Pancreatic Enzyme Replacement Therapy Dosing and Nutritional Outcomes in Children with Cystic Fibrosis

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Objectives To utilize the Cystic Fibrosis Foundation Patient Registry to evaluate whether pancreatic enzyme dose is associated with better nutritional status as measured by average body mass index (BMI) percentile.

Study design A retrospective analysis of the Cystic Fibrosis Foundation Patient Registry from 2005-2008 was performed. The final analysis included 42 561 patient visits from 14 482 patients 2-20 years of age taking pancreatic enzyme replacement therapy from 179 programs. Cystic fibrosis care programs were assigned to quartiles based on adjusted mean patient BMI percentiles. Differences in median lipase dose between programs in the highest and lowest BMI quartiles were examined using a mixed effects model that adjusted for individual patient BMI, age, race, ethnicity, forced expiratory volume in 1 second percent, acid-blocker use, presence of *Pseudomonas aeruginosa*, nutritional supplement use, growth hormone use, and diagnosis of cystic fibrosis-related diabetes.

Results A significant difference in median enzyme dose existed between the highest and lowest BMI quartiles. Multivariable analysis demonstrated the effect persisted after adjustment for covariates. Highest quartile programs had a median enzyme dose of 1755 lipase units/kg/meal compared with 1628 lipase units/kg/meal for lowest quartile programs.

Conclusion Patients attending US cystic fibrosis programs achieving highest nutritional outcomes, measured by mean BMI percentile, have higher enzyme dosing than those attending programs at lower performance levels. Further randomized clinical trials are necessary to determine the role of enzyme dose in improving nutritional outcomes. *(J Pediatr 2014;164:1110-5)*.

Cystic fibrosis (CF) is an autosomal recessive disorder that affects approximately 30 000 individuals in the US.[1] One of the hallmark features of CF is pancreatic insufficiency requiring pancreatic enzyme replacement therapy (PERT). According to the 2011 CF Foundation (CFF) Patient Registry Annual Report, 87.4% of individuals with CF are on some form of PERT.[1] Numerous studies demonstrate nutritional status is highly predictive of pulmonary function and survival in CF.[2-7] Furthermore, there is wide variability in CF center nutrition outcomes in the US.[1]

Numerous factors contribute to nutritional status in patients with CF: pancreatic insufficiency and chronic malabsorption, recurrent sinopulmonary infections, chronic inflammation, increased energy expenditure, and suboptimal intake. Even though PERT is an integral part of optimizing nutrition, little published data specifically evaluates the impact of PERT dosing on growth and outcomes in children with CF. The CFF currently recommends that proprietary PERT be provided at a dose no greater than 10 000 lipase units/kilogram/d.[8] This recommendation was developed from a series of case reports and case control studies from the United Kingdom and US suggesting that high dose pancreatic enzyme supplementation was associated with fibrosing colonopathy.[9,10] The premise of the current dosing recommendation is based on providing doses that are unlikely to cause harm rather than those that are most effective. Not surprisingly, wide variation in PERT dosing exists among the US population with CF. For example, in 2010, the range of pancreatic enzyme dosing in children 2-19 years of age was between 1000 and 3000 lipase units/kg/meal with a mean of 1820 lipase units/kg/meal at US CF programs.[1]

To investigate whether pancreatic enzyme dosing might be a determinant of better nutritional status, as measured by average body mass index (BMI) percentile, we undertook a retrospective analysis of the CFF Patient Registry (CF Registry). A center based analysis was used to avoid the problem of indication bias.[11] This approach has been used in a previous analysis of pulmonary outcomes to reflect general practice patterns and to provide a potential basis for quality improvement initiatives.[12,13]

BMI	Body mass index
CF	Cystic Fibrosis
CFF	Cystic Fibrosis Foundation
CF Registry	CFF Patient Registry
FEV1%	Forced expiratory volume in 1 second percent
PERT	Pancreatic enzyme replacement therapy

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Methods

Patients 2-20 years of age taking PERT who were included at anytime in the CF Registry from January 1, 2005-December 31, 2008, were included in this analysis. A description of the CF Registry is published in an annual report by the CFF.[1] Data collected on each patient includes demographics, use of chronic therapies, results of pulmonary function testing, results of respiratory cultures, information on growth and nutrition, and details related to acute changes in management. The CF Registry started recording pancreatic enzyme doses in 2005. This study was reviewed and approved by the CFF Registry Committee and the institutional review board at the Ann and Robert H. Lurie Children's Hospital of Chicago.

Analyses were completed at the patient level as well as aggregated by CF center. Programs with fewer than 10 unique patients on enzyme supplementation were excluded from the center level analyses. Center level BMI percentile performance quartiles were established according to the 2008 mean adjusted BMI percentile from each center, which were provided by the CF Registry. The patient level BMI percentile values used to calculate the mean center level BMI percentile were calculated from the mean of the highest BMI percentile value reported per quarter in the registry. Mean center BMI percentile is case-mix adjusted to account for intrinsic patient and disease characteristics that influence patient outcomes, including average patient age, race/ethnicity, median family income by zip code, age at diagnosis, presentation (meconium ileus, respiratory and gastrointestinal symptoms, respiratory symptoms alone, gastrointestinal symptoms alone, other), and use of pancreatic enzymes.

The pancreatic enzyme replacement dose used for our calculations was the highest reported enzyme dose on any encounter during the year. Individual enzyme dose was compared for all patients at programs within the top and bottom BMI percentile quartiles. Patient and center level characteristics and median center enzyme dose was also compared between top and bottom BMI-percentile performance quartiles.

Demographic and clinical factors that may be confounders associated with nutritional outcomes were determined after a review of the CF literature and considered for inclusion in a multivariable model. These included both static variables, such as age at diagnosis, sex, and race, as well as covariates that vary over time, such as forced expiratory volume in 1 second percent (FEV1%) predicted. Data provided by the CF Registry is adjusted for socioeconomic status, and, therefore, these variables were not further adjusted in our analysis. Center level analysis was aggregated over patients, as proportion of patients with dichotomous characteristics (eg, proportion of patients with nutritionist evaluation) and average of linear characteristics (eg, FEV1%). Static characteristics were compared between bottom and top BMI performance quartiles using t test, χ^2 analysis, or Wilcoxon rank sum test as appropriate. Characteristics that varied over time were compared between lowest and highest quartiles using mixed models with a fixed effect of year and a covariance structure nesting patients within programs, and results are presented as least square means and SEs. In addition, a similar mixed model including patient BMI, age, race, ethnicity, FEV1%, acid-blocker use, presence of *Pseudomonas aeruginosa*, supplemental feed use, growth hormone use, and diagnosis of CF-related diabetes as covariates while still modeling a nested covariance structure with patient within programs was used to assess if any differences in enzyme dose by quartile was still evident after adjusting for these potential confounders; estimated least squared means and SEs are presented. Secondary analyses of enzyme dose by quartile were similarly performed with Centers for Disease Control and Prevention weight for age and Centers for Disease Control and Prevention height for age percentiles substituted for patient BMI percentile.

The trend of enzyme dose within and between all quartiles over time was also examined. As enzyme dose was significantly skewed, medians and quartiles are presented. Both the median of patient doses, as well as the median of programs' doses are presented and compared using Wilcoxon signed rank and Wilcoxon rank sum tests. These results are unadjusted and are presented both as the median of all patients, as well as the median patient level of the programs.

All statistical tests were 2-sided at a type I error rate of 5%. All analyses were performed with SAS v 9.3 (SAS Institute, Cary, North Carolina).

Results

The final analysis included 42 561 patient visits from 14 482 patients from 179 programs. Each quartile ultimately contained 45 programs, with the exception of the lowest quartile, which contained 44 programs. The median (25th, 75th percentile) enzyme dose from the last visit of all patients was 1755 (1329, 2150) lipase units/kg/meal, and the average BMI percentile of all patients was the 45.2 percentile (SD 27.0%). The Spearman correlation coefficient of enzyme dose and BMI percentile was −0.176, which, because of the large sample, was statistically significant ($P < .001$), but not clinically meaningful.

The numbers of patients in the top and bottom BMI quartiles were 3475 and 3205, respectively. Several statistically significant differences exist between the patient characteristics of lowest and highest quartile programs (**Table I**). Patients at top quartile programs were younger, despite not showing a statistically significant difference in age at diagnosis. Top quartile programs had fewer patients diagnosed by electrolyte imbalance, failure to thrive/malnutrition, meconium ileus, and steatorrhea. Furthermore, programs with best BMI performance had more patients diagnosed by way of newborn screening and demonstrated higher lung function as measured by FEV1% predicted, forced vital capacity percent predicted, and FEV1%/forced vital capacity percent. Top quartile and

Table I. Patient level characteristics in lowest and highest BMI quartiles

Characteristics	Total sample	Lowest quartile (3205)	Highest quartile (3475)	*P* value*
Patients/center				.001*
Median (25th, 75th percentile)	58 (27, 99)	32 (16, 55)	70 (28, 93)	
Range	1-358	1-210	4-201	
Age (center mean in y)	11.0 ± 5.1	12.1 ± 5.3	10.6 ± 4.9	<.001
Age at diagnosis (mo)	18.9 ± 33.1	20.8 ± 35.6	19.1 ± 34.0	.097
Sex (male)	7151 (51.2%)	1019 (52.0%)	1694 (50.8%)	.386
Race (White)	13 166 (94.3%)	1817 (92.8%)	3151 (94.5%)	.010
Race (Black)	676 (4.8%)	110 (5.6%)	145 (4.4%)	.038
Ethnicity (Hispanic)	1225 (8.8%)	187 (9.6%)	318 (9.5%)	.993
CDC BMI percentile	-	39.5 (0.3)	50.7 (0.2)	<.001†
CDC height percentile	-	31.6 (0.3)	33.6 (0.2)	.028†
CDC weight percentile	-	31.7 (0.3)	40.4 (0.2)	<.001†
delF508 (homozygous)	6905 (54.8%)	903 (53.8%)	1665 (54.2 %)	.224
delF508 (heterozygous)	4336 (34.4%)	561 (33.4%)	1064 (34.6%)	
Birth complications	3124 (22.4%)	481 (24.6%)	730 (21.9%)	.026
Diagnosis suggested by				
Acute respiratory symptoms	6123 (43.9%)	876 (44.7%)	1400 (42.0%)	.053
Edema	129 (0.9%)	20 (1.0%)	24 (0.7%)	.244
Electrolyte imbalance	565 (4.1%)	114 (5.8%)	139 (4.2%)	.007
Failure to thrive/malnutrition	5756 (41.2%)	898 (45.8%)	1245 (37.3%)	<.001
Family history	1989 (14.2%)	313 (16%)	511 (15.3%)	.528
Genotype	703 (5.0%)	110 (5.6%)	207 (6.2%)	.380
Liver problems	207 (1.5%)	36 (1.8%)	59 (1.8%)	.857
Meconium ileus	3161 (22.6%)	489 (25%)	734 (22.0%)	.014
Nasal polyps/sinus disease	314 (2.3%)	49 (2.5%)	72 (2.2%)	.422
Prenatal diagnosis (CVS, amniocentesis)	189 (1.4%)	24 (1.2%)	50 (1.5%)	.411
Newborn screening	881 (6.3%)	41 (2.1%)	332 (10.0%)	<.001
Rectal prolapse	524 (3.8%)	70 (3.6%)	121 (3.6%)	.916
Steatorrhea	4094 (29.3%)	637 (32.5%)	875 (26.2%)	<.001
FEV1% (LSM [SE])	-	81.3 (0.30)	90.3 (0.22)	<.001†
FVC% (LSM [SE])	-	90.3 (0.26)	96.9 (0.19)	<.001†
FEV1/FVC (LSM [SE])	-	0.79 (0.001)	0.82 (0.001)	<.001†

CVS, chorionic villus sampling; *FVC*, forced vital capacity percent; *LSM*, least square mean; *N*, number of total patients in given quartile; *%*, percentage of patients in given quartile, excluding patients missing the characteristic.
*Wilcoxon rank sum test.
†Type 3 F test based on mixed model.

bottom quartile patients also demonstrated statistically significant differences in height and weight for age percentile. Statistically significant differences in certain program level characteristics distinguished the highest from the lowest quartile (**Table II**). Highest quartile programs had more patients receiving nasogastric supplemental feeds and gastrostomy tube feeds and fewer patients receiving parenteral nutrition; acid blocker use was more common in highest quartile programs. Complications of CF were found more commonly in highest quartile programs, with bone fractures and gastroesophageal reflux diseases being more prevalent in highest quartile programs. Lowest quartile programs reported more patients with CF-related diabetes, chronic insulin use, and osteoporosis. A statistically significant difference was found in median enzyme dose of all patients attending the highest quartile programs compared with those attending the lowest quartile programs in all 4 years of the study (**Table III**). Compared at the center level (unweighted for size of patient population), a statistically significant difference in enzyme replacement dose was present in 2 years of the analysis period: 2006 and 2007 (**Table IV**). Multivariable analysis demonstrated that the difference in mean enzyme dose between highest and lowest quartile programs persists after adjustment for multiple covariates. Highest quartile programs had a mean enzyme dose of 1755 lipase units/kg/meal (95% CI: 1722, 1788) compared with 1628 lipase units/kg/meal (95% CI: 1595, 1660) for lowest quartile ($P < .001$). Please refer to **Tables V** and **VI** (available at www.jpeds.com) for complete review of the model and for BMI percentile comparisons across quartiles during the study period.

Discussion

We completed a retrospective analysis of the CF Registry to evaluate the association of PERT dosing with nutritional outcomes in children with CF. We demonstrate that patients attending US CF programs achieving best nutritional outcomes, as defined by BMI percentile, have significantly higher average enzyme dosing than those attending lower quartile programs. Although a number of other characteristics differentiated highest and lowest quartile programs, this study suggests the potential importance of addressing enzyme dose as a part of the necessary multidisciplinary approach to achieve recommended nutrition outcome targets.

The first clinical guidelines for PERT appeared in 1995 after a series of case reports demonstrated the risk of developing fibrosing colonopathy with increased enzyme doses.[9,10,14-16] In 2002, the CFF generated a clinical guideline

Table II. Center level characteristics based on patient level features predicting presence in lowest or highest performance quartile

Characteristics	Total sample	Lowest quartile	Highest quartile	*P* value
Nutritionist evaluation	14 897 (96.1%)	1919 (95.4%)	3340 (94.6%)	.162
Any form of supplemental nutrition	11 819 (76.2%)	1470 (73.1%)	2643 (74.8%)	.156
Oral supplemental feed	11 198 (94.8%)	1382 (94.0%)	2513 (95.1%)	.143
Nasogastric supplemental feed	389 (3.3%)	38 (2.6%)	120 (4.5%)	.002
Gastrostomy tube supplemental feed	2792 (23.6%)	282 (19.2%)	613 (23.2%)	.003
Parental nutrition	62 (0.5%)	15 (1.0%)	10 (0.4%)	.011
Sputum culture at CF center	15 007 (97.6%)	1880 (95.2%)	3454 (98.4%)	<.001
Normal flora in sputum culture	13 003 (84.6%)	1656 (83.9%)	3011 (85.8%)	.050
Pseudomonas present in sputum culture	9910 (64.4%)	1299 (65.8%)	2187 (62.3%)	.011
Private insurance	10 605 (68.4%)	1346 (66.9%)	2572 (72.8%)	<.001
State insurance	8681 (56.0%)	1038 (51.6%)	1928 (54.6%)	.033
CHAMPUS* insurance	399 (2.6%)	81 (4.0%)	54 (1.5%)	<.001
Any acid blocker use	9629 (62.4%)	1076 (53.8%)	2287 (64.9%)	<.001
Any complication	9717 (62.7%)	1050 (52.2%)	2189 (62.0%)	<.001
Bone fracture	95 (0.6%)	8 (0.4%)	10 (0.3%)	.471
CFRD	1880 (12.1%)	273 (13.6%)	396 (11.2%)	.009
Cirrhosis	382 (2.5%)	42 (2.1%)	88 (2.5%)	.341
Distal intestinal obstruction syndrome	876 (5.7%)	95 (4.7%)	137 (3.9%)	.131
Gastroesophageal reflux disease	3165 (20.4%)	265 (13.2%)	921 (26.1%)	<.001
Osteopenia	436 (2.8%)	40 (2.0%)	87 (2.5%)	.257
Osteoporosis	279 (1.8%)	46 (2.3%)	44 (1.3%)	.003
Pancreatitis	101 (0.7%)	12 (0.6%)	15 (0.4%)	.376
Peptic ulcer	13 (0.1%)	2 (0.1%)	2 (0.1%)	.625
Growth hormone use	722 (4.7%)	101 (5.2%)	135 (3.9%)	.022
Oral corticosteroid use (any)	1798 (11.6%)	178 (8.9%)	562 (15.9%)	<.001
CFRD with chronic insulin use	1437 (9.3%)	215 (10.7%)	301 (8.5%)	.008
Enzyme dose >2000 lipase units/kg/meal	6899 (47.1%)	714 (37.1%)	1814 (52.3%)	<.001
Lipase units/kg/meal (LSM [SE])	-	1649 (9)	1799 (6)	<.001
Lipase units/kg/meal (adjusted LSM [SE])	-	1597 (27)	1780 (26)	<.001
Lipase units/kg/meal (adjusted LSM [SE])†	-	1549 (27)	1724 (26)	<.001
Lipase units/kg/meal (adjusted LSM [(SE])‡	-	1559 (27)	1702 (26)	<.001

CDC, Centers for Disease Control and Prevention; *CFRD*, cystic fibrosis-related diabetes; *CHAMPUS*, Civilian Health and Medical Program of the Uniformed Services; *%*, percentage of patients in given quartile.
*CHAMPUS.
†Adjusted for year, patient age, FEV1%, acid blocker use, growth hormone use, F508, race, ethnicity, *Pseudomonas* present in culture, supplemental feed, CFRD, and CDC weight percentile.
‡Adjusted for year, patient age, FEV1%, acid blocker use, growth hormone use, F508, race, ethnicity, *Pseudomonas* present in culture, supplemental feed, CFRD, and CDC height percentile.

for the nutritional management of patients with CF. The report recommended that proprietary PERT be provided at a dose no greater than 10 000 lipase units/kg/d or no greater than 2500 lipase units/kg/meal.[17] This dosing strategy was intended as protective and did not take into account what dosing might be associated with optimal absorption and nutritional outcome.

In 2005, Baker et al completed the first large scale study investigating the relationship between pancreatic enzyme therapy dosing and nutritional outcomes and gastrointestinal symptoms in patients with CF.[18] In this survey-based study of 1215 patients cared for at CF programs, no relationship was found between enzyme dosing and growth. However, no attempt was made to account for the possibility that CF clinicians may have prescribed higher enzyme doses to patients in response to poor weight gain or gastrointestinal symptoms (ie, confounding by indication). At the time, this was the largest study exploring the relationship between enzyme dose and nutritional outcomes. Enzyme doses were not recorded in the CF Registry until 2005.

Although the registry is a powerful tool for performing observational studies, the limitations of such analyses must

Table III. Patient level lipase units/kg/meal median (25th, 75th percentile) categorized by center-based BMI percentile performance quartiles*

Year	Lowest quartile	Highest quartile	*P* value
2005	1628 (1128, 2047) N = 1708	1787 (1294, 2235) N = 2930	<.001
2006	1632 (1144, 2020) N = 1605	1836 (1341, 2250) N = 2906	<.001
2007	1633 (1193, 2029) N = 1461	1829 (1355, 2225) N = 2901	<.001
2008	1690 (1257, 2062) N = 1451	1835 (1372, 2221) N = 3045	<.001

N, number of patients in each quartile.
*Quartiles defined by 2008 data.

Table IV. US CF center level median lipase units/kg/meal (25th, 75th percentile) categorized by center-based BMI percentile performance quartiles

Year	Lowest quartile (N = 44)	Highest quartile (N = 45)	*P* value
2005	1651 (1448, 1763)	1710 (1455, 1928)	.660
2006	1637 (1323, 1806)	1777 (1562, 1982)	.018
2007	1647 (1406, 1821)	1745 (1522, 1924)	.037
2008	1603 (1449, 1841)	1742 (1501, 1991)	.246

N, number of CF programs within each quartile.

be recognized. Selection bias, information bias, and confounding are common pitfalls limiting the validity of analyses of registry data. The most important and difficult challenge of using registry data to examine the relationship of therapies to outcomes is the susceptibility of any such analysis to confounding by indication, or indication bias.[11,19] Indication bias occurs when the treatment of interest is preferentially prescribed to patients at greater risk for the outcome of interest. If all indications for treatment are measured and recorded in the database, then multivariable modeling can control for them; however, unmeasured characteristics that lead to an increased likelihood of both adverse outcome and treatment will lead to residual confounding. Indication bias can produce deceiving estimates of the direction and/or size of treatment effects, and its consequences are well described in outcomes studies using the CF Registry.[11,20] Novel approaches to overcome, or lessen, this bias were used, including using center-level outcomes and including BMI percentile in the multivariable model.[21,22] We attempted the approach of using average program practice and outcomes as a type of ecologic study to address the problem of indication bias, as used in 2 previous studies.[12,13] Our use of multivariable modeling to additionally control for differences in patient characteristics is similar to what is done when defining instrumental variables in an attempt to grapple with indication bias, and has the same limitations.[23]

We avoided selection bias by including all patients taking PERT, which accounts for approximately 90% of the population with CF captured in the registry. Because the study population was not limited to patients with severe mutations as predicted by the McKone classification, who are generally pancreatic insufficient, there may be a small number of patients in this study who were prescribed PERT and are not actually pancreatic insufficient.[24] This population is small and therefore unlikely to affect the outcome of this study. Information bias may also be present. Accurate reports of observational studies from database analysis are dependent on the accuracy and type of the information entered in the database. Although rounding or data entry errors may exist, this is unlikely to bias our findings given the large size of the population.

Even though most patients included in this cohort used some form of oral caloric supplementation, top performing programs demonstrate increased use of caloric supplementation via nasogastric and gastrostomy tube. Bradley et al and Best et al demonstrated the positive effect of gastrostomy tube placement and caloric supplementation in patients with CF.[25,26] Our study was not designed to determine what form of caloric supplementation has the greatest affect on nutritional outcomes. In addition, the CF registry does not include specific details of the type (formula brand and caloric content) and quantity of supplementation. However, use of tube feeding in our cohort appears to be associated with higher BMI percentile.

Although the top quartile programs' median enzyme dose was significantly higher than that of the bottom quartile, the median enzyme dose was lower than the maximum dose recommended by the CF foundation, ranging from 1787-1836 lipase units/kg/meal, less than the maximum recommended dose of 2500 lipase units/kg/meal. Note these values are less than the enzyme doses reported in the most recent CF Registry, reflecting the general trend of increased enzyme dose over time. Although 52% of patients in top quartile programs had enzyme doses greater than 2000 lipase units/kg/meal, there were no cases of fibrosing colonopathy in children reported during the study period. Although this potential significant adverse event of enzyme replacement therapy was not identified, the CF Registry is not designed to capture all adverse events of enzyme replacement therapy.

The findings of this study cannot be used to identify or recommend a specific PERT dose for patients with CF but demonstrate that CF programs in the top quartile for BMI percentile prescribe higher PERT doses than bottom quartile programs. Other variables that predict the presence of a center or patient in the top quartile were also identified. Top quartile programs included more patients diagnosed by newborn screening. As demonstrated by Farrell et al, newborn screening results in a number of improved outcomes in CF, including nutritional status.[27] Early diagnosis may play a role in the explaining the difference in nutritional status between the groups. Lung function was also significantly different between top and bottom quartiles, which is not surprising given the difference in nutritional status. Even after accounting for significant differences in patient and center characteristics and confounding effects, the difference in enzyme dosing persisted. The prescription of higher doses of PERT might be one of the driving contributors to improved nutritional outcomes, or it may just be a "marker" of a more proactive approach to nutrition care that is seen at the top quartile programs.

Yen et al demonstrated that weight for age, specifically a weight for age percentile >50% at age 4, is associated with greater height, better pulmonary function, fewer complications of CF, and better survival through age 18 years.[28] In our study, patients in top performing programs demonstrated a clinically and statistically significant difference in weight for age. Height-for-age had a statistically significant difference, but it was not clinically significant. This highlights the fact that the difference in BMI percentile was due to a difference in weight, not height. This difference may be due to the difference in enzyme dosing or a reflection of an aggressive nutritional program at top performing programs.

In summary, this analysis shows that CF centers that prescribe higher average pancreatic enzyme dosing have better nutritional outcomes, as measured by average BMI percentile. Even though the magnitude of difference in PERT dose may not appear large, only ~150 lipase units/kg/meal, reducing minor malabsorption at each meal could enhance weight gain over time. There are probably other unrecognized or unmeasured variables that were not included in our analysis and that may have contributed to the findings, such as adherence to PERT and other therapies, dietary recommendations, or other CF center practices. Nevertheless, regularly assessing pancreatic enzyme replacement dosing

in all patients with CF who are pancreatic insufficient may be an important component of a successful nutritional program, as higher doses could play a role in obtaining better outcomes. Further randomized clinical trials comparing enzyme doses are necessary to determine if increasing enzyme dose is a reasonable approach to improving nutritional outcomes. ■

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Table V. US CF center BMI performance quartile mean BMI percentile categorized by center-based BMI percentile performance quartiles

Year	Q1	Q2	Q3	Q4	*P* value*
2005	38.0	43.2	46.8	51.6	<.001
2006	40.4	44.1	47.9	52.3	<.001
2007	40.4	45.0	48.8	51.5	<.001
2008	41.5	45.7	49.9	51.9	<.001
P value†	.002	<.001	<.001	.599	

*Comparison within years across quartile.
†Comparison within quartile across years.

Table VI. Fixed effects model parameter estimates and standard errors from model predicting mean lipase dose

Effect	Estimate	SE
Intercept	2302.5	26.8
BMI percentile	−5.10	0.15
Age	−32.92	1.00
Non-White race	−35.48	15.71
Hispanic origin	−94.52	12.66
FEV1%	−0.19	0.19
Any acid blocker use	207.55	6.96
Culture result: *P aeruginosa*	40.82	7.19
Any supplemental feed use	57.44	7.67
Growth hormone use	−8.60	21.78
Diagnosis of CFRD	80.59	11.86
Center quartile 1	−132.15	10.5
Center quartile 2	−103.13	9.75
Center quartile 3	17.43	9.63