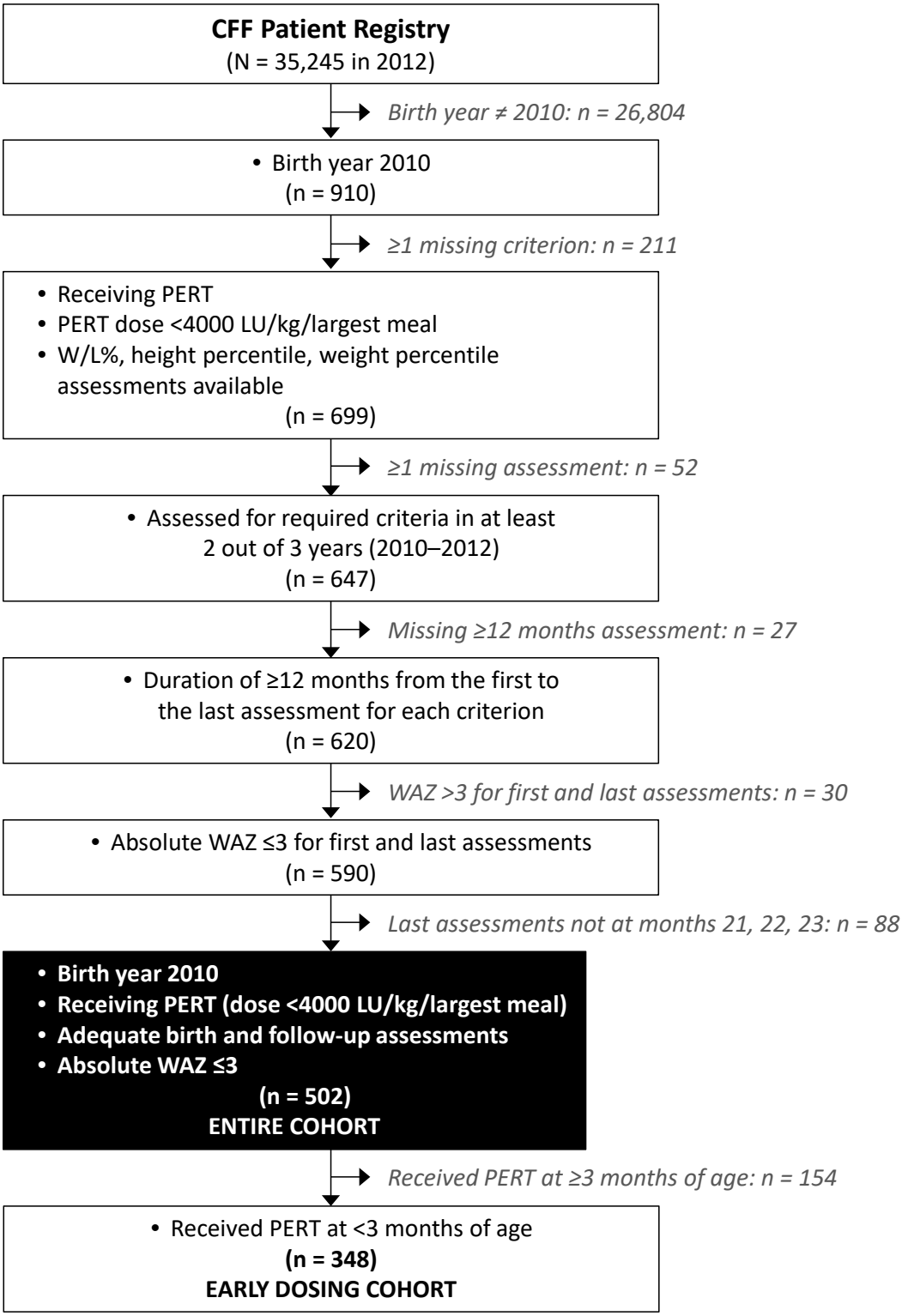
Supplemental Digital Content Figure 1. Flowchart of patients included in the study population showing the two cohorts.

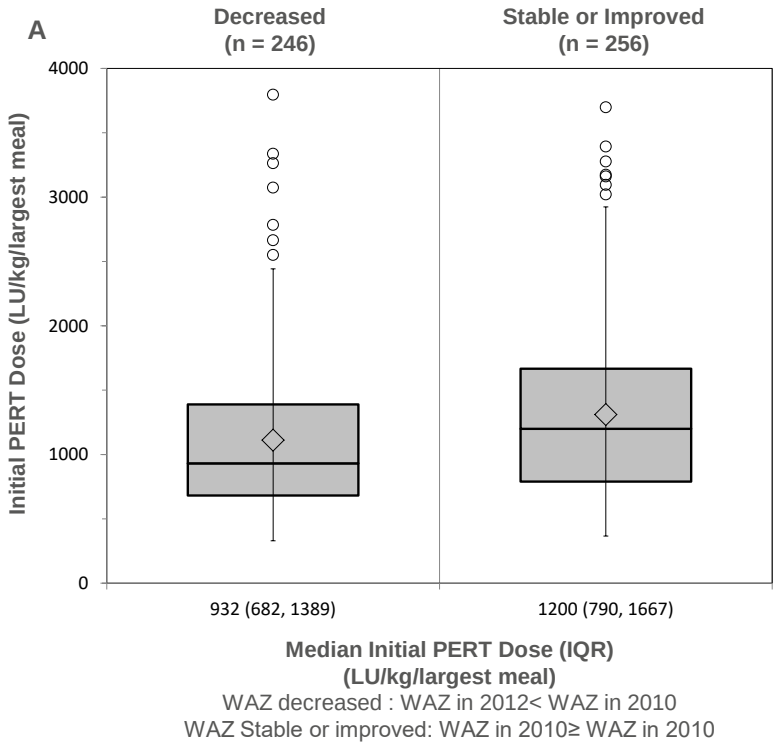


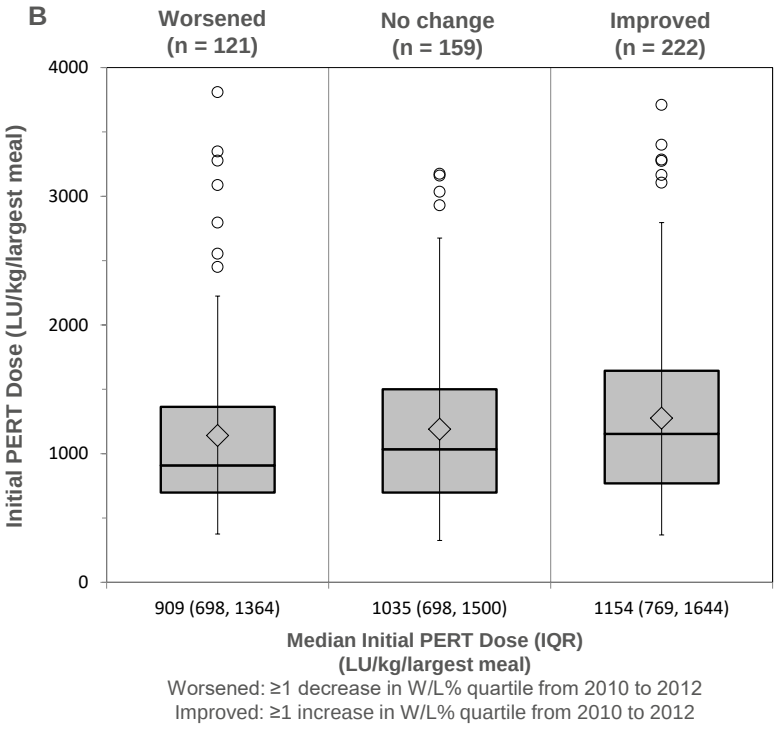
CF = cystic fibrosis, CFF = CF Foundation, PERT = pancreatic enzyme replacement therapy, WAZ = weight-for-age z score, W/L% = weight-for-length percentile.

Supplemental Digital Content Figure 2.

A. Median initial PERT dose in patients by WAZ attainment in 2012

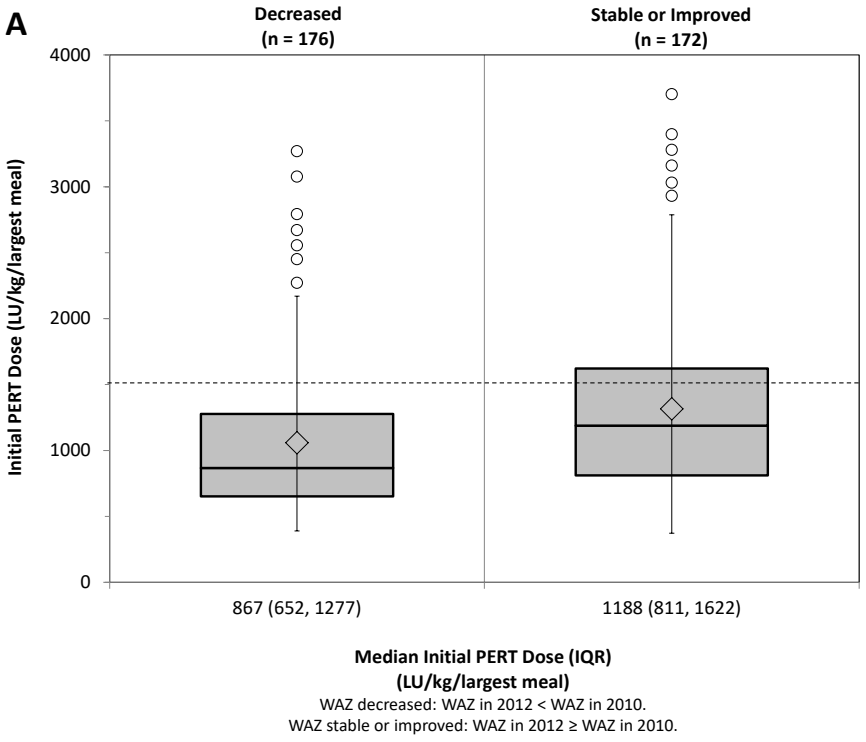
B. Median initial PERT dose in patients by change in W/L% in 2012

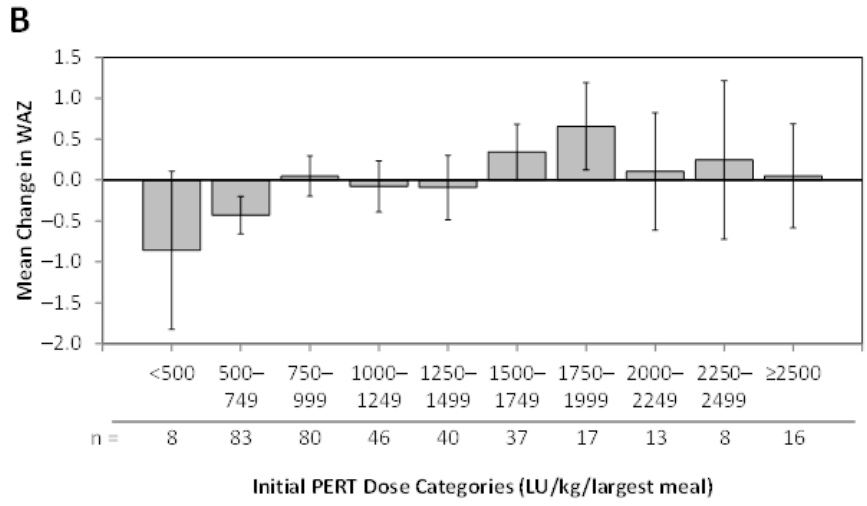




PERT = pancreatic enzyme replacement therapy, WAZ = weight-for-age *z* score, W/L% = weight-for-length percentile.

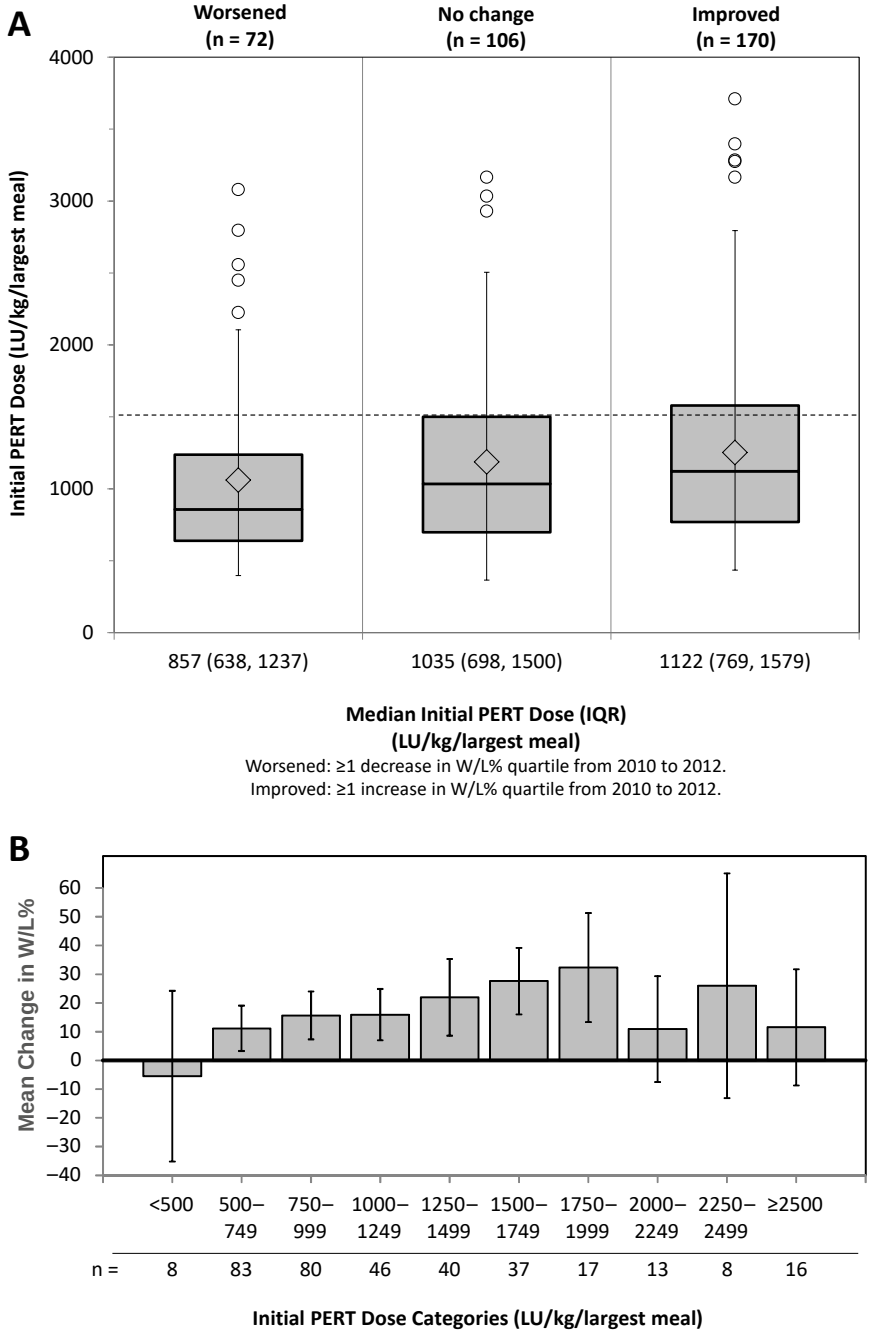
Supplemental Digital Content Figure 3.
A. Initial PERT dose in patients whose WAZ decreased vs. that of patients whose WAZ was stable or improved for early dosing cohort
B. Mean change in WAZ by initial PERT dose category for the early dosing cohort.





IQR = interquartile range, LU = lipase units, PERT = pancreatic enzyme replacement therapy, WAZ = weight-for-age *z* score.
Error bars in B are 95% confidence intervals.

Supplemental Digital Content Figure 4.
A. Initial PERT dose by change in W/L% quartile group for the early dosing cohort.
B. Mean change in W/L% by initial PERT dose category for the early dosing cohort.



IQR = interquartile range, LU = lipase units, PERT = pancreatic enzyme replacement therapy, W/L% = weight-for-length percentile.
Error bars in B are 95% confidence intervals.

Supplemental Digital Content Table 1. Baseline characteristics for WAZ categories

Characteristic	All patients (*N* = 502)	ΔWAZ<median (2012WAZ<2010WAZ) (*n* = 246)	ΔWAZ≥median (2012WAZ≥2010WAZ) (*n* = 256)	ΔWAZ<75th percentile (2012WAZ-2010WAZ <0.8) (*n* = 379)	ΔWAZ≥75th percentile (2012WAZ-2010WAZ ≥0.8) (*n* = 123)
Gender, %					
Male	52.2	50.0	54.3	53.3	48.8
Race, %					
White	91.8	91.5	92.2	91.6	92.7
Black	6.8	6.1	7.4	6.3	8.1
Ethnicity, %					
Hispanic	11.2	12.6	9.8	11.3	10.6
Insurance, %					
Private	41.8	39.4	44.1	40.9	44.7
Medicaid	42.8	40.2	45.3	42.2	44.7
Diagnosis suggested by: %					
Acute respiratory symptoms	3.2	4.5	2	3.4	2.4
Failure to thrive/malnutrition	6.0	5.7	6.3	6.1	5.7
Family history	11.4	12.6	10.2	11.9	9.8
Genotype	21.1	19.5	22.7	19.8	25.2
Meconium ileus	15.7	13.8	17.6	13.7	22.0[b]
Prenatal diagnosis (CVS, AC)	6.6	4.9	8.2	5.3	10.6
Newborn screening	80.5	80.9	80.1	82.3	74.8
Steatorrhea	5.8	5.3	6.3	6.1	4.9
CFTR genotype, %					
Severe (Class I–III)	79.3	78.5	80.1	79.2	79.7
Mild (Class IV–V)	2.8	2.4	3.1	2.9	2.4
Unknown	17.9	19.1	16.8	17.9	17.9
Any form of supplemental	83.9	89.4	78.5[a]	86.3	76.4 [b]
Oral supplemental feeding	82.9	88.6	77.3[a]	85.0	76.4 [b]
Nasogastric supplemental	3.8	3.7	3.9	4.0	3.3
Gastrostomy tube feeding	12.7	13.8	11.7	12.9	12.2
H2 blocker use, %	51.8	48.4	55.1	51.5	52.8
Proton pump inhibitor use, %	55.0	52.8	57.0	55.4	53.7
Exclusive breast milk feeding reported at any visit, %	28.7	31.7	25.8	30.3	23.6
Breast milk and formula reported at any visit, %	32.5	35.4	29.7	33.8	28.5
Exclusive formula feeding reported at any visit, %	71.5	67.9	75	70.4	74.8
Normal flora on sputum culture, %	77.5	76.4	78.5	75.7	82.9
Pseudomonas aeruginosa present on respiratory culture, %	50.4	48.4	52.3	50.9	48.848.
DIOS, %	8	7.3	8.6	7.7	8.9
Gastroesophageal reflux disease, %	40.4	37.8	43	41.2	38.2
Cystic fibrosis liver disease, %	4.4	2.8	5.9	4.5	4.1
Age (months) at initial PERT encounter, mean (range)	1.4 (0, 2)	1.2 (0, 2)	1.6 (0, 2)	1.3 (0, 2)	1.6 (0, 2)
Prematurity, %	11.8	4.1	19.1[a]	6.9	26.8[b]
Birth weight (kg), median (IQR)	3.2 (2.7, 3.5)	3.3 (3.0, 3.6)	2.9 (2.6, 3.3)[a]	3.2 (2.9, 3.6)	2.8 (2.4, 3.2)[b]
Weight at initial PERT encounter (kg), median (IQR)	4.6 (3.7, 5.7)	4.8 (3.9, 5.7)	4.1 (3.5, 5.4)[a]	4.7 (3.8, 5.7)	4 (3.4, 5.2)[b]
Weight-for-age percentile at initial PERT encounter, median (IQR)	18.4 (5.9, 40.1)	30.4 (13.6, 56.3)	8.7 (2.5, 26.3)[a]	23.0 (8.9, 48.4)	7.5 (1.8, 18.6)[b]
W/L% at initial PERT encounter, median (IQR)	35.1 (12.0, 60.0)	42 (17.5, 67.4)	27.3 (9.1, 54.6)[a]	37.9 (14.0, 63.2)	23.3 (8.2, 46.3)[b]
WAZ at initial PERT encounter, median (IQR)	−0.3 (−1.1, 0.5)	0.2 (−0.6, 0.9)	−0.8 (−1.5, −0.2)[a]	−0.1 (−0.8, 0.6)	−1.1 (−1.8, −0.5) [b]

AC = amniocentesis, CVS = chorionic villus sampling, DIOS = distal intestinal obstruction syndrome, IQR = interquartile range, PERT = pancreatic enzyme replacement therapy, WAZ = weight-for-age *z* score, W/L% = weight-for-length percentile.

Note: Insurance, DIOS, *Pseudomonas* infection, H2 blocker, proton pump inhibitor, and supplemental feeding are recorded for the year.

[a]$p \leq 0.05$, ΔWAZ≥median vs. ΔWAZ<median, , [b]$p \leq 0.05$, ΔWAZ≥75th percentile vs. ΔWAZ<75th percentile.

Supplemental Digital Content Table 2. Baseline characteristics for W/L% categories

Characteristic	All patients (*N* = 502)	ΔW/L%<median ([2012W/L%-2010W/L%]<10%) (*n* = 249)	ΔW/L%≥median ([2012W/L%-2010W/L%]≥10%) (*n* = 253)	ΔW/L%<75th percentile ([2012W/L%-2010W/L%]<40%) (*n* = 384)	ΔW/L%≥75th percentile ([2012W/L%-2010W/L%]≥40%) (*n* = 118)
Gender, %					
Male	52.2	48.6	55.7	50.3	58.5
Race, %					
White	91.8	91.2	92.5	90.9	94.9
Black	6.8	5.6	7.9	6.5	7.6
Ethnicity, %					
Hispanic	11.2	10.4	11.9	11.5	10.2
Insurance, %					
Private	41.8	42.6	41.1	41.1	44.1
Medicaid	42.8	39.4	46.2	42.2	44.9
Diagnosis suggested by: %					
Acute respiratory symptoms	3.2	4.4	2.0	3.4	2.5
Failure to thrive/malnutrition	6.0	6.8	5.1	6.0	5.9
Family history	11.4	10.4	12.3	12.0	9.3
Genotype	21.1	18.5	23.7	21.4	20.3
Meconium ileus	15.7	13.3	18.2	14.6	19.5
Prenatal diagnosis (CVS, AC)	6.6	5.2	7.9	6.0	8.5
Newborn screening	80.5	80.7	80.2	80.5	80.5
Steatorrhea	5.8	6.4	5.1	6.0	5.1
CFTR genotype, %					
Severe (Class I–III)	79.3	80.7	77.9	78.9	80.5
Mild (Class IV–V)	2.8	2.8	2.8	2.6	3.4
Unknown	17.9	16.5	19.4	18.5	16.1
Any form of supplemental nutrition, %	83.9	88.4	79.4[a]	87.2	72.9[b]
Oral supplemental feeding	82.9	86.7	79.1[a]	86.2	72.0[b]
Nasogastric supplemental feeding	3.8	5.2	2.4	4.2	2.5
Gastrostomy tube feeding	12.7	15.7	9.9	13.8	9.3
H2 blocker use, %	51.8	53.0	50.6	51.3	53.4
Proton pump inhibitor use, %	55.0	55.8	54.2	57.0	48.3
Exclusive breast milk feeding reported at any visit, %	28.7	26.1	31.2	27.9	31.4
Breast milk and formula reported at any visit, %	32.5	36.1	28.9	33.9	28.0
Exclusive formula feeding reported at any visit, %	71.5	71.9	71.1	71.1	72,9
Normal flora on sputum culture, %	77.5	77.5	77.5	76.0	82.2
Pseudomonas aeruginosa present on respiratory culture, %	50.4	44.6	56.1[a]	47.9	58.5[b]
DIOS, %	8.0	5.2	10.7[a]	7.0	11.0
Gastroesophageal reflux disease, %	40.4	40.6	40.3	42.4	33.9
Cystic fibrosis liver disease, %	4.0	4.8	4.0	4.7	3.4
Age (months) at initial PERT encounter, mean (range)	1.4 (0, 2)	1.5 (0, 2)	1.3 (0, 1)	1.4 (0, 2)	1.3 (0, 2)
Prematurity, %	11.8	12.9	10.7	12.8	8.5
Birth weight (kg), median (IQR)	3.2 (2.7, 3.5)	3.2 (2.7, 3.5)	3.2 (2.8, 3.4)	3.1 (2.7, 3.5)	3.2 (2.9, 3.4)
Weight at initial PERT encounter (kg), median (IQR)	4.6 (3.7, 5.7)	4.7 (3.8, 5.8)	4.3 (3.7, 5.3)[a]	4.7 (3.7, 5.8)	4.0 (3.6, 5.2)[b]
Weight-for-age percentile at initial PERT encounter, median (IQR)	18.4 (5.9, 40.1)	19.8 (5.5, 43.5)	17.6 (6.1, 37.4)	20.7 (5.6, 43.6)	14.1 (6.9, 27.4)
W/L% at initial PERT encounter, median (IQR)	35.1 (12.0, 60.0)	51.2 (27.4, 77.4)	20.6 (7.9, 43.6)[a]	45.1 (21.8, 69.7)	12.2 (5.4, 24.0)[b]
WAZ at initial PERT encounter, median (IQR)	−0.3 (−1.1, 0.5)	−0.3 (−1.2, 0.5)	−0.3 (−1.0, 0.4)	−0.3 (−1.2, 0.6)	−0.4 (−1.0, 0.1)

AC = amniocentesis, CFTR = cystic fibrosis transmembrane conductance regulator, CVS = chorionic villus sampling, DIOS = distal intestinal obstruction syndrome, IQR = interquartile range, PERT = pancreatic enzyme replacement therapy, WAZ = weight-for-age *z* score, W/L% = weight-for-length percentile.

Note: Insurance, DIOS, *Pseudomonas* infection, H2 blocker, proton pump inhibitor, and supplemental feeding are recorded for the year.

[a] $p \leq 0.05$, ΔW/L%≥median vs. ΔW/L%<median.

[b] $p \leq 0.05$, ΔW/L%≥75th percentile vs. ΔW/L%<75th percentile.

Supplemental Digital Content Table 3. Achievement of median change (10%) and top quartile change (40%) in W/L% from 2010 to 2012 by initial PERT dose category

	Initial PERT Dose Category (2010)						
Change in W/L% 2012–2010, n (%)	**<1500 LU/kg/largest meal** (*n* = 362)	**≥1500 LU/kg/largest meal** (*n* = 140)	***p*-value**	**<1750 LU/kg/largest meal** (*n* = 421	**≥1750 LU/kg/largest meal** (*n* = 81)	***p*-value**	**Total** (*N* = 502)
<10%	188 (51.9)	61 (43.6)		215 (51.1)	34 (42.0)		249 (49.6)
≥10% (median)	174 (48.1)	79 (56.4)	0.093	206 (48.9)	47 (58.0)	0.134	253 (50.4)
<40%	287 (79.3)	97 (69.3)		327 (77.7)	57 (70.4)		384 (76.5)
≥40% (top quartile)	75 (20.7)	43 (30.7)	0.018	94 (22.3)	24 (29.6)	0.156	118 (23.5)

LU = lipase units, PERT = pancreatic enzyme replacement therapy, W/L% = weight-for-length percentile.

Supplemental Digital Content Text

W/L% analysis

The analysis of the changes in W/L% between 2010 and 2012 showed that 121 (23.4%) patients of the cohort decreased at least one W/L quartile, 159 (31.7%) stayed within the same quartile, and 222 (44.2%) increased at least one W/L quartile. The median change in W/L% for the entire population was 10.4%. An increase in W/L% by >38.8% was achieved by the top quartile of patients. Thus, a W/L% change of 10% was the approximate median and a change of 40% was approximately the top quartile. These numbers were used for subsequent modeling. Characteristics of the population are shown in Supplemental Digital Content Table 2. Patients whose change in W/L% was above the median were more likely to have had a lower mean weight and W/L% at initial PERT encounter, were more likely to have had DIOS and a positive culture for *Pseudomonas aeruginosa,* and less likely to have received nutritional supplementation.

There was a significant association in median initial PERT dose with changes in W/L quartile (p=0.019 Spearman correlation) (Supplemental Digital Content Figure 1). Simple linear and multiple linear regressions showed that the W/L% attainment was not statistically associated with PERT dose across the entire dosing range (p=0.123 and p=0.08, respectively). The bottom panel of Figure 2 shows the relationship between the initial PERT dose (grouped into 250 LU/kg/largest meal intervals) and the mean change in W/L%. However, it is clear from the figure that an increase in initial PERT dose was associated with an increased attainment in W/L% up to the 1750–2000 LU dosing interval, and when the regression was limited to patients

who received a PERT dose <2000 LU/kg/largest meal, the *p* value was 0.004 for simple regression and was 0.006 for multiple regression models.

As shown in Supplemental Digital Content Table 3, 56.4% of patients whose initial PERT dose was ≥1500 LU/kg/largest meal showed a W/L% change ≥10% at their last measurement in 2012, compared with 48.1% of those with a lower initial PERT dose (p=0.093). The adjusted OR of finishing in 2012 with a W/L% change ≥10% was 1.40 in the high-dose compared with the low-dose groups (95% CI: 0.93–2.11, p=0.107). On the other hand, 30.7% of patients in the high-dose group compared with 20.7% in the low-dose group were in the top quartile for change in W/L% (an increase of 40%) in 2012 (p=0.018). Patients receiving a PERT dose ≥1500 LU/kg/largest meal had an adjusted OR of 1.83 (95% CI: 1.15–2.90, p=0.011) for achieving a change in the top quartile of W/L% compared to the patients whose dose was <1500 LU/kg/largest meal. Similar findings were obtained when comparing infants who had been started on ≥1750 LU/kg/largest meal with those started on <1750 LU/kg/largest meal, but neither logistic models attained statistical significance (OR=1.47, CI: 0.89–2.41, p=0.130 for a 10% increase in W/L%; OR=1.60, CI: 0.92–2.77, p=0.096 for a 40% increase in W/L%).

As in the WAZ analysis, the W/L% analysis was also repeated for a restricted population of 348 patients who were started on PERT before the third month of life. Again, the findings in this group were similar to those seen in the entire cohort (Supplemental Digital Content Figure 3).