 2014 were used to assess lung function in people with CF with F/RF and F/F genotypes, none of whom were receiving CFTR modulator therapy during this study period. RF mutations were identified based on clinical or in vitro evidence of residual ion transport. RF mutations are listed in the Supplementary Material (Table S1). Individuals were excluded if they had presumed CF-related metabolic syndrome, in which an R117H mutation was detected by newborn screening and sweat chloride level was < 60 mmol/L or no sweat test result was recorded. Clinic encounters recorded in the 2006–2014 period were censored at death, lung transplant, ivacaftor treatment initiation, or last encounter, whichever occurred first. The study included individuals who had a qualifying genotype, were aged 6–45 years, and had ≥ 3 ppFEV1 measurements spanning ≥ 0.5 years in a randomly chosen two-calendar year period beginning at the first ppFEV1 measurement in the calendar year.

Analysis was performed in three subpopulations: (1) F/F; (2) F/RF (all), comprising participants with F508del on one allele and any RF mutation on the second allele; and (3) F/RF (excluding R117H), comprising participants with F508del on one allele and any RF mutation except R117H on the second allele. In each subpopulation, the following age groups were analyzed: 6–12 (children), 13–17 (adolescents), 18–24 (young adults), and ≥ 25 years (adults). Inclusion age in the study was between 6 and 45 years to ensure balanced proportions of participants with F/RF and F/F genotypes in each age group.
Data Analysis

Initially, the 2006–2014 period was divided into overlapping two-calendar year periods (i.e., 2006–2007, 2007–2008 ... 2013–2014). We identified analyzable periods in which individuals had ≥3 ppFEV₁ measurements spanning ≥0.5 years in a randomly chosen 2-year period beginning at the first ppFEV₁ measurement in the calendar year. Age was defined as age at the first encounter (i.e., baseline) in each of these randomly chosen 2-year periods.

Demographic and baseline clinical characteristics were descriptively summarized for each subpopulation. The F/F subpopulation was compared with the other two subpopulations using the t-test for continuous measurements and chi-square test for discrete measurements.

The intercept and slope (rate of change) of ppFEV₁, based on 2012 Global Lung Initiative equations [19], were estimated over 2-year periods using all available measurements. Two repeated-measures models were developed: one comparing F/F with F/RF (all) and one comparing F/F with F/RF (excluding R117H). The dependent variable was ppFEV₁, with mutation group, age group, calendar year, and time (years since baseline) as fixed effects. All interaction terms, except those with both age group and calendar year, were included. Compound symmetry was specified as the covariance structure to account for correlated data within each individual. The intercept and slope estimates were calculated overall and by each age group from these models. The proportion of participants in each age group was used to calculate the overall values.

Sensitivity analyses using Wang–Hankinson equations [20, 21] for ppFEV₁ were also performed.

All statistical tests were two sided. P-values ≤0.05 were considered statistically significant. The analysis was performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Compliance with Ethical Guidelines

This study was conducted in accordance with the current Good Clinical Practice Guidelines as described by the International Council for Harmonisation, the Declaration of Helsinki, and all applicable local regulations. People with CF provided informed consent to participate in the US Cystic Fibrosis Foundation Patient Registry and to have their data included in the registry. The study did not involve primary data collection and used only de-identified data; thus, institutional review board approval was not required.

RESULTS

Participants and Baseline Characteristics

A total of 1242 participants with F/RF genotypes and 11,916 with the F/F genotype were included in the analysis. The most common RF mutations were R117H [n = 353 (28.4%)], 3849 + 10KBC → T [n = 228 (18.4%)], and 2789 + 5G → A [n = 206 (16.6%)] (Supplementary Material, Table S1). The mean (SD) baseline ppFEV₁ was 80.4 (24.8), 78.6 (25.3), and 73.4 (26.5) percentage points (Table 1), respectively, in the F/RF (all), F/RF (excluding R117H), and F/F cohorts. Staphylococcus aureus, Pseudomonas aeruginosa, Haemophilus influenzae, Aspergillus, Stenotrophomonas maltophilia, and Burkholderia cepacia were detected in all genotype groups at baseline (Table 1). The F/RF (all) cohort had significantly lower rates of P. aeruginosa (P < 0.001), Aspergillus (P < 0.001), B. cepacia (P < 0.001), S. maltophilia (P < 0.01), and S. aureus (P < 0.05) than the F/F cohort, whereas rates were more similar between the F/RF (excluding R117H) and F/F cohorts (Table 1).

Lung Function

The F/RF (all) cohort exhibited progressive lung function loss, with an estimated annualized ppFEV₁ rate of decline of −0.70 percentage points per year (95% CI −1.09, −0.30). When
participants with an R117H mutation were excluded, the rate of decline was −1.05 percentage points per year (95% CI −1.51, −0.60). The rate of decline in the F/F cohort was −1.91 percentage points per year (95% CI −2.01, −1.80). The difference in the annual rate of decline between the F/RF (all) cohort and the F/F cohort was 1.29 percentage points per year (95% CI 0.88, 1.70; \(P < 0.001\); Fig. 1), and the difference between the F/RF (excluding R117H) cohort and the F/F cohort was 0.95 percentage points per year (95% CI 0.48, 1.41; \(P < 0.001\)).

The F/RF genotype cohorts [F/RF (all) and F/RF (excluding R117H)] demonstrated lung function decline in all age groups (Fig. 2). The rates of decline in children with F/RF (all) and F/RF (excluding R117H) genotypes were −0.30 (95% CI −0.93, 0.34) and −0.80 (95% CI −1.58, −0.02) percentage points per year, respectively (Fig. 2). These were similar to the rates of lung function decline in adolescents [F/RF (all), −0.30 (95% CI −1.05, 0.45) percentage points per year; F/RF (excluding R117H), −0.57 (95% CI −1.41, 0.28) percentage points per year] (Fig. 2). In young adults and adults, the rates of lung function decline were greater in magnitude, with rates of −1.38 (95% CI −2.14, −0.61) and −0.94 (95% CI −1.45, −0.44) percentage points per year in the F/RF (all) cohort and −1.85 (95% CI −2.69, −1.01) and −1.06 (95% CI −1.64, −0.48) percentage points per year in the F/RF (excluding R117H) cohort, respectively. Although the rates of decline were slower for all age groups in the F/RF (all) cohort than in the F/F cohort, rates between the F/RF (excluding

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**Table 1** Demographic and Clinical Characteristics, by Mutation

| Characteristic                  | F/F (n = 11,916) | F/RF (all) (n = 1242) | P-valuea | F/RF (excluding R117H) (n = 889) | P-valueb |
|--------------------------------|-----------------|-----------------------|----------|---------------------------------|----------|
| Age, years, mean (SD)          | 18.0 (9.6)      | 23.0 (12.1)           | < 0.001  | 23.6 (11.8)                     | < 0.001  |
| Female, n (%)                  | 5698 (47.8)     | 645 (51.9)            | 0.006    | 473 (53.2)                      | 0.002    |
| Height-for-age z-score, mean (SD) | −0.49 (1.03)   | 0.04 (1.03)           | < 0.001  | −0.01 (1.02)                    | < 0.001  |
| Weight-for-age z-score, mean (SD) | −0.48 (1.11)   | 0.36 (1.14)           | < 0.001  | 0.29 (1.15)                     | < 0.001  |
| BMI for-age z-score, mean (SD)  | −0.29 (1.08)    | 0.36 (1.09)           | < 0.001  | 0.29 (1.10)                     | < 0.001  |
| ppFEV\(_1\) at baseline visit, mean (SD) | 73.4 (26.5)     | 80.4 (24.8)           | < 0.001  | 78.6 (25.3)                     | < 0.001  |

Patients with positive microbiology n (%)c

| Microorganism                      | F/F (n = 11,916) | F/RF (all) (n = 1242) | P-valuea | F/RF (excluding R117H) (n = 889) | P-valueb |
|-----------------------------------|-----------------|-----------------------|----------|---------------------------------|----------|
| Staphylococcus aureus             | 5386 (45.2)     | 524 (42.2)            | 0.042    | 402 (45.2)                      | 0.99     |
| Pseudomonas aeruginosa            | 4131 (34.7)     | 277 (22.3)            | < 0.001  | 234 (26.3)                      | < 0.001  |
| Haemophilus influenzae            | 662 (5.6)       | 69 (5.6)              | 1.00     | 49 (5.5)                        | 0.96     |
| Aspergillus species               | 688 (5.8)       | 42 (3.4)              | < 0.001  | 32 (3.6)                        | 0.007    |
| Stenotrophomonas maltophilia      | 677 (5.7)       | 48 (3.9)              | 0.008    | 38 (4.3)                        | 0.078    |
| Burkholderia cepacia              | 237 (2.0)       | 7 (0.6)               | < 0.001  | 7 (0.8)                         | 0.012    |

BMI body mass index, F508del, ppFEV\(_1\) percent predicted forced expiratory volume in 1 s, RF residual function

\(a\)F/F versus F/RF (all)

\(b\)F/F versus F/RF (excluding R117H)

\(c\)At first visit in the 2-year period

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R117H) versus F/F cohorts were not statistically significantly different in children [difference, 0.52 percentage points per year (95% CI −0.27, 1.31)] or young adults [difference, 0.67 percentage points per year (95% CI −0.19, 1.53)] (Fig. 2). The estimated intercepts and rates of decline in the overall population and by age group were similar in sensitivity analyses using the Wang–Hankinson equations (Table 2).

DISCUSSION

We sought to better understand the rate of lung function decline in people with CF who have an RF CFTR mutation. We used data from 2006 to 2014 to ensure an adequate sample size for CFTR modulator-untreated cohorts. Our data showed a decline in ppFEV1 in those with F/RF genotypes across all age groups, although the rate of decline varied by age. Overall, the rate of ppFEV1 decline observed in participants with F/RF genotypes was slower than that in participants with F/F genotypes, consistent with the findings reported by Leung et al. [22]. When participants with an R117H mutation were excluded from the analyses, rates of lung function decline in children and young adults were not statistically significantly different compared with rates in the same age groups in the F/F cohort. This finding indicates that, despite having better preserved lung function compared with the F/F cohort at baseline, the F/RF (excluding R117H) cohort also experienced a progressive decline in lung function. The findings of this study demonstrate the progressive nature of CF in people with the F/RF genotype, highlighting the importance of beginning treatment to preserve lung function as early as possible. Since the analysis, several CFTR modulators have become available for this patient population, including ivacaftor (Kalydeco), tezacaftor/ivacaftor and ivacaftor (Symdeko), and, most recently, elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta) [23–25].

This retrospective study had several limitations. The severity of disease in individuals with F/RF genotypes was highly variable and influenced by several factors, including environment and the presence of modifier genes [10]. It is possible that in the current era of widespread newborn CF screening, children with F/RF genotypes with mild symptoms are being diagnosed with CF more frequently, while the adult F/RF population in this study may have been diagnosed due to being symptomatic (instead of via newborn screening) and therefore may exhibit greater lung function decline than younger F/RF populations. Phenotypic variability in people with CF who have an R117H mutation has also been shown to be influenced by polymorphisms in the polythymidine tract of intron 8 of the CFTR gene [26]; this could not be examined in these analyses due to lack of data availability in the registry.
Table 2  Estimated intercept and annualized slope for ppFEV₁ using Wang–Hankinson equations (sensitivity analysis)

| Characteristic         | F/F⁵⁰ (n = 11,916) | F/RF (all) (n = 1242) | F/RF (excluding R117H) (n = 889) |
|------------------------|--------------------|------------------------|----------------------------------|
| **Intercept (95% CI)** |                    |                        |                                  |
| Overall                | 74.88 (74.49, 75.28) | 86.25 (84.92, 87.58)  | 85.49 (83.89, 87.10)            |
| 6–12 years of age      | 91.88 (91.21, 92.55) | 99.85 (97.34, 102.36) | 100.52 (97.32, 103.71)          |
| 13–17 years of age     | 81.18 (80.26, 82.10) | 92.02 (88.76, 95.28)  | 90.12 (86.32, 93.92)            |
| 18–24 years of age     | 64.86 (64.02, 65.70) | 80.98 (77.97, 83.99)  | 79.78 (76.39, 83.17)            |
| ≥ 25 years of age      | 56.02 (55.21, 56.83) | 68.34 (66.48, 70.21)  | 66.58 (64.40, 68.76)            |
| **Slope (95% CI)**     |                    |                        |                                  |
| Overall                | -1.93 (-2.03, -1.82) | -0.74 (-1.14, -0.34)  | -1.09 (-1.56, -0.63)           |
| 6–12 years of age      | -0.75 (-0.90, -0.59) | 0.13 (-0.52, 0.78)    | -0.43 (-1.23, 0.36)            |
| 13–17 years of age     | -3.56 (-3.75, -3.37) | -1.26 (-2.03, -0.49)  | -1.43 (-2.30, -0.57)           |
| 18–24 years of age     | -2.51 (-2.70, -2.33) | -1.39 (-2.17, -0.61)  | -1.84 (-2.70, -0.98)           |
| ≥ 25 years of age      | -1.88 (-2.07, -1.69) | -1.01 (-1.52, -0.49)  | -1.11 (-1.71, -0.52)           |

F/F⁵⁰del, ppFEV₁ percent predicted forced expiratory volume in 1 s, RF residual function

*Intercepts and slopes were calculated by weighting each age group category pooled across the F/F and F/RF (all) cohorts

Fig. 2  Estimated slope of ppFEV₁, by mutation and age group. F/F⁵⁰del, ppFEV₁ percent predicted forced expiratory volume in 1 s, RF residual function. Annual rates of ppFEV₁ decline were based on 2012 Global Lung Initiative equations [19]. Error bars represent SE; values in parentheses are the 95% CI of the slope. *P < 0.05 versus F/F; †P < 0.001 versus F/F
CONCLUSION

These results demonstrate substantial disease burden characterized by progressive lung function decline in people with CF across all age groups evaluated, regardless of genotype. The decline across all age groups reinforces the importance of early treatment intervention and clinical monitoring to preserve lung function in people with CF, including people with F/RF genotypes.

ACKNOWLEDGEMENTS

Funding. This study was funded by Vertex Pharmaceuticals Incorporated (Boston, MA, USA), which participated in the design, statistical analysis, and interpretation of the data; provided editorial and writing assistance; and funded the journal’s rapid service fee.

Medical Writing, Editorial, and Other Assistance. Editorial coordination and support were provided by Nathan Blow, PhD. NB is an employee of Vertex Pharmaceuticals Incorporated and may own stock or stock options in that company. Medical writing and editorial support were provided by Liz Phipps, PhD, CMPP, and Jackie Highland, PhD, of ArticulateScience, LLC, and was funded by Vertex Pharmaceuticals Incorporated. This work resulted from a scientific advisory group formed by Vertex Pharmaceuticals Incorporated and the US Cystic Fibrosis Foundation. All authors had full access to the study data, and the corresponding author had the final responsibility for the decision to submit for publication.

Author Contributions. All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. Individual author contributions are as follows: GSS: conceptualization, writing – original draft, writing – review and editing, and supervision. MWK: conceptualization, methodology, investigation, writing – original draft, writing – review and editing, and visualization. EFM: conceptualization, writing – review and editing, and project administration. RBM: investigation, writing – review and editing, and supervision. BL: conceptualization, methodology, writing – review and editing, and visualization. ES: conceptualization, methodology, validation, writing – review and editing, visualization, supervision, and funding acquisition. SJM: methodology, software, formal analysis, and writing – review and editing. DJP: methodology, software, formal analysis, and writing – review and editing. NM-H: conceptualization, methodology, and writing – review and editing. CHG: conceptualization, formal analysis, and review – writing and editing. WJM: conceptualization and writing – review and editing. MED: conceptualization, resources, data curation, writing – original draft, writing – review and editing, and supervision. YY: conceptualization, methodology, validation, writing – original draft, writing – review and editing, visualization, supervision, project administration, and funding acquisition.

Prior Presentation. This manuscript is based on work that was previously presented at the American Thoracic Society International Conference (Washington, DC; May 19–24, 2017).

Disclosures. All authors received nonfinancial assistance (assistance with manuscript preparation) from ArticulateScience, LLC, which received funding from Vertex Pharmaceuticals. Additional disclosure are as follows: GSS reports grants to his institution, travel support, and participation on an advisory board for Vertex Pharmaceuticals. MWK reports grants to his institution for clinical trial participation, honoraria for advisory board meetings, fees for consulting and speaker bureau, and travel reimbursement/support from Vertex Pharmaceuticals; grants to his institution for clinical trial participation, personal fees, and travel reimbursement/support from the US Cystic Fibrosis Foundation; grants to his institution for clinical trial participation, travel reimbursement/support, and consulting fees
from Laurent Pharmaceuticals; grants and consulting fees from AzurRx; personal fees (honoraria for advisory board meeting) from Insmed, Ionis Pharmaceuticals, Nabriva Therapeutics, and Santhera; consulting and speaker bureau fees and travel reimbursement/support from Chiesi; consulting fees and travel support/reimbursement from Merck; consulting fees from Cystetic Medicines, Mylan, and Paranta Biosciences; and grants to his institution from the National Institutes of Health. **EFM** reports research grants, consulting fees (steering committee), and payment/honoraria (educational materials) from Vertex Pharmaceuticals; consulting fees (advisory board) from Janssen Pharmaceuticals, Viatris Pharma, and Enterprise Pharma; and payment/honoraria (lecture) from Pfizer. **RBM** reports chapter authorship royalties from UpToDate; consulting fees from 4D Molecular Therapeutics, Aridis Pharmaceuticals, Nob Hill Therapeutics, and Zambon; and stock or stock options in Pfizer, Regeneron Pharmaceuticals, and Sanoﬁ. **BL** is a former employee of Vertex Pharmaceuticals. **ES**, **MED**, and **YY** are employees of Vertex Pharmaceuticals and may own stock or stock options in that company. **SJM** is a former employee and consultant of ICON plc (was an employee/consultant at the time of the study) and may own stock or stock options with that company. **SJM** is currently an employee of Unlearn.AI. **SJM** reports payments from Vertex Pharmaceuticals to ICON; grants or contracts from various pharmaceutical, biotech, and device companies to ICON; support (for attending meetings and/or travel) from ICON; and payments from various pharmaceutical, biotech, and device companies to ICON for support for attending meetings and/or travel. **DJP** is a former employee and consultant of ICON plc (was an employee/consultant at the time of the study), which received funding from Vertex Pharmaceuticals for this study and which receives grants or contracts from various pharmaceutical, biotechnology, and device companies for providing clinical research services; is a former employee and 50% owner of DMA Corporation, which received grants or contracts from various pharmaceutical, biotechnology, and device companies; reports consulting fees and payments for advisory board participation to themself and/or DMA Corporation from the US Cystic Fibrosis Foundation; reports payments or honoraria to themself and/or DMA Corporation from various pharmaceutical, biotech, and device companies; reports support for attending meetings and/or travel from ICON (while an employee); and reports payments from various pharmaceutical, biotech, and device companies to ICON for support for attending meetings and/or travel. **DJP** may own stock or stock options with ICON plc and DMA Corporation. **DJP** is currently retired from DMA Corporation. **NM-H** reports honorarium to herself for participation on the US Cystic Fibrosis Foundation Registry Committee and grants to her institution from the US Cystic Fibrosis Foundation; payments to herself for advisory board participation and grants to her institution from the National Institutes of Health; and consulting fees from and advisory board participation for Vertex Pharmaceuticals. **CHG** reports funding from the US Cystic Fibrosis Foundation (for conducting exacerbation studies, studies of gallium to treat infections, and clinical trial coordination in CF), the National Institutes of Health (to support clinical research in CF and clinical trials in other disease entities and to support multicenter clinical trials), and the US Food and Drug Administration (for studies of gallium to treat infections in CF); consulting fees (serving on an advisory board) from Enterprise Therapeutics; honoraria (to serve as chair of a grant review committee) from Gilead Sciences; payment or honoraria (to serve as a data safety monitoring board chair for a trial supported by Novartis and the European Commission) from Novartis; payment or honoraria (to serve as a US lead in a phase 2 trial of a novel therapy for CF) from Boehringer Ingelheim; honoraria and travel expenses (for talk at UK LEAD conference) from Vertex Pharmaceuticals; support to travel to grant review sessions from Gilead Sciences; served as a data safety monitoring board chair (for a trial supported by Novartis and the European Commission) for Novartis; served as an advisor for Aer Therapeutics; served on an advisory board for Enterprise Therapeutics; and owns stock or stock options (for serving as an advisor) with Aer Therapeutics. **WJM** reports grants from the
National Institutes of Health National Heart, Lung, and Blood Institute (funding for Tucson Children’s Respiratory Study [Co-I], ORBEX – asthma prevention study [site PI, executive committee], the National Institutes of Health National Institute of Allergy and Infectious Disease (consultant to PARK – asthma prevention study), and the US Cystic Fibrosis Foundation (participation as chair of the CFF data safety monitoring board [does not directly oversee the Vertex studies]); consulting fees (CFF data safety monitoring board and CFF Comparative Effectiveness Research/Registry Committee) from the US Cystic Fibrosis Foundation; honorarium (speaker at biennial Pediatric Pulmonary Board Preparation Course) from the American College of Chest Physicians; and funding for Healthcare.

**Compliance with Ethics Guidelines.** This study was conducted in accordance with the current Good Clinical Practice Guidelines as described by the International Council for Harmonisation, the Declaration of Helsinki, and all applicable local regulations. People with CF provided informed consent to participate in the US Cystic Fibrosis Foundation Patient Registry and to have their data included in the registry. The study did not involve primary data collection and used only de-identified data; thus, institutional review board approval was not required.

**Data Availability.** The data sets generated during and/or analyzed during the current study are available from the US Cystic Fibrosis Foundation Patient Registry, https://www.cff.org/researchers/patient-registry-data-requests. The US Cystic Fibrosis Foundation Patient Registry collects and manages its own data and maintains processes for researchers to request summarized data.

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