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A Six-Month Real-World Effectiveness Investigation of Elexacaftor/Tezacaftor/Ivacaftor According to Baseline Lung Function in People with Cystic Fibrosis

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Abstract

Background: Highly effective CFTR modulator therapy has substantially changed the clinical course of cystic fibrosis (CF), but the magnitude of treatment response may vary according to baseline lung function. We evaluated the real-world effects of elexacaftor/tezacaftor/ivacaftor (ETI) in people with CF aged >6 years across a broad range of baseline lung function. Methods: In this observational study, 62 people with CF (23 male; age range 7.8–36.8 years) who were eligible for ETI according to genotype underwent assessment at treatment initiation and after 6 months. Assessments included spirometry, respiratory oscillometry, body composition and biochemical measurements. Results: Mean ppFEV1 increased from 94% at baseline to 108% after 6 months ($p < 0.001$), while mean FEF25–75 increased from 77% to 100% predicted ($p < 0.001$). Lower baseline ppFEV1 was associated with a greater ppFEV1 response ($r = -0.596$, $p < 0.001$), and baseline ppFEV1 remained the only significant factor associated with ppFEV1 change in multivariable analysis ($\beta = -0.21$, $p = 0.006$). Improvement was greater among participants with baseline ppFEV1 < 90%, although a measurable increase was also observed in those with ppFEV1 ≥ 90%. BMI increased significantly. HDL and LDL cholesterol increased ($p = 0.007$ and $p = 0.011$, respectively), whereas C-reactive protein decreased ($p < 0.001$). Changes in oscillometry were modest and provided limited additional information beyond spirometry in this cohort. Conclusions: ETI was associated with significant improvements in lung function in people with CF aged >6 years, including those with preserved baseline spirometry. The magnitude of ppFEV1 improvement was greatest in participants with lower baseline ppFEV1. These findings support measurable physiological benefit from ETI across a broad spectrum of baseline lung function, while highlighting the need for longer-term studies of outcomes in people with near-normal spirometry.

Keywords: cystic fibrosis; elexacaftor; tezacaftor; ivacaftor; CFTR modulators; lung function; spirometry; oscillometry; real-world study

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1. Introduction

Cystic fibrosis (CF) is a multisystem genetic disorder caused by pathogenic variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene [1,2]. CFTR functions

primarily as an epithelial anion channel, and defective CFTR activity results in abnormalities affecting the respiratory, gastrointestinal, hepatobiliary and reproductive systems.

Until the introduction of CFTR modulators, treatment was directed predominantly at the downstream consequences of CFTR dysfunction. Ivacaftor, the first CFTR modulator, was approved in 2012 for selected CFTR variants. Subsequent modulator combinations expanded the proportion of people with CF eligible for genotype-directed therapy. In 2019, the triple combination elexacaftor/tezacaftor/ivacaftor (ETI) was approved for people with CF carrying at least one F508del allele, including those with a second minimal-function variant. ETI is a triple-combination therapy consisting of two correctors (elexacaftor and tezacaftor) and one potentiator (ivacaftor), which together improve CFTR protein processing and function. Randomised controlled trials established substantial improvements in lung function and other clinical outcomes, and subsequent real-world studies have confirmed the effectiveness of ETI across a range of clinical settings [3].

However, the magnitude and clinical interpretation of spirometric change, as well as the potential contribution of complementary physiological and metabolic measures, remain relevant. Respiratory oscillometry can be easily performed in older children and adults and was therefore selected as a potential complementary method for lung function assessment in this study. Furthermore, the study included subjects irrespective of their baseline spirometric values, including those with preserved lung function, whereas the majority of previous studies have focused on subjects with suboptimal spirometric values. The initial hypothesis was that subjects with normal or near-normal lung function might derive less benefit from ETI treatment.

The aim of this observational study was to evaluate the 6-month real-world effects of ETI on (a) lung function, as assessed by spirometry and respiratory oscillometry, with particular emphasis on the relationship between baseline lung function and treatment response; (b) nutritional and body composition measures; and (c) biochemical indices in people with CF aged ≥6 years.

The age cut-off of 6 years was selected because the triple combination was approved in Europe for this age group in November 2023, while recruitment for the current study began in 2021.

2. Methods

2.1. Study Population and Design

Participants were enrolled following the introduction of ETI in Greece (2021). The study included 62 consecutive people with CF aged >6 years who:

(a) Were eligible for ETI according to their genotype (F508del homozygous or F508del compound heterozygous);
(b) Agreed to participate in the study during a two-year period (April 2021–April 2023);
(c) Were able to perform spirometry.

Individuals were excluded if they (a) had experienced a pulmonary exacerbation requiring oral or intravenous antibiotics within the preceding three months, (b) had hepatic cirrhosis, (c) had undergone organ transplantation, or (d) were pregnant. Therefore, all assessments were performed while participants were clinically stable.

Measurements were obtained immediately before ETI initiation and after 6 months of treatment. Recorded variables included sex, age, spirometric indices, respiratory oscillometry, body composition and biochemical measurements. Patients with missing data were excluded from the analysis.

2.2. Lung Function and Oscillometry

Spirometry included percent-predicted forced expiratory volume in 1 s (ppFEV1) and forced expiratory flow between 25% and 75% of forced vital capacity (FEF25–75), measured according to ERS/ATS standards [4].

All spirometric measurements were performed using the same spirometer (CareFusion Germany 234 GmbH/Vyntus, REF: V-996002, Höchberg, Germany) and by the same technician throughout the study. Oscillometry was likewise performed using the same equipment (CareFusion Germany 234 GmbH/Vyntus IOS, REF: V-176430, Höchberg, Germany) and by the same technician. The reference equations used for ppFEV1 and ppFEF25–75 were those of Zapletal et al. for participants aged 17 years or younger, whereas the ECCS 1993 reference values were used for those older than 17 years.

Respiratory oscillometry included resistance at 5 Hz (R5) and 20 Hz (R20), reactance at 5 Hz (X5) and 20 Hz (X20), and area of reactance (AX), following published technical standards [5–8]. Oscillometry was performed with participants seated upright, breathing quietly through a mouthpiece, with their cheeks supported and a nose clip in place. The reference equations used for R5, R20, X5 and X20 were those of Denker and Malberg (2006) for participants aged 11 years or younger, those of Berdel and Lechtenberger (1998) for participants aged 12–17 years, and those of Vogel-Schmidt for participants older than 18 years.

2.3. Body Composition and Biochemical Measurements

Body composition was assessed by bioelectrical impedance analysis using a Tanita device (Hong Kong, China) and included body mass index (BMI), percentage fat mass, percentage muscle mass, bone mass and phase angle. Biochemical measurements included total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and direct bilirubin, and C-reactive protein (CRP). All blood samples were collected after an overnight fast of 10–12 h.

2.4. Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, version 31 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Kolmogorov–Smirnov or Shapiro–Wilk test, as appropriate. Paired pre- and post-treatment measurements were compared using paired *t*-tests or Wilcoxon signed-rank tests according to data distribution. Between-group comparisons were performed using independent-samples *t*-tests or Mann–Whitney U tests, as appropriate. Correlations were assessed using Pearson's correlation coefficient.

A multivariable linear regression model was used to explore factors associated with changes in ppFEV1. Candidate variables included sex, age category, genotype and baseline ppFEV1, selected on the basis of clinical relevance and the prior literature. Backward elimination was applied, with variables removed at $p > 0.05$. An exploratory receiver operating characteristic (ROC) analysis was also performed to assess the ability of baseline ppFEV1 to discriminate between participants who achieved an improvement of at least 10 percentage points in ppFEV1 and those who did not. All tests were two-sided, with statistical significance set at $p < 0.05$ (Figure 1).

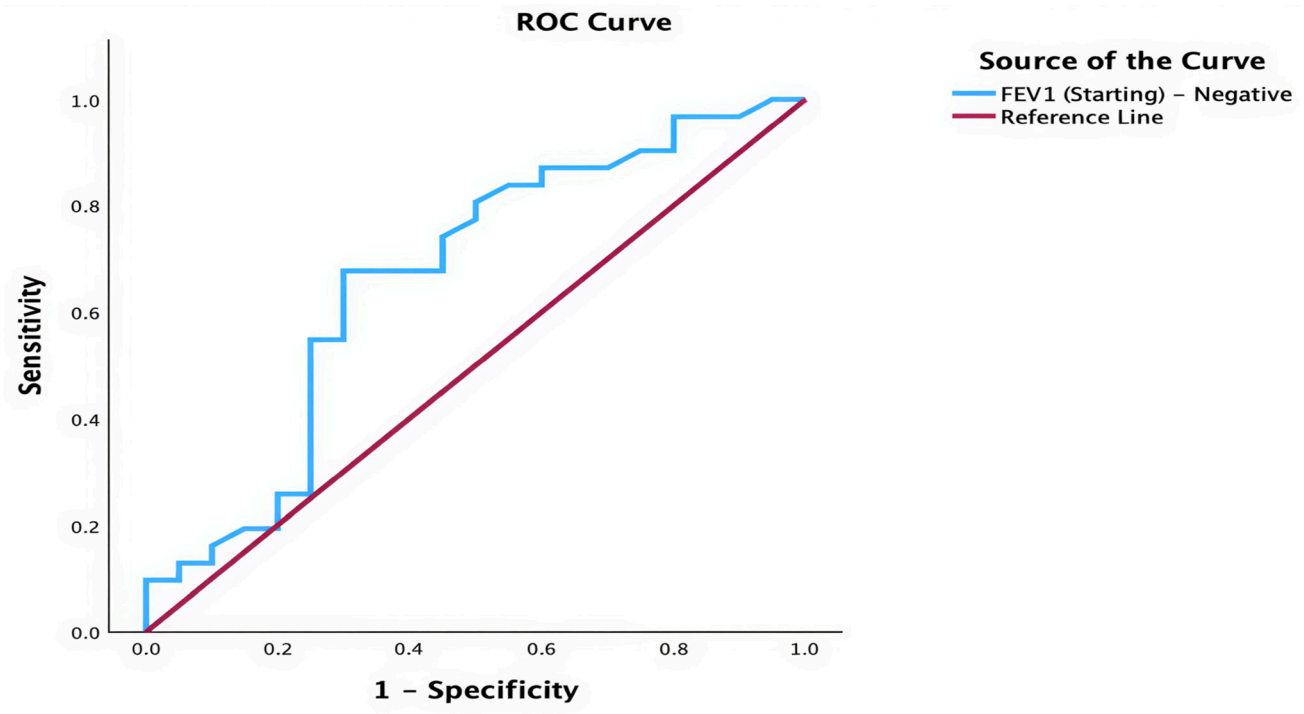


Figure 1. Receiver operating characteristic curve using baseline ppFEV1 to predict an improvement of ≥10 percentage points in ppFEV1 in 6 months. ROC: Receiver Operating Characteristic. FEV1: Forced Expiratory Volume in 1 s.

A post hoc power analysis was performed for the primary endpoint, improvement in ppFEV1, using a paired *t*-test framework. With a sample size of 62 participants and a two-sided α level of 0.05, the estimated statistical power exceeded 95%, based on the effect-size assumptions used in the calculation. Power was estimated using a publicly available online tool *[StatsCalculators Team. (2026). Sample Size & Power Analysis Calculator. StatsCalculators. Retrieved 5 October 2026, from https://statscalculators.com/calculators/hypothesis-testing/sample-size-and-power-analysis-calculator].*

2.5. Ethics

The study was approved by the institutional ethics committee (approval no. 6293/2-4-2021). Written informed consent was obtained from all adult participants and from the parents or legal guardians of participating paediatric patients.

3. Results

3.1. Study Population

Sixty-two people with CF were included, with an age range of 7.8–36.8 years (mean 16.3 years; median 15.6 years). Twenty-three were male (age range 8.8–36.8 years; mean 16.9 years; median 15.5 years) and 39 were female (age range 7.8–30.1 years; mean 15.9 years; median 15.7 years). Twenty-four participants were homozygous for F508del and had previously received lumacaftor/ivacaftor, whereas the remaining 38 were compound heterozygous for F508del and a minimal-function variant and had not previously received any CFTR modulator therapy. All participants were pancreatic insufficient (Table 1).

Table 1. Baseline Patient Demographics.

Age, median (Q25, Q75)	15.4 (12.8, 17.7)
Genotype (F508del homozygous), n (%)	24 (38.7)
Gender (Female), n, (%)	39 (62.9)
Hepatic Disease (+), n (%)	17 (27.4)
Diabetes Mellitus (+), n (%)	8 (12.9)

3.2. Spirometry

Both ppFEV1 and FEF25–75 improved significantly after 6 months of ETI (Table 2). Participants were stratified into two groups according to baseline ppFEV1 (<90% and ≥90%), with the latter group considered to have normal or near-normal lung function. Improvement in ppFEV1 was significantly greater in those with baseline ppFEV1 < 90% ($p = 0.019$). Baseline ppFEV1 was inversely correlated with post-treatment improvement in ppFEV1 ($r = -0.596$, $p < 0.001$), and baseline FEF25–75 was similarly inversely correlated with change in FEF25–75 ($r = -0.513$, $p < 0.001$). Change in ppFEV1 was strongly correlated with change in FEF25–75 ($r = 0.838$, $p < 0.001$).

Table 2. Lung function and oscillometry before and 6 months after ETI.

Parameter	**n**	**Baseline, Mean ± SD or Median (Q25–Q75)**	**6 Months, Mean ± SD or Median (Q25–Q75)**	***p* Value**
ppFEV1 (% predicted)	62	94.3 ± 21.9	114 (101–120)	<0.001 [a]
FEF25–75 (% predicted)	62	77.2 ± 34.8	106.5 (79.5–129)	<0.001 [a]
R5 (z-score)	60	0.17 (−0.24–0.825)	0.38 ± 0.81	0.732 [b]
R20 (z-score)	60	−0.12 (−0.425–0.70)	0.325 (−0.28–0.96)	0.011 [a]
X5 (z-score)	60	−0.59 ± 0.99	−0.40 ± 0.95	0.048 [a]
X20 (z-score)	60	−0.60 (−1.175, −0.14)	−0.51 ± 0.77	0.092 [b]
AX (absolute value)	57	0.63 (0.395, 1.165)	0.45 (0.23–0.93)	<0.001 [b]

[a]: Paired-samples *t*-test, [b]: Wilcoxon signed-rank test, ppFEV1: Percent-predicted Forced Expiratory Volume in 1 s; FEF25-75: Forced Expiratory Flow between 25% and 75% of forced vital capacity; R5: Resistance at 5 Hz; R20: Resistance at 20 Hz; X5: Reactance at 5 Hz; X20: Reactance at 20 Hz; AX: Area of Reactance; SD: Standard Deviation; Q25: 25th percentile; Q75: 75th percentile.

The magnitude of ppFEV1 improvement did not differ significantly by sex or between participants homozygous for F508del and those compound heterozygous for F508del and a minimal-function variant. In the multivariable linear regression model, baseline ppFEV1 was the only variable significantly associated with change in ppFEV1 ($\beta = -0.21$, $p = 0.006$).

In an exploratory ROC analysis, a baseline ppFEV1 threshold of 97% yielded a sensitivity of 77% and a specificity of 74% for identifying participants who achieved an improvement of at least 10 percentage points in ppFEV1. Given the sample size and the data-derived nature of the threshold, this finding should be considered exploratory.

3.3. Respiratory Oscillometry

Oscillometry findings are shown in Table 2. R20 and X5 z-scores changed significantly, and absolute AX decreased significantly. The direction of change in X5 and AX was consistent with improved respiratory mechanics, whereas R20 increased. The clinical relevance of the R20 change is therefore uncertain.

3.4. Body Composition

BMI increased significantly after 6 months of ETI, as did BMI z-score among participants aged <20 years (Table 3). Percentage fat mass and percentage muscle mass did not change significantly. Absolute bone mass increased significantly. However, bone mass estimated by bioelectrical impedance analysis should not be interpreted as a direct measure of bone health. Phase angle (head-to-leg) also increased significantly (p = 0.038, 95% CI: 0.006–0.2).

Table 3. Body-composition indices before and 6 months after ETI.

Parameter	n	Baseline, Mean ± SD	6 Months, Mean ± SD	p Value
BMI (kg/m^2)	62	19.8 ± 3.0	20.6 ± 2.8	<0.001 [a]
BMI z-score (participants < 20 years)	52	−0.20 ± 0.89	0.09 ± 1.00	<0.001 [a]
Fat mass (%)	62	23.3 ± 5.9	23.7 ± 5.5	0.20 [a]
Muscle mass (%)	62	72.7 ± 5.2	72.3 ± 5.6	0.17 [a]
Bone mass (kg)	62	1.98 ± 0.48	2.08 ± 0.46	<0.001 [a]

[a]: Paired-samples *t*-test. BMI: Body Mass Index; SD: Standard Deviation.

3.5. Biochemical Indices

Liver enzyme concentrations remained broadly stable. Total and direct bilirubin increased significantly (Table 4), the clinical significance of these changes requires interpretation in relation to individual values and laboratory reference ranges. Total bilirubin exceeded the upper limit of normal in 24 participants and direct bilirubin in 19. ALT exceeded the upper limit of normal in six participants. These patients underwent closer monitoring of liver function without discontinuation of ETI. HDL and LDL cholesterol increased significantly. Although LDL cholesterol increased significantly, no participant had an LDL cholesterol level above 110 mg/dL. CRP decreased significantly after 6 months of treatment.

Table 4. Biochemical indices before and 6 months after ETI.

Parameter	n	Baseline, Median (Q25–Q75)	6 Months, Median (Q25–Q75)	p Value
AST (U/L)	61	22.0 (18.75–27.75)	22.0 (18.0–27.0)	0.253 [a]
ALT (U/L)	61	23.5 (17.0–29.25)	22.0 (18.0–33.5)	0.774 [a]
Total bilirubin (mg/dL)	53	0.46 (0.24–0.73)	0.92 (0.49–2.84)	<0.001 [a]
Direct bilirubin (mg/dL)	54	0.17 (0.11–0.29)	0.27 (0.15–0.40)	<0.001 [a]
Total cholesterol (mg/dL)	60	123 (107–143)	129 (114–151)	0.012 [a]
Triglycerides (mg/dL)	59	78 (56–101.5)	71 (53–96)	0.363 [a]
HDL cholesterol (mg/dL)	60	48 (41.5–56)	52 (45.5–60)	0.007 [a]
LDL cholesterol (mg/dL)	58	58 (45–69)	59 (49–73)	0.011 [a]
CRP (mg/L)	53	1.70 (1.35–3.31)	1.32 (1.00–1.66)	<0.001 [a]

[a]: Wilcoxon signed-rank test. AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; CRP: C-Reactive Protein; Q25: 25th percentile; Q75: 75th percentile.

4. Discussion

In this real-world cohort of children, adolescents and young adults with CF, lung function improved substantially during the first 6 months of ETI treatment. The cohort had a high mean baseline ppFEV1 (94.24%), which allowed us to examine response in people whose spirometry was already relatively well preserved. The increase in ppFEV1 was larger in participants with lower baseline values, but improvement was also seen in those starting treatment with ppFEV1 > 90%.

Our results are in keeping with previous real-world studies showing improvement with ETI across different levels of baseline lung disease. Sheikh et al. reported larger ppFEV1 gains in participants with lower baseline lung function and found no clear difference according to genotype [9]. In a separate analysis, the same group found that previous CFTR modulator exposure did not substantially alter the clinical response to ETI [10]. Longitudinal UK data have also shown sustained benefit in young people receiving ETI [11]. Of particular relevance to our cohort, Yaacoby-Bianu et al. and Nichols et al. reported benefit in people with mildly reduced or normal baseline lung function [12,13]. Schütz et al. identified baseline FEV1 and age as predictors of spirometric response at 12 months [14]; in our cohort, age was not independently associated with response.

The inverse relationship between baseline ppFEV1 and subsequent change should, however, be interpreted with care. People starting with lower ppFEV1 have more room for measurable improvement, whereas a ceiling effect is likely when baseline spirometry is near normal. Regression to the mean and the mathematical relationship between a baseline value and its subsequent change may also contribute to this association. Thus, although the subgroup, correlation and multivariable analyses point in the same direction, our data do not support using baseline ppFEV1 alone as a causal predictor of individual response. Furthermore, imaging studies and lung clearance index (LCI) measurements, which were not included in our study design, might provide additional information on the clinical relevance of lung function improvement in participants with well-preserved baseline lung function.

Respiratory oscillometry changed less consistently than spirometry. R20, X5 and AX showed statistically significant changes, but the clinical meaning of these findings was not uniform. Previous studies have reported differences in oscillometric indices between clinical stability and pulmonary exacerbation [15], whereas Bayfield et al. found limited sensitivity for detecting structural abnormalities on chest CT in school-aged children with CF [16]. More recently, Kogias et al. reported improvement in respiratory resistance after ETI [17]. In our cohort, the reduction in AX and improvement in X5 were compatible with improved respiratory mechanics; in contrast, R20 increased, although values remained within the normal range. Therefore, routine oscillometry testing may not be justified in this age group. It may still be useful in younger children who cannot perform reliable spirometry, a question that requires specific study.

4.1. Nutritional and Body-Composition Effects

BMI increased significantly after ETI, while percentage fat mass and muscle mass did not change significantly. Published studies of body composition after ETI have not been entirely consistent: some report increases mainly in fat mass and others in fat-free mass [18,19]. Differences in baseline disease severity, diet, physical activity and follow-up duration may partly explain these findings. Regardless of the mechanism, increasing BMI in the modulator era supports a shift away from the traditional emphasis on a high-calorie CF diet towards balanced, individualised nutritional advice, particularly as overweight and obesity become more common [20].

4.2. Lipids and Systemic Inflammation

HDL and LDL cholesterol increased significantly after 6 months of ETI. Similar increases in lipid fractions have been reported in the PROMISE substudy and in recent reviews [18,21], although other real-world studies have described potentially favourable changes in triglyceride-related indices [22]. The long-term cardiometabolic significance remains uncertain, particularly because ETI may increase circulating lipid concentrations while at the same time reducing chronic systemic inflammation [23]. Furthermore, in our study, LDL cholesterol levels did not exceed 110 mg/dL in any participant, a level generally considered acceptable in individuals at low cardiovascular risk. However, it remains unclear whether people with CF should be considered at low, moderate or high risk of atherosclerotic cardiovascular disease and what the appropriate LDL cholesterol target should be for this population.

CRP fell significantly after 6 months, consistent with a reduction in systemic inflammation. A recent systematic review likewise found that ETI improves, but does not completely normalise, airway and systemic inflammatory markers [24]. Longer follow-up will be needed to understand how these anti-inflammatory effects interact with the observed changes in lipid profile and what they mean for future cardiometabolic risk.

4.3. Strengths and Limitations

Strengths of this study include the real-world setting, the predominantly paediatric and young cohort with relatively preserved baseline lung function, and the assessment of respiratory, nutritional and biochemical outcomes using the same equipment and personnel throughout follow-up.

The study also has limitations. It was conducted at a single centre, the sample was modest, and follow-up was limited to 6 months. There was no untreated control group, and adherence to ETI and concomitant symptomatic therapies was not formally assessed. Previous modulator exposure was closely linked to genotype in this cohort, so their independent effects cannot be separated reliably. The ROC-derived ppFEV1 threshold was exploratory and requires external validation; it should not be interpreted as a clinical decision threshold. Finally, part of the association between baseline ppFEV1 and subsequent change may reflect ceiling effects, regression to the mean and mathematical coupling.

Recommendations for Future Research

Long-term studies are needed to assess the extent to which improvements in lung function are sustained over a period of three to five years. Additionally, longitudinal studies are needed to evaluate changes in lipid profiles over time.

5. Conclusions

ETI was associated with significant improvement in spirometric parameters in people with CF aged >6 years across a broad range of baseline spirometric values. Improvement was greatest in participants with lower baseline ppFEV1, but measurable benefit was also observed in those with preserved lung function. ETI was additionally associated with increased BMI and lipid concentrations and reduced CRP, findings that alter to opposite direction the subjects' atherosclerosis risk. Longer-term, multicentre studies are needed to define the clinical significance of these changes and to determine the most informative monitoring strategies for people with CF who begin highly effective modulator therapy with near-normal lung function.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and was approved by the institutional ethics committee (approval no. 6293/2-4-2021), approval date 2 April 2021.

Informed Consent Statement: Written informed consent was obtained from all adult participants and from the parents or legal guardians of participating paediatric patients.

Data Availability Statement: The raw data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of Interest: Ioanna Loukou has received advisory board reimbursements from Vertex Pharmaceuticals. The remaining authors declare no conflicts of interest.

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