Comparison of Longitudinal Outcomes in Children with Primary Ciliary Dyskinesia and Cystic Fibrosis

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Author Contributions:
All authors have given approval to the final version of this manuscript. BK: Conception of design, analysis design and interpretation of data, writing of the manuscript. MR: conception of design, acquisition of data, analysis design and interpretation of data, writing of the manuscript, and review of manuscript. ES, FO, RS, MB: Biostatistician, analysis design, interpretation of data, development of tables and figures. TF, SS, SD, CM, AS, KS, MZ, JP, MK: conception of design, acquisition of data, manuscript review. SD: conception of design, acquisition of data, analysis design, and manuscript review. ML: conception of design, acquisition of data, analysis design and interpretation of data, review of manuscript.

Financial Support:
Support provided by the Genetic Disorders of Mucociliary Clearance Consortium. The Genetic Disorders of Mucociliary Clearance (U54HL096458) is a part of the National Center for Advancing Translational Sciences (NCATS) Rare Diseases Clinical Research Network. Rare Diseases Clinical Research Network is an initiative of the Office of Rare Diseases Research,

ANNALSATS Articles in Press. Published October 09, 2024 as 10.1513/AnnalsATS.202311-1008OC

NCATS, funded through a collaboration between NCATS and NHLBI; Clinical and Translational Science Awards NIH/NCATS UNC ULTR000083; NIH/NCATS Colorado Clinical and Translational Science Awards grant number UM1 TR004399; and Intramural Research Program of NIH/National Institute of Allergy and Infectious Diseases. We would also like to acknowledge the Cystic Fibrosis Foundation for access and use of CFF Patient Registry data.

Running Title: Clinical Outcomes in Children with PCD and CF

ATS Subject: 14.08 (Primary Ciliary Dyskinesia)

Keywords: Primary ciliary dyskinesia, cystic fibrosis, lung function

Word count: 3528

This article has an online data supplement, which is accessible at the Supplements tab.

ANNALSATS Articles in Press. Published October 09, 2024 as 10.1513/AnnalsATS.202311-1008OC

ABSTRACT

Rationale: Primary ciliary dyskinesia (PCD) and cystic fibrosis (CF) are both genetic diseases of mucociliary clearance resulting in progressive lung disease with onset in early life. PCD is often considered to be milder in childhood than CF, based on minimal evidence. Similar to CF, genotype-phenotype associations exist in PCD: pathogenic variants in *CCDC39* and *CCDC40,* causing inner dynein arm/microtubular defects (IDA/MTD) are associated with more severe disease.

Objectives: To compare longitudinal outcomes in matched children with PCD and CF. We hypothesized that children with PCD with IDA/MTD defects would have lower lung function but better nutritional indices than matched children with CF with minimal function genotypes (*i.e.,* those associated with pancreatic insufficiency).

Methods: Children with PCD enrolled in a prospective, multicenter, observational study were matched with CF patients from the CF Foundation Patient Registry by birth cohort, age, sex, race/ethnicity and year of study visit. The association of disease group overall and by severity class (PCD-IDA/MTD versus all other defects and CF-minimal versus residual function) with longitudinal outcomes up to age 17 was evaluated with cubic spline mixed effects models.

Measurement and Main Results*:* Groups included 136 children with PCD (40 IDA/MTD, 96 other) and 476 with CF (446 minimal function, 30 residual function). Below age 14, the PCD group had similar or lower estimated mean FEV_1 % predicted compared to CF (e.g., at age 10, -5.4 % predicted lower (95% CI: -7.7, -3.1)). Compared to the CF-minimal function (pancreatic

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insufficient) group, the PCD-IDA/MTD group had similar BMI; estimated mean FEV_1 % predicted was significantly lower by age 10 (mean difference -10.6% (95% CI: -14.7, -6.4), increasing to -15.7% (95% CI: -20.3, -11.2) at age 14. The CF cohort had increased prevalence of *Pseudomonas aeruginosa* cultured on one or more occasions compared to children with PCD (67% vs 27%, $p<0.001$); there was no difference in prevalence of *P. aeruginosa* between children with PCD-IDA/MTD and PCD-other**.**

Conclusions: In childhood, average lung function abnormalities in PCD are not milder than CF, particularly for those with IDA/MTD ciliary defects. New guidelines and treatments to improve outcomes in PCD are urgently needed.

ANNALSATS Articles in Press. Published October 09, 2024 as 10.1513/AnnalsATS.202311-1008OC

INTRODUCTION

Primary ciliary dyskinesia (PCD) and cystic fibrosis (CF) are both genetic disorders of mucociliary clearance. While their underlying pathophysiology differs, both are characterized by chronic endobronchial bacterial infection, progressive obstructive lung disease and structural airway damage with onset in early life (1, 2).

PCD is widely considered to have a milder course compared to CF (3-5), though direct comparisons of outcomes in these two conditions are largely limited to small, cross-sectional, one- or two-center studies (4, 6-12), many of which actually conclude that pulmonary disease severity is similar in these two conditions. Recently, Halbeison and colleagues (13) compared retrospective spirometry data from a large international PCD cohort with published data from UK CF patients and reported that FEV_1 was similarly reduced in childhood, but less impaired in young adults with PCD than CF. To date, however, there have been no prospective, multicenter, longitudinal studies comparing disease severity and progression in PCD and CF.

In CF, genotype-phenotype associations are well established. Individuals with CF transmembrane conductance regulator (*CFTR*) minimal function genotypes (defined as both alleles with class 1-3 variants (including F508del); associated with exocrine pancreatic insufficiency, ~85% of the CF population) generally have more severe disease than those with residual function genotypes (defined as at least one allele with a class 4 to 6 variant; generally associated with pancreatic sufficiency) (14). In PCD, genotype-phenotype associations are also emerging. Individuals with pathogenic variants in *CCDC39* and *CCDC40*, causing inner dynein arm defects and microtubular disorganization (IDA/MTD), generally have more severe disease

ANNALSATS Articles in Press. Published October 09, 2024 as 10.1513/AnnalsATS.202311-1008OC

than those with pathogenic variants in other PCD-related genes or other ciliary defects, with, on average, lower FEV_1, greater FEV_1 decline, lower nutritional indices, and more airway disease on chest CT (9, 13, 15, 16).

We sought to compare longitudinal spirometric parameters, nutritional indices, and respiratory microbiology between a cohort of children with PCD and a contemporary cohort of age, sex and race/ethnicity-matched children with CF. First, we compared outcomes between the PCD and CF cohorts as a whole. Then, to minimize within-disease cohort heterogeneity, we further divided the cohorts by ultrastructural ciliary defect (PCD) or genotype functional class (CF), as PCD-IDA/MTD and CF-minimal function groups have on average more severe disease than their counterparts, the PCD-Other and CF-residual function groups. We hypothesized that the PCD IDA/MTD group would have lower lung function but better nutritional indices than the CF-minimal function group.

METHODS

Participants

The PCD cohort consisted of participants with definite PCD enrolled in the Genetic Disorders of Mucociliary Clearance Consortium (GDMCC) multicenter, prospective, observational study (9, 15, 17) at 7 North American sites between 2006 and 2011. Participants were ≤ 18 years of age at enrollment with confirmed PCD, defined as abnormal ciliary ultrastructure by transmission electron microscopy and/or identification of two pathogenic variants in a PCD-associated gene, along with compatible clinical features (1).

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PCD participants were matched 1:4 with CF individuals from the U.S. CF Foundation National Patient Registry (18) by year of birth, sex, race, ethnicity, and presence of at least one encounter during the year in which the matched PCD participant had a study visit. None of the CF participants were on CFTR modulator therapy at baseline (which was prior to 2012, year of approval of the first modulator, ivacaftor, in the U.S.) and none were on the highly effective modulator therapy elexacaftor/tezacaftor/ivacaftor during the study period (approved in U.S. in 2019).

Study Procedures and Data

As previously described (9, 15, 17), PCD participants completed annual study visits for up to 5 years, conducted ≥4 weeks after any respiratory illness. At these visits, nutritional indices (weight, height, body mass index) and respiratory microbiology from expectorated sputum or deep oropharyngeal swabs were collected and spirometry performed (19). To align with the PCD cohorts' annual study visits, for each CF participant, nutritional, culture and spirometric data from the non-exacerbation encounter closest to the date of the matched PCD participant's annual encounter were extracted from encounter-based Registry data from 2006-2018.

Institutional review board approval was obtained at each participating site for the PCD study and the CF Registry; informed consent and/or assent when indicated were obtained from all participants. An Observational Safety Monitoring Board reviewed and approved the PCD protocol, and the CF Foundation reviewed and approved the Registry data request.

Statistical Analysis

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The PCD cohort was grouped by ciliary ultrastructural defect: 1) PCD IDA/MTD, and 2) all other defects (outer dynein arm (ODA), ODA/inner dynein arm, central apparatus, oligocilia, normal-near normal). The CF cohort was grouped by *CFTR* functional class: minimal function (both pathogenic variants in classes 1 to 3) versus residual function (at least one variant in classes 4 to 6) (14, 20).

Lung function was expressed as percent of predicted based on 2012 Global Lung Initiative reference ranges (21) and nutritional indices as percentiles from Centers for Disease Control (CDC) reference equations (22).

The associations of disease group with spirometric and nutritional indices were evaluated using restricted natural cubic spline mixed effects models, with disease group as a fixed effect and matched pairs as random effects. The choice of restricted cubic splines and knots for the splines at ages 8, 12, and 15 years were based on Akaike Information Criteria. Interactions between disease group and age were tested via a Likelihood Ratio Test to assess whether splines differed by disease group. Analyses were truncated at age 17 due to sparse data.

For respiratory microbiology, the prevalence of each pathogen (proportion of participants with ≥1 positive culture among those with culture results) was plotted by age and disease group. Chi-square tests were utilized to compare proportions. Two-sided tests and 5% level of significance were used. Analyses were conducted using Stata 16.1 (Stata Corp., College Station, TX).

RESULTS

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Cohort Matching, Characteristics and Follow-Up

The PCD cohort consisted of the 141 children with definite PCD in the GDMCC longitudinal cohort, as previously described (9). As shown in **Figure 1,** one was excluded due to no observations prior to age 18, and 4 due to no successful CF match; all were of Asian race, which is very rare in CF. The final analysis cohort consisted of 136 children with PCD (40 (29%) with IDA/MTD ultrastructural defects and 96 (71%) with other defects) and 476 children with CF (446 (94%) children with minimal function and 30 (6%) with residual function genotypes).

Baseline demographic characteristics are summarized in **Table 1**. The distribution of pathogenic variants in the PCD cohort is summarized in **Table E1** in the online data supplement. The PCD and CF cohorts were well matched by age, sex, race, ethnicity, and baseline encounter year. Mean age at diagnosis was 4.0 (SD 3.8) years for children with PCD compared to 1.1 (2.3) years for children with CF. The PCD-IDA/MTD group had the lowest mean age at enrollment and the CF-minimal function group had the highest proportion of white participants. Mean (SD) years of observation for children with PCD-IDA/MTD was 4.5 (1.1) years, PCD-Other 4.5 (1.3) years, CF-Minimal 4.4 (1.3) years, and CF-Residual 4.7 (0.7) years.

Association of Disease Group with Longitudinal Outcomes

We first compared outcomes between the entire PCD and CF groups. The association between disease group and outcome differed by age (i.e., there was a significant interaction between disease group and age), so outcomes need to be compared between disease groups at specific ages and a comparison of outcomes across all ages combined is not valid. Thus, results (**Figure 2)** are presented as plots of longitudinal outcomes by disease group (left panel) and the estimated

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mean (95% CI) for each disease group and the difference between them displayed at three representative ages (right panel).

The PCD cohort had similar or lower estimated mean FEV_1 % predicted compared to the CF cohort through age 14, most pronounced at age 10 (5.4% predicted lower (95% CI: -7.7, -3.1), p<0.001). After age 15, the mean FEV_1 % predicted was higher in the PCD than the CF cohort, though not significantly. The difference in FEF_{25-75} between the two cohorts was more prominent. The PCD cohort had significantly lower FEF_{25-75} % predicted compared to the CF cohort at ages 6, 10 and 14, most pronounced at age 6 (21.4% predicted lower (95%CI: -29.5, -13.4). As shown in **Supplemental Figure 1**, FEV_1/FVC and FVC were also significantly lower in the PCD cohort through age 14 years. BMI percentile was similar between the PCD and CF cohorts until age 10; after that age, it was significantly lower in the CF cohort (at age 10, 6.0 percentile lower (95% CI 2.8, 9.1), p<0.001, **Figure 2**). However, the CF cohort had significantly lower weight and height percentiles than the PCD cohort after age 6, with the gap widening with age (**Supplemental Figure 1**).

Next, we compared outcomes between disease groups further divided by ultrastructural defect (PCD) or genotype functional class (CF) (**Figure 3**). The PCD-IDA/MTD group had the lowest estimated mean FEV_1 % predicted of all four groups, and the gap between the PCD-IDA/MTD and the other groups widened with advancing age. At age 10 , the estimated mean difference between the PCD-IDA/MTD and CF-minimal function groups was -10.6 (95% CI: -14.7, -6.4), p<0.001), increasing at age 14 to -15.7 (95% CI: -20.3, -11.2), p<0.001). In contrast, the PCD-Other and CF-minimal function groups had similar mean FEV_1 % predicted at all ages. The

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lower lung function among the PCD IDA/MTD cohort was even more pronounced for FEF_{25-75} % predicted (**Figure 3**) and FEV1/FVC (**Supplemental Figure 2**). Compared to the CF-minimal function group, the PCD-IDA/MTD group had significantly lower estimated mean BMI percentile before age 6 and similar thereafter (**Figure 3**), even though PCD is not associated with pancreatic dysfunction. While weight did not differ between the PCD-IDA/MTD and CF-minimal function groups, the CF-minimal function group had significantly lower height starting at age 6 (**Supplemental Figure 2**).

Figure 4 shows the prevalence of respiratory pathogens by age for each disease group. The most common bacterial pathogens isolated from PCD participants across all ages were *Haemophilus influenzae* and *Staphylococcus aureus*, whereas for CF participants they were *Staphylococcus aureus* and *Pseudomonas aeruginosa*, both of which were more prevalent among CF than PCD children (*S. aureus:* 431/474 (91%) children with CF with isolation of the organism on one or more occasions compared to 67/135 (50%) children with PCD, $p<0.001$; *P. aeruginosa:* 320/476 (67%) children with CF compared to 36/135 (27%) children with PCD, $p<0.001$**).** The prevalence of NTM was low in all disease groups in this young cohort. As expected, children with CF-minimal function had a higher prevalence of *P. aeruginosa* than children with CF-residual function. In contrast, there was no difference in prevalence of *P. aeruginosa* between children with PCD-IDA/MTD and PCD-other**.**

DISCUSSION

PCD and CF are both rare genetic disorders of mucociliary clearance characterized by recurrent sinopulmonary infections and progressive suppurative lung disease, though the underlying

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pathophysiology differs. Children with these two disorders are generally cared for by the same providers, so the two conditions are frequently compared. To our knowledge, this is the first longitudinal prospective, multicenter comparison of outcomes in PCD and CF in childhood. Our results challenge the widely held paradigm that children with PCD have mild lung disease compared to children with CF (4, 6-8, 10-12, 23). Our PCD cohort had similar or lower mean FEV_1 values through early adolescence compared to matched children with CF, even though this study was conducted prior to the advent of highly effective CF modulator therapies. Furthermore, when comparing the more severe disease groups within PCD and CF, children with PCD with IDA/MTD ciliary defects had lower lung function and similar nutritional deficits compared to children with CF with minimal function genotypes, even though PCD is not associated with maldigestion or malabsorption. The differences in lung function between the PCD and CF cohorts was most prominent for FEV_1/FVC and FEF_{25-75}.We also found clear differences in respiratory microbiology between children with PCD and CF, as has been observed in prior studies (4, 24), with *P. aeruginosa* and *S. aureus* much less prevalent in children with PCD.

Prior comparisons of PCD and CF have been largely limited to small, cross-sectional studies. Cohen-Cymberknoh and colleagues (4) were the first to directly compare outcomes in children and adults with PCD (N=34) and CF (N=130) through a retrospective review of clinical data. They reported the severity of lung disease as assessed by FEV_1 and chest CT scores to be most severe in the CF-PI group while less severe – and comparable – in the PCD and CF-PS groups. Mean BMI was lower in the PCD group than either CF group. Other small studies have reported similar pulmonary disease severity in PCD and CF, assessed using chest imaging (8), tests of

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exercise fitness (10, 11), lung clearance index (12, 23) and spirometry (4, 6, 7, 10, 11, 23). Recently, Halbeisen and colleagues (13) performed a cross-sectional comparison of lung function from the retrospective, large, international iPCD cohort (one measurement per participant) to published lung function from a UK CF cohort and showed that FEV_1 was similar between the conditions in childhood but more impaired in CF than in PCD beginning at about age 17, similar to our findings. Utilizing this same iPCD cohort, Goutaki and colleagues also reported reduced height-for-age (25), a finding we did not observe in our PCD cohort.

Children with PCD had significantly lower FEV_1/FVC and FEF_{25-75} compared to children with CF, as has been demonstrated previously in a smaller cohort (23). Compared to CF, individuals with PCD have more atelectasis and mucus plugging on chest computed tomography (CT), which is even more pronounced in children with IDA/MTD defects (26), and likely a contributing factor to the lower FEF_{25-75} and (to a lesser extent) FEV_1 observed in the PCD cohort. The contribution of mucus plugging to other airway disease including asthma (24, 25) and chronic obstructive pulmonary disease (COPD) (24) is receiving growing recognition. In the Severe Asthma Research Program cohort, mucus plugs on CT were common and associated with lower FEV_1 and worse ventilation defects (25, 26). Asthma as a co-morbidity was not captured in either the PCD or CF cohort, but differences in the prevalence of asthma in the two groups could serve a possible explanation for the different spirometric patterns. Bronchodilator responsiveness was not uniformly collected for either cohort. Preliminary evidence suggests that mucus plugging in asthma may be mediated through pathologically relevant changes in MUC5AC and MUC5B in the airway mucus gel (28). Similarly, non-CF bronchiectasis exhibits distinctive proximal and distal bronchiolar disease characterized by mucus plugging and ectatic

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bronchioles, with elevated MUC5AC and MUC5B mucins (27). The role of mucus plugging in PCD airway disease deserves further investigation.

The pathophysiology leading to abnormalities of mucociliary clearance differs in PCD and CF. PCD is caused by pathogenic variants in genes responsible for motor cilia assembly, resulting in ciliary dysfunction. In contrast, CF is caused by pathogenic variants in the *CFTR* gene encoding a chloride and bicarbonate channel expressed on epithelial cells, resulting in desiccated, acidic airway surface liquid. How these different abnormalities in mucociliary clearance manifest in disease expression is only partially understood. Mucus from people with PCD and CF are both hyperconcentrated (28, 29), and there are no apparent differences in the biophysical or transport properties of expectorated sputum between children with PCD and CF (3), though this observation deserves further investigation. As reported by us and others (4, 24), respiratory microbiology differs between PCD and CF, with a higher prevalence of *Haemophilus influenzae* and lower prevalence and later acquisition of *P. aeruginosa* in children with PCD compared to CF (30). Interestingly, the relationship between bacterial pathogens and lung disease severity seems to differ between the two conditions: while we found the prevalence of pathogens to differ between CF with minimal versus residual function, the profile of pathogens in the PCD-IDA/MTD and PCD-other subgroups (*i.e.,* those with on average more versus less severe pulmonary disease) were similar. These results suggest that, during childhood, *P. aeruginosa* is not a primary driver of lung disease severity in PCD.

While both PCD and CF are characterized by neutrophil-dominant airway inflammation (31), comparisons of inflammatory markers in sputum between PCD and CF have yielded mixed

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results. At stable baseline, sputum interleukin-8 (3, 32) and tumor necrosis factor alpha (32) concentration have been shown to be greater in PCD than age- and FEV_1-matched CF patients. At the onset of a pulmonary exacerbation, sputum absolute neutrophil counts were higher in PCD, though interleukin-8 concentrations were similar compared to CF (31). With treatment of the exacerbation, absolute neutrophil count and elastase activity responded more in PCD than CF, though the interleukin-8 response was similar (31).

In our cohorts, mean age of diagnosis for children with PCD was lower than for children with CF (4 years vs. 1.1 years). Newborn screening for CF has been universal in the U.S. for nearly 15 years, allowing for earlier diagnosis and implementation of disease-modifying therapies (33). In contrast, the diagnosis of PCD is often delayed (34, 35) despite its neonatal manifestations, due to the heterogeneity of the disease and limitations in current diagnostic testing. Increasing awareness of PCD and improving the sensitivity of diagnostic testing is essential for earlier diagnosis.

Our study has several strengths. Children with PCD were enrolled in a multicenter, prospective, longitudinal study with rigorous diagnostic criteria and standardized data collection at research visits rather than at clinical encounters. We matched children with PCD and CF by birth year, sex, race/ethnicity and years of data collection. We evaluated longitudinal trajectories of lung function and nutritional indices using mixed effects models with restricted natural cubic splines, allowing a non-linear association between age and outcomes. In addition to comparing PCD to CF, we further divided the disease groups by severity class to decrease within-group heterogeneity.

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Limitations of this study must also be acknowledged. Our study was limited to children under age 18 so our results cannot be generalized to adults. Our results suggest that lung function abnormalities after age 18 are likely milder in PCD than CF, as reported by Halbeisen, et al (13), though maybe not for individuals with IDA/MTD defects. Many participants in both cohorts in our study received their care in specialized PCD or CF centers; even though care at these centers was not standardized, clinical outcomes outside of these centers may differ. Additional clinical data, including medications and therapies, as well as respiratory co-morbidities (e.g., asthma), were not collected, and these unmeasured confounders could have affected our results. We were unable to match on (or evaluate) socioeconomic status, since these data were not recorded in the PCD study. Similarly, we were not able to compare rates of pulmonary exacerbations between the two conditions because of limited data collection in the PCD cohort. As expected for a rare disease, our PCD sample size was small, limiting power to detect differences between groups. While serial chest CTs were performed in the PCD study, the CF Registry does not record imaging results, and neither cohort routinely underwent multiple breath washout testing. Finally, whereas CF is generally diagnosed in infancy, even before universal newborn screening, PCD is generally diagnosed symptomatically, often at an older age compared to CF. In this study, individuals with IDA/MTD defects were diagnosed earlier than those with other ultrastructural defects (15, 17). Thus, the average age at enrollment in our study was younger for the PCD-IDA/MTD group than the PCD-other group, though we had less data from older IDA/MTD subjects, decreasing the precision of our estimates at those ages. Our CF comparator group included very few children with residual-function CFTR defects (n=30) due to our complex matching schema based on year of birth, sex, race, ethnicity, and presence of at a least one

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encounter during the year in which the matched PCD participant had a study visit. The small size of the residual-function CFTR cohort limits precision of the estimates for this group as well as generalizability. This study was conducted prior to the approval of elexacaftor-tezacaftor-ivacaftor. In the current treatment era, with improved outcomes in modulator-eligible children with CF, the differences in lung function between children with PCD and CF would likely be more pronounced. Lastly, we were unable to evaluate survival in this 5-year study in children.

CONCLUSION

In summary, in this longitudinal, prospective, multicenter comparison of clinical outcomes in CF and PCD, we demonstrate that in childhood from about ages 8 to 12 years of age, FEV_1 is similar or lower in PCD compared to CF. In children with PCD and IDA/MTD ciliary defects, representing 30% of the PCD cohort, average lung function is lower than in minimal function CF and the gap does not appear to close in later adolescence. Additionally, children with PCD-IDA/MTD defects have nutritional deficits similar to children with CF with minimal function genotypes, who have pancreatic insufficiency leading to malabsorption. Earlier diagnosis, standardized treatment protocols, attention to nutritional management and new therapies are clearly needed to improve outcomes in children with PCD.

ACKNOWLEGEMENTS

We would like to thank the participants in the PCD study and the research coordinators at each participating site. We would also like to thank the CF Foundation for the use of the CF Foundation Patient Registry data and the patients, care providers, and clinic coordinators at CF

ANNALSATS Articles in Press. Published October 09, 2024 as 10.1513/AnnalsATS.202311-1008OC

centers throughout the United States for their contributions to the CF Foundation Patient Registry.

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FIGURE LEGENDS

Figure 1. Flowchart of cohort constitution. Children with PCD were matched 1:4 with children with CF from the U.S. CF Foundation National Patient Registry (17) by year of birth, sex, race, ethnicity, and presence of at least one encounter during the year in which the matched PCD patient had a study visit.

Figure 2. Mean estimated spirometric indices and growth parameters by age and specific indices at representative ages (2, 6, 10, and 14 years), stratified by disease group (PCD versus CF): a) forced expiratory volume in one second (FEV_1) percent predicted; b) forced mid-expiratory flow (FEF_{25-75}) percent predicted, and c) body mass index (BMI) percentile by age, stratified by disease cohort (PCD versus CF).

FIGURE 3. Mean estimated spirometric indices and growth parameters by age and specific indices at representative ages (2, 6, 10, and 14 years), stratified by disease group (PCD IDA/MTD, PCD-other, CF-minimal function, CF-residual function): a) forced expiratory volume in one second (FEV_1) percent predicted; b) forced mid-expiratory flow (FEF_{25-75}) percent predicted, and c) body mass index (BMI) percentile.

FIGURE 4. Prevalence of respiratory bacterial pathogens by age, stratified by disease group (PCD-IDA/MTD, PCD-other, CF-minimal function, CF-residual function).

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TABLE 1. Baseline Demographic Characteristics by Disease Group

	PCD N= 136	**CF N= 476**	**PCD IDA/MTD N=40**	**PCD Other N=96**	**CF Minimal* N=448**	**CF Residual* N=30**
Age, years, mean (SD)	8.4 (4.6)	8.2 (4.6)	6.7 (4.5)	9.2 (4.5)	8.2 (4.6)	7.9 (4.5)
Age at diagnosis, years, mean (SD)	4.0 (3.8)	1.1 (2.3)	2.5 (2.9)	4.6 (4.0)	1.0 (2.0)	3.1 (4.3)
Female, n (%)	69 (50.7%)	236 (49.6%)	19 (47.5%)	50 (52.1%)	221 (49.6%)	15 (50.0%)
Race, n (%)						
American Indian/Alaskan Native	4 (2.9%)	6 (1.3%)	1 (2.5%)	3 (3.1%)	6 (1.3%)	0 (0.0%)
Asian	13 (9.6%)	16 (3.4%)	3 (7.5%)	10 (10.4%)	11 (2.5%)	5 (16.7%)
Black/African American	3 (2.2%)	9 (1.9%)	2 (5.0%)	1 (1.0%)	8 (1.8%)	1 (3.33%)
White	114 (83.3%)	438 (92.0%)	32 (80.0%)	82 (85.4%)	415 (93.0%)	23 (76.7%)
Other	2 (1.5%)	7 (1.5%)	2 (5.0%)	0 (0.0%)	6 (1.3%)	1 (3.3%)
Hispanic Ethnicity, n (%)	14 (10.3%)	45 (9.5%)	5 (12.5%)	9 (9.4%)	42 (9.4%)	3 (10.0%)
Baseline encounter year						
2006	5 (3.7%)	19 (4.0%)	2 (5.0%)	3 (3.1%)	19 (4.3%)	0 (0.0%)
2007	57 (41.9%)	198 (41.6%)	11 (27.5%)	46 (47.9%)	190 (42.6%)	8 (26.7%)
2008	31 (22.8%)	109 (22.9%)	13 (32.5%)	18 (18.8%)	97 (21.7%)	12 (40.0%)
2009	28 (20.6%)	95 (20.0%)	6 (15.0%)	22 (22.9%)	90 (20.2%)	5 (16.7%)
2010	10 (7.4%)	35 (7.4%)	7 (17.5%)	3 (3.1%)	30 (6.7%)	5 (16.7%)
2011	5 (3.7%)	20 (4.2%)	1 (2.5%)	4 (4.2%)	20 (4.5%)	0 (0.0%)

Definition of abbreviations: CF = cystic fibrosis; PCD = primary ciliary dyskinesia; ODA = outer dynein arm; IDA = inner dynein arm; MTD = microtubular disorganization.

*CF minimal function is defined as both alleles with variants in class 1 to 3 (including F508del), associated with pancreatic insufficiency. CF residual function is defined as at least one allele with a variant in class 4 to 6, associated with pancreatic sufficiency

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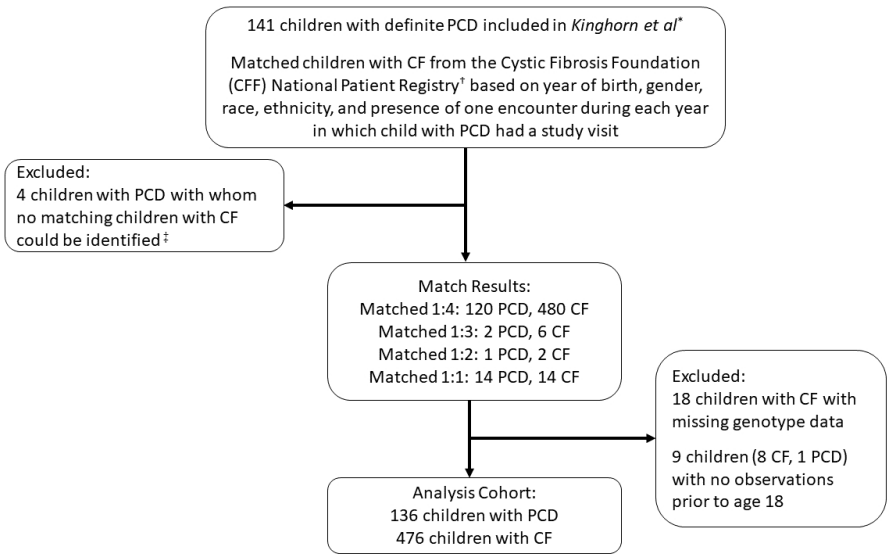

Figure 1. Flowchart of cohort constitution. Children with PCD were matched 1:4 with children with CF from the U.S. CF Foundation National Patient Registry (17) by year of birth, sex, race, ethnicity, and presence of at least one encounter during the year in which the matched PCD patient had a study visit.Footnote: Definitions of abbreviations: PCD = primary ciliary dyskinesia; CF = cystic fibrosis; CFF = Cystic Fibrosis Foundation.*Definite PCD defined as abnormal ciliary ultrastructure by transmission electron microscopy and/oridentification of two pathogenic variants in a PCD-associated gene along with compatible clinical features (9).†Cystic Fibrosis Foundation (CFF) National Patient Registry (17).‡ Four children with PCD did not successfully match, all of Asian race, which is very rare in cystic fibrosis.

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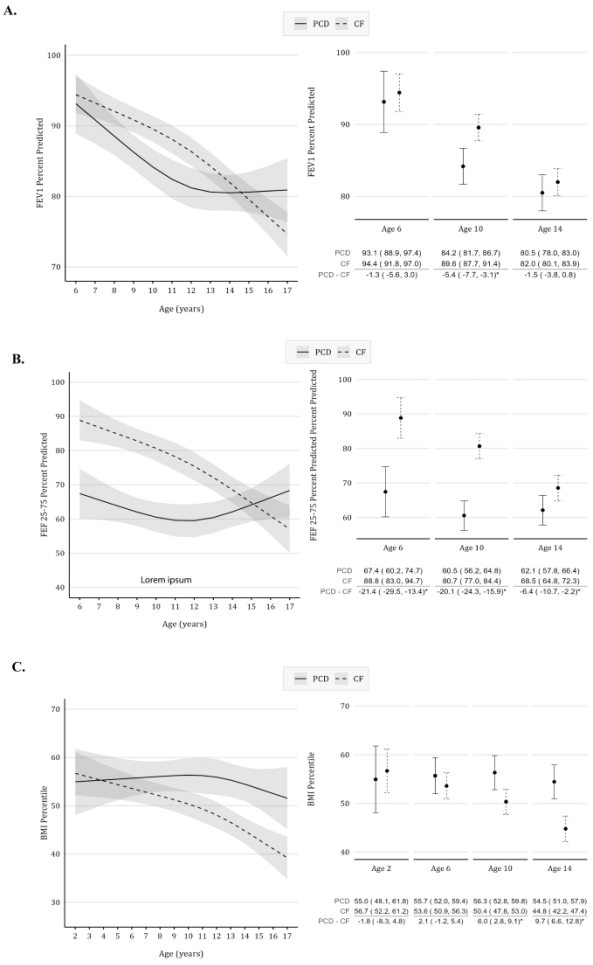

Figure 2. Mean estimated spirometric indices* and growth parameters† by age and specific indices at representative ages (2, 6, 10, and 14 years), stratified by disease group (PCD versus CF): a) forced expiratory volume in one second (FEV1) percent predicted; b) forced mid-expiratory flow (FEF25-75) percent predicted, and c) body mass index (BMI) percentile by age, stratified by disease cohort (PCD versus CF). Footnote: Definition of abbreviations: BMI = body mass index; CF = Cystic Fibrosis; FVC: forced vital capacity; FEV1 = forced expiratory volume in 1 second; FEF25-75 = forced mid-expiratory flow; PCD = Primary Ciliary Dyskinesia.* Spirometric values were expressed as percent predicted based on the Global Lung Initiative reference equations (21).† Growth parameter estimates were derived from the U.S. Centers for Disease Control and Prevention reference data (22).

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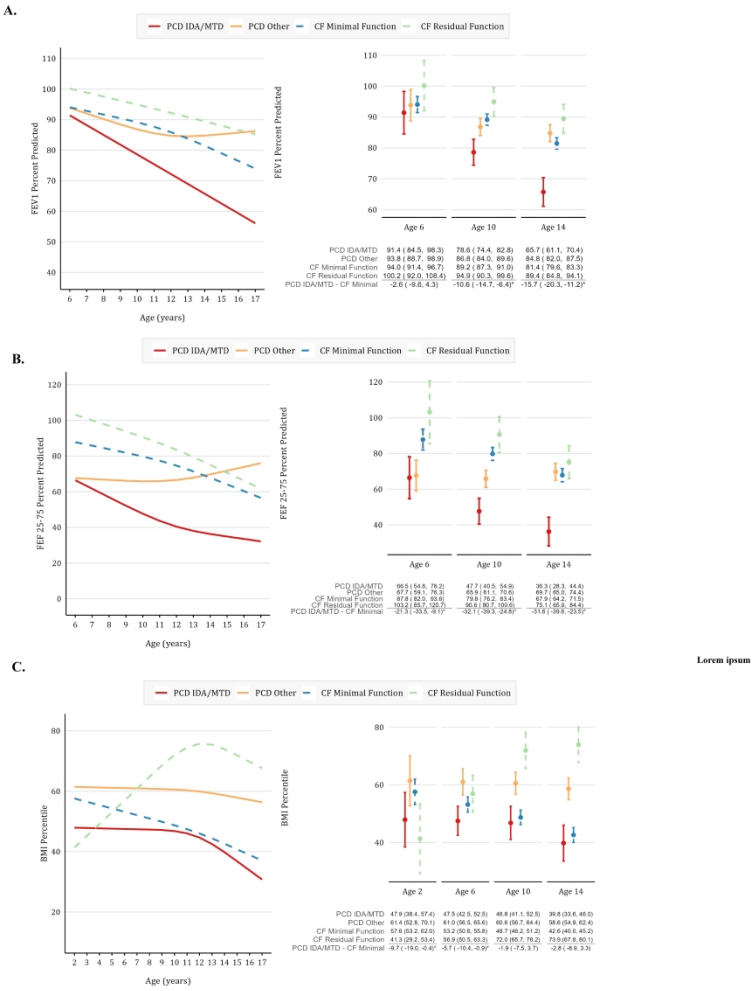

FIGURE 3. Mean estimated spirometric indices* and growth parameters† by age and specific indices at representative ages (2, 6, 10, and 14 years), stratified by disease group (PCD IDA/MTD, PCD-other, CF-minimal function, CF-residual function): a) forced expiratory volume in one second (FEV1) percent predicted; b) forced mid-expiratory flow (FEF25-75) percent predicted, and c) body mass index (BMI) percentile.

Footnote:
Definition of abbreviations: BMI = body mass index; CF = Cystic Fibrosis; FVC: forced vital capacity; FEV1 = forced expiratory volume in 1 second; FEF25-75 = forced mid-expiratory flow; IDA = inner dynein arm; MTD = microtubular disorganization; PCD = Primary Ciliary Dyskinesia.
* Spirometric values were expressed as percent predicted based on the Global Lung Initiative reference equations (21).
† Growth parameter estimates were derived from the U.S. Centers for Disease Control and Prevention reference data (22).

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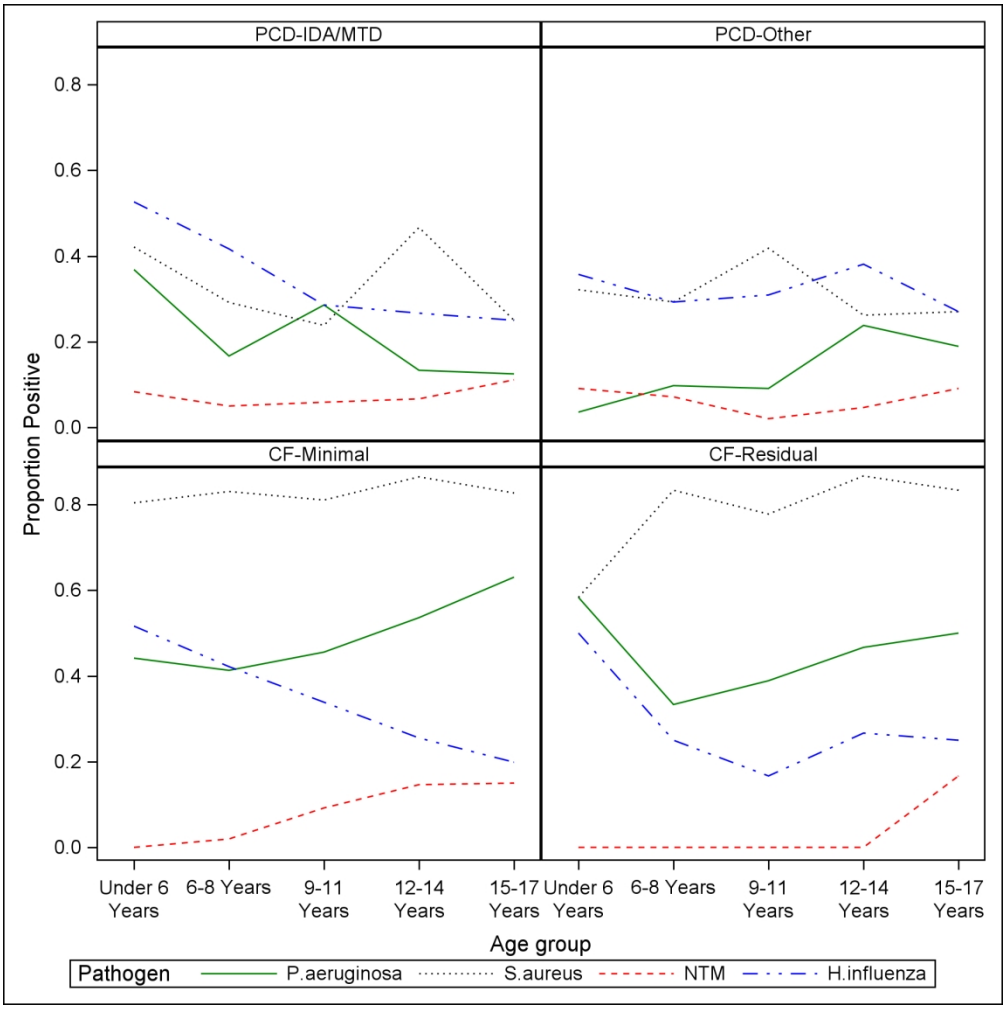

FIGURE 4. Prevalence of respiratory bacterial pathogens by age, stratified by disease group (PCD-IDA/MTD, PCD-other, CF-minimal function, CF-residual function)*

Footnote:
Definitions of abbreviations: CF = Cystic Fibrosis; H. influenzae = Haemophilus influenzae; IDA = inner dynein arm; MTD = microtubular disorganization; NTM = non-tuberculosis mycobacterium; PCD = Primary Ciliary Dyskinesia; P. aeruginosa = Pseudomonas aeruginosa; S. aureus = Staphylococcus aureus.
*Respiratory data was collected at least once during the follow-up period in 135 (99%) children with PCD and 478 (100%) children with CF. Nontuberculous mycobacterium (NTM) data were available for 307 (69%) children with CF-Minimal, 14 (47%) children with CF-Residual, 36 (90%) children with PCD-IDA/MTD, and 78 (81%) children with PCD-other.

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Comparison of Longitudinal Outcomes in Children with Primary Ciliary Dyskinesia and Cystic Fibrosis

BreAnna Kinghorn, Margaret Rosenfeld, Erin Sullivan, Frankline M. Onchiri, Marshall D. Brown, Rhonda Szczesniak, Thomas W. Ferkol, Scott D. Sagel, Sharon D. Dell, Carlos Milla, Adam J. Shapiro, Kelli M. Sullivan, Maimoona A. Zariwala, Jessica E. Pittman, Michael R. Knowles, Stephanie D. Davis, Margaret W. Leigh, for the Genetic Disorders of Mucociliary Clearance Consortium

ONLINE DATA SUPPLEMENT

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Table E1. Ultrastructural and Genetic Findings of the 136 children with PCD.

PCD-Causing Gene	ODA	ODA/IDA	IDA/MTD	Normal/Near Normal	Total
None Identified	-	1	1	-	2
DNAH5	40	-	-	-	40
DNAI1	9	-	-	-	9
DNAI2	5	-	-	-	5
CCDC114	2	-	-	-	2
ARMC4	1	-	-	-	1
LRRC6	-	3	-	-	3
DNAAF4 (DYX1C1)	-	3	-	-	3
CCDC103	-	2	-	-	2
DNAAF4 (HEATR2)	-	2	-	-	2
SPAG1	-	2	-	-	2
DNAAF1(LRRC50)	-	2	-	-	2
DNAAF2 (KTU)	-	1	-	-	1
DNAAF3	-	2	-	-	2
PIH1D3 (X-linked)	-	1	-	-	1
CCDC40	-	-	21	-	21
CCDC39	-	-	18	-	18
DNAH11	-	-	-	11	11
RPGR (X-linked)	-	-	-	1	1
CCNO	-	-	-	4	4
RSPH4A	-	-	-	3	3
RSPH1	-	-	-	1	1
RSPH9	-	-	-	1	1
HYDIN	-	-	-	3	3
PIK3CD	-	1	-	0	1
Total	57	20	40	24	141

Definition of abbreviations: IDA = inner dynein arm; MTD = microtubular disorganization; ODA = outer dynein arm; PCD = primary ciliary dyskinesia.

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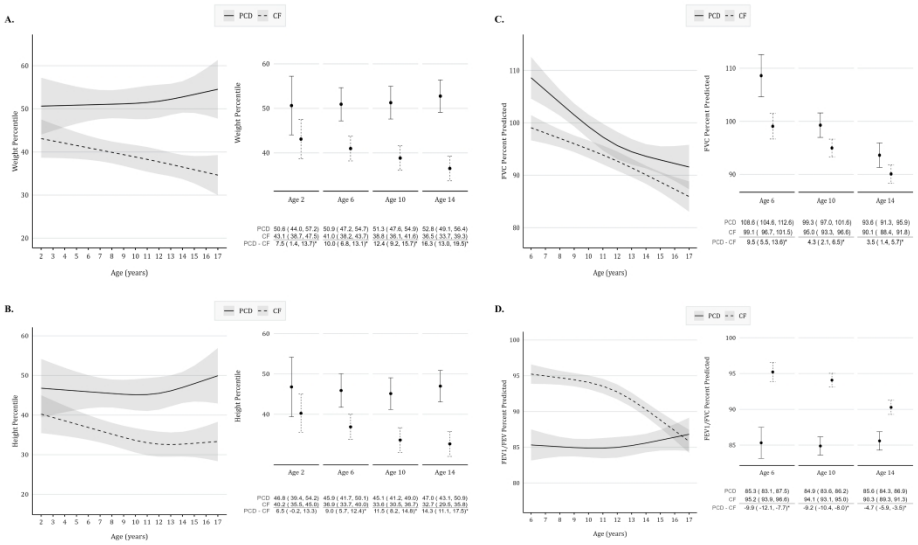

Supplemental Figure 1. Mean estimated spirometric indices* and growth parameters† by age and specific indices at representative ages (2, 6, 10, and 14 years), stratified by disease group (PCD versus CF): a) weight; b) height; c) forced vital capacity (FVC); and d) forced expiratory volume in one second (FEV1)/FVC percent predicted by age, stratified by disease cohort (PCD versus CF).

Footnote:
Definition of abbreviations: CF = Cystic Fibrosis; FVC: forced vital capacity; FEV1 = forced expiratory volume in 1 second; IDA = inner dynein arm; PCD = Primary Ciliary Dyskinesia; MTD = microtubular disorganization.
*Spirometric values were expressed as percent predicted based on the Global Lung Initiative reference equations (21).
†Growth parameter estimates were derived from the U.S. Centers for Disease Control and Prevention reference data (22).

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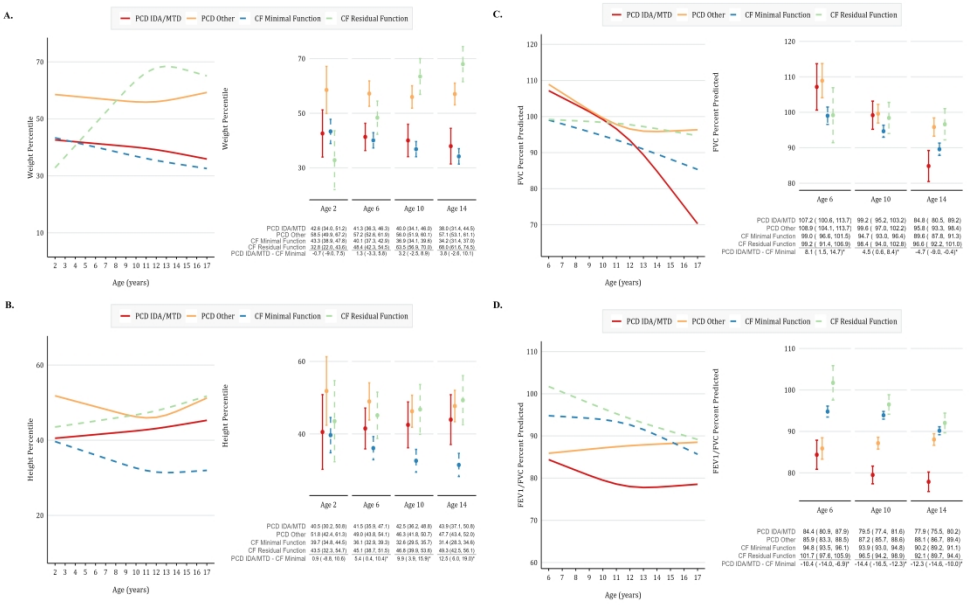

Supplemental Figure 2. Mean estimated spirometric indices* and growth parameters† by age and specific indices at representative ages (6, 10, and 14 years), stratified by disease group (PCD IDA/MTD, PCD-other, CF-minimal function, CF-residual function): a) weight; b) height; c) forced vital capacity (FVC); and d) forced expiratory volume in one second (FEV1)/FVC percent.Footnote:Definition of abbreviations: CF = Cystic Fibrosis; FVC: forced vital capacity; FEV1 = forced expiratory volume in 1 second; PCD = Primary Ciliary Dyskinesia.*Spirometric values were expressed as percent predicted based on the Global Lung Initiative reference equations (21).†Growth parameter estimates were derived from the U.S. Centers for Disease Control and Prevention reference data (22).

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