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Predictors of Sinonasal Improvement After Highly Effective Modulator Therapy in Adults with Cystic Fibrosis

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Objectives: The 22-question SinoNasal Outcome Test (SNOT-22) assesses chronic rhinosinusitis (CRS) severity. We aimed to identify predictors of SNOT-22 score improvement following highly effective modulator therapy (HEMT) initiation and to corroborate the SNOT-22 minimal clinically important difference (MCID) in adults with cystic fibrosis (CF).

Methods: Prospective observational data was pooled from four studies across 10 US centers investigating people with CF (PwCF) and CRS. Three studies evaluated HEMT's impact on CRS. For participants enrolled prior to HEMT initiation, SNOT-22 scores were obtained at baseline and after 3–6 months of HEMT. Multivariate regression identified predictors of improvement. Cronbach's alpha and four distribution-based methods were used to assess internal consistency and calculate the MCID of the SNOT-22.

Results: A total of 184 PwCF participated with mean baseline SNOT-22 scores ranging from 18.1 to 56.7. Cronbach's alpha was ≥0.90 across sites. Participants at sites with pre- and post-HEMT data reported improvement in SNOT-22 scores after initiating HEMT (all $p < 0.05$). Worse baseline SNOT-22 score (odds ratio (OR): 1.05, $p < 0.001$, 95% CI: 1.02–1.08), F508del homozygosity (OR: 4.30, $p = 0.040$, 95% CI: 1.14–18.99), and absence of prior modulator therapy (OR: 4.99, $p = 0.017$, 95% CI: 1.39–20.11) were associated with greater SNOT-22 improvement. The mean MCID calculated via distribution-based methods was 8.5.

Conclusion: Worse baseline sinonasal symptoms, F508del homozygosity, and absence of prior modulator therapy predicted greater improvement after HEMT initiation. The mean MCID for SNOT-22 in PwCF is 8.5 points, similar to non-CF individuals with CRS, and provides a threshold specifically for PwCF. The SNOT-22 has strong internal consistency in PwCF.

Key Words: CFTR modulator therapy, chronic rhinosinusitis, cystic fibrosis, elexacaftor/tezacaftor/ivacaftor, minimal clinically important difference.

Level of Evidence: 3

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INTRODUCTION

Chronic rhinosinusitis (CRS) is prevalent in people with cystic fibrosis (PwCF).[1–3] CRS in PwCF is associated with diminished quality of life (QOL), olfactory dysfunction, worse lower airway health, and increased treatment burden.[4–6] Management approaches for CF-CRS are shifting with the introduction of highly effective CF transmembrane conductance regulator (CFTR) modulator therapy (HEMT), such as elexacaftor/tezacaftor/ivacaftor (ETI), which cause marked improvement in a wide variety of CF manifestations beyond sinus disease.[7–10] In PwCF, HEMT improves patient-reported sinonasal symptoms and objective measures of CRS; however, these studies were of modest size, potentially limiting their power to identify predictors of response.

While spirometry is frequently used to track severity in lung disease, CRS severity is often evaluated with the 22-question SinoNasal Outcome Test (SNOT-22), a patient-reported measure of CRS symptoms' impact on QOL.[11] This instrument has been recommended for sinonasal symptom assessment by the CF Foundation,[3] has strong psychometric properties in general populations,[11] and has assessed QOL changes post-intervention.[12–14] The minimal clinically important difference (MCID) establishes the minimum threshold for clinically meaningful change that is both noticeable to the patient and statistically significant in a measurement tool. While the MCID for SNOT-22 is well established in persons with CRS, the MCID for SNOT-22 scores and measures of internal consistency have not been determined in PwCF. Because of the systemic nature of their disease and associated mucociliary defect, PwCF may have a distinct disease burden than non-CF CRS individuals, highlighting the importance of calculating CF-specific MCID values.

Establishing a CF-specific MCID is important because it gives insight into current data around the effects of HEMT on sinus disease and because it may inform future clinical and translational work. Sinonasal outcomes from HEMT in PwCF may be influenced by unique factors such as their lung disease and global treatment needs compared to non-CF CRS individuals, so extrapolating the general MCID to the CF population has validity limits. In the current work, determining predictors of SNOT-22 improvement may augment understanding of treatment outcomes, guide personalized treatment plans, and help patients set realistic expectations.[14,15] The SNOT-22 as a patient-reported outcome is a frequent study endpoint in CF sinus disease[7–9,16]; ensuring there is robust and accurate understanding of instrument performance, including the MCID in PwCF, informs future clinical study design and allows comparison of future treatments with existing datasets.

Therefore, the goals of this research were three-fold. First, we identified clinical and disease factors that predicted improvement in SNOT-22 scores after HEMT was initiated using pooled primary data from multiple prospective studies encompassing a wide range of PwCF and care centers across the United States. Second, we quantified the MCID for the SNOT-22 in PwCF to provide context in which to evaluate these results. Third, using our newly determined MCID, we evaluated if the originally identified predictors of improvement exceeded the estimated population-specific clinical relevance threshold.

MATERIALS AND METHODS

Population and Study Design

Study data originated from four prospective, observational investigations. Three of the four studies evaluated whether clinically prescribed ETI improved CF-CRS[7–9] and the fourth study investigated treatment outcomes for CF-CRS (NCT04469439).[16]

Study 1. DiMango et al. enrolled PwCF ≥18 years of age from Columbia University (New York, NY) and evaluated the response to ETI after 3 months of treatment.[17]

Study 2. Beswick et al. enrolled PwCF ≥18 years of age from National Jewish Health (NJH; Denver, CO) and assessed response to ETI over 6 months.[7]

Study 3. Stapleton et al. enrolled PwCF ≥12 years of age at two centers (University of North Carolina (Chapel Hill, NC) and University of Pittsburgh (Pittsburgh, PA)) and investigated response to ETI over 6 months.[9]

Study 4. The cohort from the fourth study,[16] which will be referred to as "multi-center," was comprised of PwCF ≥18 years of age who enrolled from eight US CF-accredited centers coordinated from University of California, Los Angeles. Supplemental Table 1 lists sites. Participants in study 4 are distinct from study 2.

Pooling all studies, participants were enrolled from 10 CF centers. Participants provided informed consent at their local centers for the original Institutional Review Board (IRB)-approved studies and completed questionnaires.

In studies 1–3, participant demographics, baseline health status, and baseline clinical outcome predictors were collected before and after HEMT initiation. Studies 1, 2, and 3 established that improvements in SNOT-22 total score plateaued after 1 month and remained stable after that time, which is consistent with timing and stability of improvement seen in pulmonary function and other organ systems in Phase 3 trials of ETI.[18] Consequently, we pooled data from 3- and 6-month post-HEMT questionnaires from studies 1–3, under the assumption that the treatment effect stabilizes within 1 month of ETI initiation.[7,9] In the fourth study, participant demographics, baseline health status, and baseline SNOT-22 score from the single baseline time point were used. Data from Study 4 were utilized in calculations to estimate the MCID because only a baseline time point was required for this analysis. Data from Study 4 were not used to evaluate predictors of response to HEMT because study 4 was not intended for that purpose.

Main Outcome Measure

In all four studies, the SNOT-22 instrument evaluated QOL impairment related to CRS (total score range: 0–110) across multiple scale subdomains, with higher values indicating worse QOL.[19] We focused on total SNOT-22 score.

Statistical Analysis

Individual subject data were available from each study and pooled for analysis. All study data were secured and protected in a de-identified manner. Baseline SNOT-22 scores from studies 1–4 were pooled to enhance the statistical power for calculating

distribution-based MCID calculations. Only baseline SNOT-22 scores were necessary for calculating distribution-based MCIDs, which allowed the combining of study 4, with its distinct design, with the longitudinal studies 1–3. The pooling of data was also considered appropriate due to the uniformity of outcome measures across the studies (SNOT-22 scores) and the homogeneity of the participant populations, which included individuals aged ≥12 years with confirmed diagnosis of cystic fibrosis. These elements were critical for ensuring the validity of combining datasets for MCID analysis.

Data from longitudinal studies 1–3, which included baseline and follow up SNOT-22 scores, were pooled to determine predictors of therapeutic response. In addition to the combined prospective data, data for the analysis of predictive factors were supplemented via retrospective review from one site (Columbia University). Internal consistency of the SNOT-22 was evaluated for each data source and all participants using Cronbach's alpha (α). A two-sided alpha value of 0.05 was used throughout. Statistical analyses were completed using R Statistical Software (v4.1.1; R Core Team 2021). Missing SNOT-22 questionnaire responses were imputed using K-means clustering approach.

Determining Predictors of Sinonasal Symptom Improvement: Aggregate Analysis of Longitudinal SNOT-22 Scores from Studies 1–3

Univariable and multivariable regression analysis were performed to identify factors that were associated with improvements in SNOT-22 score collected from studies 1–3. Factors included in univariable and multivariable analysis were: age, sex, body mass index (BMI), baseline percent predicted forced expiratory volume in 1 s ($ppFEV_1$), baseline SNOT-22 score, CFTR genotype, history of prior sinus surgery, history of prior modulator use, CF-related diabetes, history of *Pseudomonas* or *Staphylococcus* infection in the lung, and enrollment site. Factors a priori were included in the models due to their associations with the outcome in previous literature, to control for confounding, and to address potential multicollinearity issues.[7,17,20] Two outcomes were considered for multivariable regression: (1) a continuous outcome of change in SNOT-22 from baseline to follow-up was assessed using a multivariable linear regression model and (2) a binary outcome of whether participant responses exceeded the newly calculated MCID from baseline to follow-up was assessed using a multivariable logistic regression model.

Methods to Determine the MCID: Pooled Baseline SNOT-22 Scores from Studies 1–4

The MCID for the SNOT-22 was determined by estimating a clinical relevance threshold using four distribution-based methods using pooled data from studies 1–4[21,22]:

1. One-half the standard deviation of the baseline score was calculated, drawing from methodology in human psychology.[23]
2. One standard error of the measurement (SEM) was identified. The SEM is a fixed characteristic of a measure in a specific population. A change smaller than the SEM may be a measurement error rather than a true change.[24]
3. Cohen's effect size (d) of the smallest unit of change (0.2) was estimated.[25] The effect size estimates the magnitude of the between-group differences. This measure estimates the magnitude of the intervention's effect on QOL.
4. The minimal detectable change (MDC) value was quantified. MDC is the smallest change, which can be considered above the measurement error within a confidence interval (CI).[26]

Initially, these four MCID values were separately computed for the four centers comprising studies 1–3 and for the patient population from study 4 to determine a specific estimate of MCIDs for each data source. Studies 1–3 were separated by site to account for variability across different centers as these studies contained pre- and post-ETI SNOT-22 score data.[21,22] Multicenter study 4 was treated as a separate group because of its distinct study design from studies 1–3.

For final estimate of MCID in PwCF, data from all studies were pooled to increase overall sample size, and MCIDs were calculated for the pooled sample using the four distribution-based approaches. Mean MCID values from the four approaches for the pooled sample were established as the MCID for SNOT-22 in PwCF. The 95% CI for MCID in the respective centers and the pooled samples were calculated based on 5000 bootstrap resamples.

RESULTS

Study Population

Overall, 184 PwCF were enrolled from 10 institutions across four studies (Table I). Mean participant age was 34 (standard deviation, SD 13) years, 62.1% were female (113/184), 66.7% had used modulator therapy before ETI (116/184), and 72.2% had undergone prior sinus surgery (127/184). The majority of our combined cohort consisted of adults with CF, with adolescents (aged 12–17 years) comprising 5% (9/184) of participants. Baseline SNOT-22 scores were available for 177 (96.2%) participants. Of the three studies that evaluated change after ETI, follow-up SNOT-22 scores were available for 96.0% (97/101) of participants. Baseline SNOT-22 scores, sex, and genotype distribution varied across sites (Supplemental Table 2). The mean improvement in SNOT-22 with ETI treatment ranged from 9.7 (SD 11.2) to 15.7 (SD 11.0) points across sites (Table II). SNOT-22 score improvement post-ETI was normally distributed with few outliers (Supplemental Figure 1).

Predictors of SNOT-22 Score Improvement after HEMT Initiation

Multivariable linear regression analysis was performed using change in SNOT-22 score as a continuous outcome variable (Table III). Baseline SNOT-22 score ($p < 0.001$), F508del homozygosity ($p = 0.003$), and absence of prior modulator use ($p = 0.005$) were associated with greater improvement in SNOT-22 scores at follow-up. Worse baseline $ppFEV_1$ trended toward association with change in SNOT-22 score ($p = 0.077$).

SNOT-22 Instrument: Internal Consistency and MCID Calculations

Cronbach's alpha for the SNOT-22 instrument was ≥0.90 at all study locations (Table IV), indicating high internal consistency. Distribution-based MCID values in the pooled cohort ($N = 177$) were: (A) 0.5*SD = 10.9, (B) SEM = 5.0, (C) d = 4.4, and (D) MDC = 13.8 (Table IV). Overall MCID obtained after averaging the four distribution-based methods for the total cohort was

TABLE I.
Characteristics of Study Participants with Cystic Fibrosis Included in this Study.

Characteristics	*N* (%)	Mean (SD)
Age (years), $n = 182$		34 (13)
Sex, $n = 182$		
Male	69 (37.9)	
Female	113 (62.1)	
Genotype, n = 184		
F508del/other	85 (46.2)	
F508del/F508del	78 (42.4)	
Other/other	21 (11.4)	
$ppFEV_1$, $n = 168$		73 (25)
BMI (kg/m^2), $n = 175$		23 (5)
Cystic fibrosis-related diabetes, $n = 184$	63 (36.0)	
History of *Staphylococcus aureus* or *Pseudomonas aeruginosa* infection, $n = 172$	143 (83.1)	
Prior CFTR modulator therapy, $n = 174$	116 (66.7)	
Prior sinus surgery, $n = 176$	127 (72.2)	
Baseline SNOT-22 score, $n = 177$	—	39 (21)
Post-ETI SNOT-22 score, $n = 133$	—	28 (21)
Care center/enrollment site, $n = 184$		
Multi-center study	83 (45.1)	
Columbia University	42 (22.8)	
National Jewish Health	25 (13.6)	
University of Pittsburgh	14 (7.6)	
University of North Carolina	20 (10.9)	

BMI = body mass index; CFTR = cystic fibrosis transmembrane conductance regulator; $ppFEV_1$ = percent predicted forced expiratory volume in 1 second; ETI = elexacaftor/tezacaftor/ivacaftor; SD = standard deviation; SNOT-22 = 22-question SinoNasal Outcome Test.

8.5 points. Although there was modest variability in MCID values across methods, mean MCID values across sites were similar. Using the entire pooled cohort, the mean MCID (95% CI) from all four methods was 8.5 (7.9, 8.8).

Predictors of Improvement Post-HEMT Exceeding a Newly Calculated MCID

To test the performance of the calculated MCID in the combined, prospective dataset of studies 1–3, we constructed a binary logistic multivariable model using the MCID to bin scores. Overall, 54% (54/97) of participants had a change in SNOT-22 that exceeded the 8.5 MCID. Univariable analysis demonstrated that older age and worse baseline SNOT-22 scores were significantly associated with post-treatment improvements exceeding the MCID (Table V). On multivariable analysis, site and baseline SNOT-22 score were strongly multicollinear (variance inflation factors >5), so site was removed from the final model. In the final model, higher baseline SNOT-22 score, F508del homozygosity, and absence of prior modulator use were associated with greater improvement in SNOT-22 score post-HEMT (Table VI). These factors were consistent with findings in the multivariable model treating SNOT-22 improvement as a continuous outcome.

Compared to PwCF who were F508del heterozygous, participants who were F508del homozygous were >4 times more likely to report improvement exceeding the MCID (odds ratio [OR]: 4.30, $p = 0.040$, 95% CI: 1.14–18.99). For every point increase in baseline SNOT-22 score in the logistic model, the odds of improving beyond the MCID at follow-up increased by 4.89% ($p < 0.001$, 95% CI: 1.02–1.08). Absence of prior modulator use before ETI also predicted significantly greater improvement in post-treatment SNOT-22 scores. Compared to individuals with a history of prior modulator use, PwCF who had no modulator use were five times as likely to report improvement exceeding the MCID (OR: 4.99, $p = 0.017$, 95% CI: 1.39–20.11).

DISCUSSION

In this study, data from 10 US centers from four prospective studies investigating the impact of ETI on CRS were combined. Pooling data permitted greater statistical power to determine predictors of QOL improvement after initiating ETI and enabled calculation of the MCID for the SNOT-22 in a large, predominantly adult CF population. We initially employed multivariable regression analysis to determine predictors of SNOT-22 improvement. To validate our findings, we then calculated a population-specific MCID using data from all four studies, providing a better estimate of the clinical significance of these factors. We subsequently applied a logistic regression model to the three studies with prospective data, aiming to identify factors that exceeded our newly established MCID. Both approaches consistently identified worse baseline disease severity, F508del homozygosity, and absence of prior modulator therapy as factors predicting SNOT-22 score improvement after ETI initiation.

Understanding predictors of symptom improvement in PwCF enables enhanced prognostication and better informs patients on the most effective treatment interventions for their individual circumstances.[13] In the non-CF CRS population, sinonasal symptom burden has been shown to be a driving factor in treatment selection between sinus surgery and continued medical therapy.[12] Prior work in the CF-CRS population demonstrated that symptom burden and ETI status were predictive of choice of treatment for CRS.[27] Conversely, knowledge of factors not associated with greater improvement, namely, CF-related diabetes and absence of prior sinus surgery, may support clinician decision-making in identifying patients at greater risk of persistent sinus disease in the post-modulator period and who may benefit from otolaryngology referral.

Our analysis reveals a consistent relationship between greater baseline SNOT-22 score severity and sinonasal symptom improvement post-ETI. For each incremental increase in baseline SNOT-22 scores, the odds of improving beyond the MCID at follow-up increased by 4.89%.This finding expands on results from the component studies in our analysis, which individually reported higher sinonasal symptom burden[7,17] and worse

TABLE II.
Change in 22-Question SinoNasal Outcome Test Score by Site after Initiation of Highly Effective Modulator Therapy for the Centers that Had Pre- and Post-Data ($n = 97$).

Care center	Time point	*N*	Mean ± SD	Change from baseline, Mean ± SD	*p*-value
Columbia	Baseline	42	56.7 ± 18.1	-	-
University	3 months	42	46.8 ± 15.5	−10.0 ± 12.6 ($n = 42$)	<0.001
National Jewish Health	Baseline	25	33.1 ± 14.5	-	-
	6 months	25	17.4 ± 11.5	−15.7 ± 11.0 ($n = 25$)	<0.001
University of North Carolina	Baseline	20*	30.0 ± 17.6	-	-
	6 months	16	11.6 ± 12.9	−15.5 ± 13.9 ($n = 16$)	<0.001
University of Pittsburgh	Baseline	14	18.1 ± 16.1	-	-
	6 months	14	8.4 ± 7.6	−9.7 ± 11.2 ($n = 14$)	0.006

SD = standard deviation.
*In the 6 month follow-up phase, the University of North Carolina cohort experienced a reduction of four participants. This attrition was attributed to circumstances related to the COVID-19 pandemic.

TABLE III.
Multivariable Linear Regression Analysis of Factors Associated with Improvement in SNOT-22 Score Treated as a Continuous Variable after Initiation of ETI.

Variable	Estimate	95% CI	*p*-value
Age (years)	−0.054	(−0.29, 0.18)	0.644
Sex, male	−0.872	(−5.58, 3.84)	0.714
BMI (kg/m^2)	−0.324	(−0.91, 0.26)	0.275
F508del/F508del	−10.043	(−16.5, −3.61)	**0.003***
No prior CFTR modulator therapy	−9.049	(−15.4, −2.73)	**0.005***
No prior sinus surgery	0.33	(−4.68, 5.34)	0.896
Baseline ppFEV$_1$	0.095	(−0.01, 0.20)	0.077
Baseline SNOT-22 score	−0.256	(−0.38, −0.14)	**<0.001***
Cystic fibrosis-related diabetes	2.175	(−2.63, 6.98)	0.37

Factors with 95% CI including 0 are non-significant.
95% CI = 95% confidence interval; BMI = body mass index; CFTR = cystic fibrosis transmembrane conductance regulator; ETI = elexacaftor/tezacaftor/ivacaftor; MCID = minimal clinically important difference; ppFEV$_1$ = percent predicted forced expiratory volume in 1 second; SNOT-22 = 22-Question SinoNasal Outcome Test.
*Denotes $p < 0.05$.

radiographic sinus disease[9] as associated with improvement in SNOT-22 following ETI initiation. There are multiple possible explanations of this effect. At a molecular level, greater airway epithelial inflammation enhances rescue of mutant CFTR and boosts efficacy of CFTR modulators, which may lead to symptom improvement.[28,29] Observations in non-CF CRS patients pursuing sinus surgery show that patients with pre-operative SNOT-22 scores ≥30 had a greater probability of achieving an improvement exceeding MCID relative to those with lower scores.[14] Our findings in PwCF are consistent with this trend of more severe pre-treatment symptoms predicting greater therapeutic impact post-intervention.

Our study uniquely identifies the subpopulation of PwCF and CRS with F508del homozygosity as a predictor of improvement, a finding likely discovered via additional statistical power.[7–9] After ETI initiation, participants with F508del homozygosity were >4 times more likely to report improvement beyond the MCID when compared to those with F508del heterozygosity. This is supported by *in vitro* findings where F508del homozygotes showed greater CFTR expression in bronchial epithelial cells than heterozygotes.[30] Despite these differences, clinical measures such as ppFEV$_1$ and sweat chloride concentrations after ETI exhibit comparable improvements in F508del homozygotes and heterozygotes.[30] Further investigation is required to determine if there are differential effects on sinonasal symptoms between these two subgroups.

Before the introduction of ETI, two less effective modulator combinations were in clinical use for individuals who were F508del homozygous,[31,32] which partially ameliorated CRS symptoms.[10] Participants with absence of prior modulator use were nearly five times more likely to experience SNOT-22 score improvement post-treatment, indicating that modulator-naïve status is a significant predictor of better outcomes compared to those with modulator use history. This is supported by one of the component studies in this article, which noted a trend toward greater sinus CT opacification improvement in PwCF naïve to modulators.[7] Similarly, other ETI studies report greater changes in ppFEV$_1$, BMI, and CF-specific QOL[33] occurred in modulator-naïve individuals compared to those taking ivacaftor at baseline.[34,35] These findings are anticipated, considering that modulator-naïve patients lack prior partial CFTR correction. Alternatively, the "ceiling effect" might explain why patients with prior treatments report less ETI benefit than untreated individuals due to less biochemical range for improvement. Nevertheless, identifying modulator-naïve status as a predictor highlights the importance of considering treatment history when evaluating potential response to new CF-CRS therapies.

Thresholds of clinical relevance are critical to interpreting patient outcomes in both clinical and research contexts. Using distribution-based approaches employed in prior studies,[21,22] our MCID estimates for SNOT-22 for PwCF were calculated to be 8.5 points. We confirmed that this CF-specific MCID is comparable to, although slightly lower, than the established MCID for non-CF individuals with CRS, reported as nine points for surgical treatment

TABLE IV.
Estimates of the MCID for the 22-Question SinoNasal Outcome Test Calculated using Distribution-Based Approaches in People with Cystic Fibrosis.

Data source	*N*	Cronbach's alpha (α)	MCID values				Mean (95% CI)
			½ baseline standard deviation	1 SEM of baseline measurement	Cohen's effect size (d)	Minimal detectable change	
Multi-center, imputed	76	0.93	10.0	5.3	4.0	14.7	8.5 (8.1, 9.0)
Columbia University	42	0.93	9.0	4.8	3.6	13.4	7.7 (7.3, 8.4)
National Jewish Health	25	0.90	7.2	4.5	2.9	12.5	6.8 (6.3, 7.5)
University of North Carolina	20	0.92	8.8	4.9	3.5	13.6	7.7 (6.7, 9.2)
University of Pittsburgh	14	0.94	8.0	3.8	3.2	10.7	6.4 (4.9, 8.7)
All participants	177	0.95	10.9	5.0	4.4	13.8	8.5 (7.9, 8.8)

The 95% CIs for the MCIDs are calculated based on 5000 bootstrap resamples.
MCID = minimal clinically important difference; SEM = standard error of the measurement; 95% CI = 95% confidence intervals.

TABLE V.
Univariable Analysis of Factors Associated with Improvement in SNOT-22 Score Exceeding MCID After Initiation of ETI.

Variable	Did not Meet/Exceed MCID *N* = 43 (%)	Met/Exceeded MCID *N* = 54 (%)	*p*-value
Mean age ± SD (years)	30.7 ± 11.0	36.1 ± 12.3	**0.027**
Sex			
Male	20 (46.5%)	21 (38.9%)	-
Female	23 (53.5%)	33 (61.1%)	0.584
Mean BMI ± SD (kg/m^2)	22.4 ± 4.8	22.5 ± 3.8	0.905
Genotype			
F508del/other	22 (51.2%)	28 (51.9%)	1
F508del/F508del	21 (48.8%)	26 (48.1%)	-
Prior CFTR modulator therapy	28 (65.1%)	32 (59.3%)	0.704
Prior sinus surgery	32 (74.4%)	35 (64.8%)	0.426
Mean baseline ppFEV1 ± SD	77.1 ± 24.0	67.9 ± 23.7	0.063
Mean baseline SNOT-22 score ± SD	31.5 ± 22.2	47.1 ± 19.9	**<0.001***
Mean post-ETI SNOT-22 score ± SD	30.1 ± 23.1	26.1 ± 19.7	0.368
Cystic fibrosis-related diabetes	14 (32.6%)	19 (35.2%)	0.956
History of Staphylococcus or Pseudomonas infection	39 (92.9%)	47 (88.7%)	0.735
Care center/enrollment site			
Columbia University	21 (48.8%)	21 (38.9%)	0.141
National Jewish Health	8 (18.6%)	17 (31.5%)	-
University of Pittsburgh	9 (20.9%)	5 (9.3%)	-
University of North Carolina	5 (11.6%)	11 (20.4%)	-

p-values are based on t-tests for continuous variables and Chi-square tests for categorical variables.
MCID = minimal clinically important difference; SD = standard deviation; BMI = body mass index; CFTR = cystic fibrosis transmembrane conductance regulator; ppFEV$_1$ = percent predicted forced expiratory volume in 1 second; ETI = elexacaftor/tezacaftor/ivacaftor; SNOT-22 = 22-Question SinoNasal Outcome Test.
*Denotes $p < 0.05$.

and 12 points for medical treatment.[19,21,36,37] The CF-specific MCID may reflect a lower clinical threshold because of surgical patients' heightened expectations for improvement, or PwCF's greater sensitivity for highly effective therapies given the chronicity and severity of sinonasal symptoms. The comparable MCIDs between PwCF+CRS and non-CF CRS individuals treated surgically may imply that both cohorts perceive a similar magnitude of change in SNOT-22 scores as clinically significant. Future research should explore anchor-based methodologies in PwCF to enhance MCID estimates using global health assessments.

Strengths of this investigation include use of prospectively collected, multi-institutional data from studies originally designed to assess CF-CRS. PwCF had varying degrees of sinonasal symptom severity across centers,

TABLE VI.
Multivariable Logistic Regression Analysis of Factors Associated with Improvement in SNOT-22 Treated as a Binary Outcome Exceeding MCID After Initiation of ETI.

Variable	Coefficient	Odds ratio	95% CI	*p*-value
Age (years)	0.025	1.026	0.98–1.08	0.334
Sex, male	−0.038	0.963	0.37–2.58	0.939
BMI (kg/m^2)	0.042	1.043	0.92–1.18	0.481
F508del/F508del	1.458	4.296	1.14–18.99	**0.040***
No prior CFTR modulator therapy	1.608	4.993	1.39–20.11	**0.017***
No prior sinus surgery	0.779	2.179	0.78–6.52	0.146
Baseline ppFEV$_1$	−0.009	0.991	0.97–1.01	0.39
Baseline SNOT-22 score	0.048	1.049	1.02–1.08	**<0.001***
Cystic fibrosis-related diabetes	0.018	1.018	0.38–2.75	0.971

Factors with 95% CI including 1 are non-significant.

95% CI = 95% confidence interval; BMI = body mass index; CFTR = cystic fibrosis transmembrane conductance regulator; ETI = elexacaftor/tezacaftor/ivacaftor; MCID = minimal clinically important difference; ppFEV$_1$ = percent predicted forced expiratory volume in 1 second; SNOT-22 = 22-Question SinoNasal Outcome Test.

*Denotes $p < 0.05$.

and the SNOT-22 survey had high internal consistency in each study and in the pooled data, suggesting results are applicable to individuals with a broad range of SNOT-22 scores. All study participants had confirmed diagnoses of CF, and MCID calculations are ideally performed in single disorder populations. Another notable aspect is the robust Cronbach's alpha value exceeding 0.9, which underscores the reliability of the SNOT-22 in PwCF and validates the use of SNOT-22 in evaluating sinonasal symptom burden in PwCF. Finally, our identified predictors of improvement were consistent in both the continuous and binary regression models, lending additional validity to our findings.

The study is also subject to the following limitations. Despite the established rigor of distribution-based approaches, our MCID calculations would have been ideal if multi-center, anchor-based data were available to further validate our distribution-based MCID. When determining predictors of response to HEMT, there were minor differences in follow-up time-point across the studies from 3 to 6 months; however, these differences are unlikely to impact the overall results given that changes in SNOT-22 scores after HEMT initiation are stable after 1 month.[7,9] Although 184 PwCF were included in this study and 97 participants were included in the analysis of predictors of response to ETI; type 2 error remains a possibility due to available sample size. Missing data occurred for a small number of study participants. Finally, individuals under age 12 years were not included in this study and very few participants were age 12–17 years so results are primarily applicable to adults and may not be generalizable to children.

CONCLUSION

Greater SNOT-22 score improvements post-ETI were associated with worse baseline sinonasal symptom severity, F508del homozygosity, and absence of prior modulator therapy in PwCF. The SNOT-22 showed strong internal consistency for varying sinonasal severities in PwCF. Distribution-based MCID was calculated to be 8.5 in this predominantly adult CF cohort initiating HEMT, comparable to clinical thresholds of non-CF CRS individuals pursuing surgery.

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CONFLICT OF INTEREST STATEMENT

DMB: In the last 36 months, DMB has received grant support from CF Foundation, International Society of Inflammation and Allergy of the Nose and the Sue Ann and John L. Weinberg Foundation, honoraria, and consulting fees from Amgen, on medicolegal cases and from Garner Health (equity); CML: NIDCD grant related to work; JBO: Grant support from NIDCD K23DC019678 for investigation not affiliated with this project; AK: Grant support from the CFF and consultant for AcclarENT not related to this work; ED: Grant support from the CFF and Vertex Pharmaceuticals, unrelated to this work; JLG: Grant support from the CF Foundation and NHLBI unrelated to this work. Honoraria from the CF Foundation and Vertex Pharmaceuticals unrelated to this work; CK: Grant support from the CFF not related to this work; BS: Consultant for Lyra Therapeutics,

Medical Center Pharmacy, Stryker, and Neurent; JCM: Has received grant support from CF Foundation related to this work in the past 36 months (BESWIC20A0); JAA: Consultant for OptiNose and Medtronic. Speaker panel GSK. GlycoMira board and equity holder. Grant support from CF Foundation related to this work BESWIC20A0; TEB: Has received grant support from CF Foundation related to this work in the past 36 months (BESWIC20A0); NIC: Unrelated to this work, NIC has received grant support from the Burroughs Wellcome Fund, American Rhinologic Society, and the National Cancer Institute; PHH: Consultant for Stryker, Medtronic, Slate Therapeutics; Equity ownership in Sound Health Systems; DAL: In the last 36 months, DAL has received grant support from the CF Foundation unrelated to this work; ZMP: Consultant/Advisory Board for Optinose, Medtronic, Dianosic, Wyndly, Third Wave Therapeutics, Regeneron/Sanofi, Mediflix, ConsumerMedical. Equity in Olfera Therapeutics; RJS: Consultant for OptiNose, Medtronic, Stryker, Cyrano. Medical Directory for Healthy Humming; ZMS: Consultant for OptiNose, Regeneron, SanofiGenzyme, and Lyra. Medical Directory for Healthy Humming; GAT: In the last 36 months, GAT has received grants from the CF Foundation unrelated to this work; MBW: None related to this work; MTS: MTS receives funding from CFF unrelated to this work; JLTC: In the last 36 months, JLT-C has received grants from the CF Foundation related to this work as well as for work unrelated to the manuscript. Unrelated to this work, she has received grants to her institution from Vertex Pharmaceuticals Incorporated, Eloxx, and 4DMT; has received fees from Vertex Pharmaceuticals Incorporated related to consultation on clinical research design, participation on advisory boards, and speaking engagements; and has served on advisory boards and/or provided clinical trial design consultation for Insmed, 4DMT, and AbbVie. She served on a DMC for AbbVie. She serves as the adult patient care representative to the CFF Board of Trustees, and on the CF Foundation's Clinical Research Executive Committee, Clinical Research Advisory Board, Racial Justice Working Group and as immediate past chair of the CF TDN's Sexual Health, Reproduction and Gender Research Working Group, on the scientific advisory board for Emily's Entourage, and on the ATS Respiratory Health Awards Working Group. She currently serves as the Chair-elect of the ATS International Conference Committee (and associated committees) and previously served on the ATS Scientific Grant Review and Clinical Problems Assembly Programming Committees. She is a member of the International Advisory Board for Lancet Respiratory Medicine and the Editorial Board for the Journal of Cystic Fibrosis; AZ, AK, DAG, JEM, JPT, ALS, PHE, KM, AEG, JTL, MN, JVN, CO, KP, KAS, TLS: none; Remaining authors did not respond with any financial disclosures.

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