



### eCysticFibrosis Review VOLUME 5, ISSUE 7

## Optimizing Nutrition in People with Cystic Fibrosis



### In this Issue...

One of the keys of appropriate cystic fibrosis (CF) care involves good nutrition. An excellent nutritional status in people with CF improves outcomes and decreases the risk of mortality. In this issue, we review recent articles from the medical literature which address the importance of nutrition in CF care, including:

- Research on pancreatic enzyme replacement therapy (PERT) dosing in relation to pediatric CF body mass index (BMI)
- New methods for evaluating protein malabsorption in people with CF
- How BMI affects health-related quality of life in children with CF
- Recent research as to how BMI, as well as other factors, can predict mortality in adolescents with CF
- The effectiveness of appetite stimulants as a modality of CF nutrition care

#### Program Information

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#### Length of Activity

- 1 hour Physicians
- 1 contact hour Nurses

#### Release Date

May 21, 2015

#### Expiration Date

May 20, 2017

## LEARNING OBJECTIVES

**After participating in this activity, the participant will demonstrate the ability to:**

- Explain how appropriate pancreatic enzyme replacement therapy (PERT) dosing is associated with an improved body mass index (BMI) as well as improved protein and fat absorption in people with cystic fibrosis (CF).
- Summarize how health-related quality of life (HRQOL) is improved in people with CF who have a good nutritional status, and why a low BMI is a risk factor for increased mortality in adolescents with CF.
- Assess the current evidence describing the use of appetite stimulants to improve weight gain in people with CF.

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## COMMENTARY

Providing good nutrition is a pillar of cystic fibrosis (CF) care as malnutrition is associated with a worse clinical prognosis, including a more rapid decline in pulmonary function.<sup>1</sup> Considering this aspect of clinical care as background, five recent articles have been chosen to represent new knowledge in the setting of CF and nutrition. We have reviewed articles looking at pancreatic enzyme replacement therapy (PERT) dosing in relation to body mass index (BMI) in children with CF, the oft-missed consideration of protein malabsorption in those with CF, health-related quality of life (HRQOL) in CF specifically related to nutritional status, prognostic markers of mortality in adolescents with CF (which include low BMI), and the potential use of appetite stimulants in relation to CF nutrition care.

Haupt et al evaluated PERT dosing in relation to CF BMI. One hundred seventy-nine United States CF programs that entered data into the national [CF Foundation Patient Registry](#) were divided into quartiles based on BMI. A significant difference in PERT dosing existed between top and bottom CF quartile centers for BMI, suggesting that PERT dosing should be followed closely for all those with CF, especially for children with CF who should be expected to have good gain weight as they grow. The authors do point out that high-performing centers were more likely to have more patients with CF diagnosed by newborn screening, were more likely to use supplemental feeding by nasogastric or gastrostomy access, and were more likely to

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use acid blockade therapy (such as proton pump inhibitors) to potentially enhance PERT efficacy. Thus, it could be argued that high-performing centers were more likely to meticulously follow nutritional outcomes. As always, care should be taken to make sure PERT dosing is not more than 10,000 units lipase/kg/day or 2500 units lipase/kg/meal to prevent fibrosing colonopathy, and frequent review of PERT dosing should occur in patients with CF by members of the CF care team to prevent risk of malnutrition.<sup>2</sup>

Engelen et al used a unique method for determining protein malabsorption in patients with CF, a nutritional issue not always considered in their care. Specifically, the ratio of serum levels of <sup>15</sup>N-labeled spirulina protein (broken down to <sup>15</sup>N-labeled phenylalanine) and <sup>2</sup>H<sub>5</sub>-labeled phenylalanine was measured every 20 minutes as patients underwent a six-hour feeding protocol with an enteral formula commonly used in CF care. PERT dosing was given two hours into the feeding protocol. Protein malabsorption was significantly reduced in patients with CF compared to a healthy control group, although protein absorption in the patients with CF improved to levels close to those of controls with use of PERT. Citrulline (a nonessential amino acid produced by enterocytes) levels were not significantly different between CF and control subjects, suggesting normal gut mucosal function in patients with CF.<sup>3</sup> Thus, while protein digestion appears to be impaired in people with CF, this defect can probably be reversed with PERT. This technique of determining protein absorption may be able to answer further questions about CF protein absorption. For example, this study brings up the intriguing question about whether growth hormone (which has been shown to reverse a protein catabolic state in people with CF) may also improve protein absorption.<sup>4</sup> Proton pump inhibitor (PPI) use did not improve protein absorption in those with CF; however, only a small number of CF patients in the study were not on a PPI, and more data is needed to answer questions about the effectiveness of PPI therapy for enhancing weight gain. Finally, longer duration of enteral feeding using various techniques (such as oral versus gastrostomy feeding), various times in which PERT is given, and other aspects of feeding must be studied to see how protein absorption in patients with CF occurs in a 24-hour setting. This study is a good first step toward answering such questions.

Shoff et al studied HRQOL in children with CF in relation to their nutritional status. HRQOL questionnaires are based on item-response theory, which is a way of modeling using scale responses to single-item questions to determine a symptom response of a patient with a disease process compared to a control group.<sup>5</sup> This study used patients from the Wisconsin Randomized Clinical Trial of CF Newborn Screening, in which all study subjects underwent annual HRQOL testing for three years using the Cystic Fibrosis Questionnaire tool. Improved dimensions of physical functioning and body image were improved as height z-scores and BMI z-scores increased. Physical functioning and body image dimensions significantly improved with higher weight z-scores. HRQOL scores were categorized as "mostly low," "mostly good," and "perfect" to prevent any potential statistical ceiling effect, and a Cystic Fibrosis Questionnaire score consistent with "mostly low" was seen between short stature and an eating disturbance as well as between a BMI below goal and body image. It should be pointed out that this study occurred in one region of the midwestern United States, and it is unknown if findings are replicable nationally or internationally. Also, the authors state that the categories ("mostly low", etc.) have not been validated in other studies, so it is somewhat unclear if these categories closely match scoring of the Cystic Fibrosis Questionnaire. However, this study does suggest the HRQOL is impaired in children with CF simply as a result of poor nutrition and resultant downstream effects such as body image.

Hulzebos et al tried to determine whether mathematical modeling could predict risk of mortality in adolescents with CF. A multivariate model to determine risk of mortality included cardiopulmonary exercise testing using a cycle ergometer (CPET), resting lung function, and nutritional status (BMI). Univariate analysis demonstrated that FEV<sub>1</sub>%<sub>predicted</sub> breathing reserve (calculated from results of the ergometer), BMI, and peak aerobic activity were significantly associated with an increased risk of mortality. A multivariate analysis model of three risk factors, including FEV<sub>1</sub>%<sub>predicted</sub>, peak ventilatory equivalent ratio, and BMI, was predictive of mortality. Adolescents with CF with two or three risk factors from the multivariate model had a significantly increased risk of mortality. Those with three risk factors had a significantly greater risk of mortality than patients with only one or two risk factors. Although these results make sense clinically, the findings are based on a modeling study, and multivariate analysis can potentially oversimplify results by decreasing the number of variables to obtain simpler results. The authors acknowledge that *Pseudomonas aeruginosa* infection can increase mortality; however, they did not include infection risk because of a strong correlation found with the peak ventilatory equivalent ratio for oxygen in the model for

predicting mortality.<sup>6</sup> Other infections known to increase mortality, such as *Burkholderia cepacia*, were not considered in this model.<sup>7</sup>

Finally, Chinuck et al evaluated the effectiveness of appetite stimulants as a therapeutic option for CF nutrition care. This study was done as a Cochrane analysis, and as is often the case in such studies, minimal data were available for evaluation. Three studies involving appetite stimulants were placebo-controlled, with one study using cyproheptadine hydrochloride and two studies using megestrol acetate. When the studies were combined, appetite stimulant use was significantly associated with increased mean weight at three and six months, while weight z-score showed a significant improvement at three months. Side effects were minimal. The authors conclude that these two appetite stimulants may be a helpful short-term option in improving appetite and weight in individuals with CF; however, there are no long-term data. Further, there are still no good data for other appetite stimulants such as dronabinol or mirtazapine. Finally, side effects of appetite stimulants are still not fully understood. As an example, megestrol acetate has been associated with life-threatening adrenal insufficiency, although data on this side effect is limited to case reports.<sup>8</sup>

These studies suggest that we still have much to learn in the realm on nutrition care for patients with CF. There appears to be a correlation between appropriate PERT use and improved nutrition in patients with CF as evidenced by BMI outcomes, and there are data showing that good BMI improves HRQOL and reduces the risk of mortality in children with CF. It is unclear if appetite stimulant use is an effective medical adjunct therapy for improving nutrition in the CF population. Longitudinal, long-term studies are needed to clarify these issues.

#### Commentary References

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8. Li J and Winkler M. [Decompensated septic shock in the setting of megace-induced severe adrenal suppression in an otherwise healthy pediatric patient: a case report](#). *Pediatr Emerg Care* 2012; 28: 802-804.

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## APPROPRIATE PANCREATIC ENZYME DOSING AND OUTCOMES IN CF

Haupt M, Kwasny M, Schechter M, et al. Pancreatic enzyme replacement therapy dosing and nutritional outcomes in children with cystic fibrosis. *J Pediatr*. 2014;164:1110-1115.



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Pancreatic enzyme replacement therapy (PERT) for the treatment for exocrine pancreatic insufficiency (PI) is one of the cornerstones of cystic fibrosis (CF) nutrition care. The Cystic Fibrosis Foundation (CFF) recommends providing PERT dosing below 10,000 lipase units/kg/day to prevent the complication of fibrosing colonopathy. However, there is wide

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variation of dosing below this level, and the effect of these PERT dosing variations on nutritional outcomes is unknown. In this study, the authors analyzed pediatric data from the CFF Patient Registry from 2005-2008 (the CFF patient registry began to record pancreatic enzyme dosing in 2005). Multiple factors, including PERT dosing, patient demographics, pulmonary function testing, and respiratory culture results, as well as long-term growth and nutrition data, were recorded. Mean body mass index (BMI) for each center was divided into quartiles for comparison.

A total of 14,482 children from 179 pediatric CF programs were included in the analysis. Statistical differences were seen between the highest and lowest quartile programs for BMI. Specifically, patients in the top quartile programs were younger (although age at diagnosis was not different between quartiles), had fewer diagnoses of failure to thrive or malnutrition, fewer diagnoses of meconium ileus, and less history of steatorrhea. Top quartile programs also were more likely to have diagnosed CF by newborn screening and demonstrated better lung function testing results, such as forced expiratory volume in one second percent predicted ( $FEV_1\%_{\text{predicted}}$ ). Nutritional supplementation (such as nasogastric or gastrostomy use) and acid blockade medication use was higher in top-quartile centers. Interestingly, statistically more patients in top-quartile centers had a history of bone fractures and gastroesophageal reflux, while bottom-quartile centers were more likely to have patients with CF-related diabetes and osteoporosis.

Pancreatic enzyme dosing was significantly higher ( $P < 0.001$ ) in top-quartile centers (mean enzyme dosing 1755 lipase units/kg/meal; 95% CI 1722, 1788) compared to the lowest-quartile centers (mean enzyme dosing 1628 lipase units/kg/meal; 95% CI 1595, 1660). Multivariate analysis demonstrated that this difference remained significant even after adjustment of covariates. This study does show that many factors are different between top and bottom BMI quartile centers that could influence findings (such as newborn screening); however, the significant difference in PERT dosing likely plays a role in BMI differences between centers. Additionally, PERT dosing differences between centers may simply be a proxy marker for centers that provide more aggressive CF care. It is unknown if there is an optimum PERT dose for children with CF, but lower dosing likely affects BMI in the pediatric age range. Obviously, PERT dosing greater than 10,000 lipase units/kg/day or greater than 2500 lipase units/kg/meal is associated with an increased risk of significant dangerous side effects, including fibrosing colonopathy, and PERT dosing at such high levels is not recommended.

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## PROTEIN DIGESTION IN CF

Engelen M, Com G, Anderson P, et al. New stable isotope method to measure protein digestibility and response to pancreatic enzyme intake in cystic fibrosis. *Clin Nutr*. 2014;33:1024-1032.



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When we think about cystic fibrosis (CF), we often think about fat malabsorption due to associated exocrine pancreatic insufficiency. However, people with CF are also at risk of a negative nitrogen balance due to protein malabsorption, although testing for protein malabsorption is difficult to perform. The authors of this study evaluated a novel method of testing for protein malabsorption as a marker of pancreatic protease function. Specifically, subjects were given a meal with  $^{15}\text{N}$ -labeled spirulina protein (a protein from blue-green algae) and  $^2\text{H}_5$ -labeled phenylalanine. The proteolytic breakdown product of  $^{15}\text{N}$ -labeled spirulina is  $^{15}\text{N}$ -labeled phenylalanine and can be compared to the  $^2\text{H}_5$ -labeled phenylalanine, which is not broken down by pancreatic proteases. This ratio determination testing is not affected by phenylalanine metabolism.

Nineteen study subjects (10 children and nine adults with CF) and eight healthy control subjects were evaluated for this study, with a majority of the patients with CF admitted to the hospital for a pulmonary exacerbation. The homozygous F508del *CFTR* mutation was present in 90% of the children and 25% of the adults with CF. Subjects received standard formula often used in CF nutrition care given over six hours either by the oral or gastrostomy route



with the addition of  $^{15}\text{N}$ -labeled spirulina and  $^2\text{H}_5$ -labeled phenylalanine. Pancreatic enzyme replacement therapy (PERT) dosing occurred two hours into the feeding regimen of subjects with CF. Protein digestion was calculated by the  $^{15}\text{N}$ -labeled spirulina/ $^2\text{H}_5$ -labeled phenylalanine ratio, and these protein levels were obtained every 20 minutes after feeds were started. Additionally, citrulline levels were obtained during the study after a pulse dose of L-[5- $^{13}\text{C}$ -2H $_2$ ]-citrulline to determine intestinal mucosal function.

Mean body mass index (BMI) was not different between adults with CF and the control group, although three adults and three children with CF were in nutritional failure. Control subjects were able to break down approximately 80% of the spirulina protein, which is considered normal for protease function. However, the patients with CF had significantly lower protease function, measured at 46.5% of control function ( $P < 0.001$ ). After PERT use in subjects with CF, spirulina protein absorption increased to 90.3% of control absorption with a maximum digestion time of 80 minutes. No significant difference was seen in protein digestion between adult and pediatric subjects with CF, and no significant difference in protein digestion was noted between those with CF, regardless of F508del mutation status, history of nutritional failure, or lung function. No difference was seen in protein absorption in the subjects with CF, regardless of proton pump inhibitor use, although the number of subjects with CF who were not using proton pump inhibitors was small ( $n = 3$ ). Plasma citrulline levels were not significantly different between control and patients with CF, suggesting normal gut mucosal function in subjects with CF.

This study demonstrates that protein malabsorption can be measured in people with CF, and importantly, protein absorption is low in this patient population, although malabsorption can be corrected with PERT.

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## NUTRITION STATUS IN PEDIATRIC CF AFFECTS QUALITY OF LIFE

Shoff S, Tluczek A, Laxova A, et al. Nutritional status is associated with health-related quality of life in children with cystic fibrosis aged 9-19 years. *J Cyst Fibros.* 2013;12:746-753.



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Ensuring good quality of life is essential in the care of people with cystic fibrosis, and patient-reported outcome studies to determine health-related quality of life (HRQOL) are important in determining how well such people perceive their well-being. This study evaluated children with CF who were being followed over time through the Wisconsin Randomized Clinical Trial of CF Newborn Screening. Ninety-five children (age range 9-19 years) underwent HRQOL testing using the Cystic Fibrosis Questionnaire, applied annually by interview or self-administration for three years during regular clinic visits. Validated questions covered seven domains of HRQOL: physical functioning, respiratory symptoms, social functioning, emotional functioning, treatment burden, body image, and eating disturbances. Scores for each domain were scored from 0 to 100, with higher scores demonstrating better HRQOL. Exocrine pancreatic status and history of meconium ileus were determined for each patient, and anthropometric parameters — including body mass index (BMI) z-scores and percentile (for age and gender), weight z-score and percentile, and height z-score and percentile — were calculated during the clinic visits in which the Cystic Fibrosis Questionnaire was used.

The mean age when the Cystic Fibrosis Questionnaire was first used was 13.5 years. Mean BMI, weight, and height did not change throughout the study. Short stature was noted in 12% of patients (defined as height percentile less than the 5th percentile), while 8% of patients were underweight (defined as BMI percentile less than the 10th percentile). BMI was less than the 50th percentile (recommended goal of the CF Foundation) in 53% of patients. Exocrine pancreatic insufficiency was present in 63% of patients, while 21% of patients had a history of meconium ileus. In general, dimension scores were high except for respiratory symptoms scoring, which was probably low because of inherent pulmonary issues related to CF. Cystic Fibrosis Questionnaire scores did not change significantly during the study duration.

Patients with a history of meconium ileus were significantly more likely to have "mostly low" scores (scores  $< 66$ ) for physical functioning ( $P = 0.04$ ) and treatment burden ( $P = .001$ )



compared to other patients with CF. Both height z-scores and BMI z-scores showed a significantly positive association with physical functioning ( $P = .02$  for both measurements) and body image ( $P = .02$  for both measurements). In other words, physical functioning and body image dimensions improved as height z-scores and BMI z-scores increased. A positive weight z-score association was seen with physical functioning ( $P = .02$ ) and body image ( $P = .009$ ). Girls showed a positive association between height z-score and eating disturbances ( $P = .008$ ) but not BMI z-score, as well as a positive association between physical functioning and height z-score ( $P = .004$ ) and BMI z-score ( $P = .04$ ). Boys demonstrated a positive association between body image and height z-score ( $P = .03$ ). Finally, the odds ratio of reaching a "mostly low" Cystic Fibrosis Questionnaire score was seen between short stature and eating disturbances (OR=4.08, 95% CI=1.20-13.79,  $P = .02$ ) as well as between being below a goal BMI and body image (OR=2.67, 95% CI=1.19-6.01,  $P = .02$ ).

This study suggests that HRQOL improves with good nutritional status, and early intervention directed at improving nutritional status may prevent a decline in HRQOL in children with CF over time.

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## CAN WE PREDICT MORTALITY IN ADOLESCENT CF PATIENTS?

Hulzebos E, Bomhof-Roordink H, van de Weert-van Leeuwen P, et al. Prediction of mortality in adolescents with cystic fibrosis. *Med Sci Sports Exerc.* 2014;46:2047-2052.



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As mean life expectancy increases for adolescents with cystic fibrosis, it becomes essential to determine which patients are at highest risk of early mortality. The authors of this study looked at a multivariate model to determine risk of mortality in adolescents with CF, including parameters of cardiopulmonary exercise testing (CPET), resting lung function, and nutritional status.

This study occurred at an academic CF medical center in the Netherlands and included 127 patients with a mean age of 12.7 years (age range 11-14). At a clinic visit in which patients were not having a pulmonary exacerbation, body mass index (BMI) and  $FEV_1\%_{\text{predicted}}$  were calculated in study subjects. CPET was determined by the Godfrey protocol using a cycle ergometer, where patients pedaled on the ergometer to reach a heart rate greater than 180 beats per minute while maintaining a pedaling rate of 50 rpm. Gas analysis was taken through a breathing mask to document oxygen and carbon dioxide exchange. Peak aerobic activity (defined as peak oxygen uptake corrected for body weight) and peak minute ventilation were recorded over the last 30 seconds of the test, corrected for body weight, and expressed as a percentage of predicted values compared to values in healthy adolescents. A peak ventilatory equivalent ratio for oxygen was defined as the ratio of peak minute ventilation to peak aerobic activity.

Mean follow-up time for the patient group was  $7.5 \pm 2.7$  years, during which time nine patients died (7.1%) and six patients required lung transplant (4.7%). Univariate analysis using Cox proportional hazard ratios revealed that  $FEV_1\%_{\text{predicted}}$ , breathing reserve (calculated from results of the ergometer), BMI, and peak aerobic activity expressed as a percentage of predicted values were significantly associated with risk of mortality. A multivariate analysis demonstrated that a model of  $FEV_1\%_{\text{predicted}}$ , peak ventilatory equivalent ratio, and BMI was predictive of mortality. The study group subsequently was evaluated longitudinally by Kaplan-Meier analysis looking at these three risk factors. Patients with two or three of these risk factors had a significant risk of mortality ( $P < .001$ ), and patients with three risk factors had a significantly greater risk of mortality compared to patients with one or two risk factors ( $P < .001$ ).

This study suggests that modeling risk factors — including  $FEV_1\%_{\text{predicted}}$ , peak ventilatory equivalent ratio, and BMI — can be helpful in identifying children with CF who are at risk of dying, as well as identifying those patients who will require extra medical resources to prevent progression of their disease.

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# APPETITE STIMULANTS AND CYSTIC FIBROSIS

Chinuck R, Dewar J, Baldwin D, et al. Appetite stimulants for people with cystic fibrosis. *Cochrane Database Syst Rev.* 2014;7:CD008190.



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Maintaining body mass index (BMI) is imperative in the care of individuals with cystic fibrosis. It is not uncommon for appetite stimulants such as cyproheptadine hydrochloride (an antihistamine with anticholinergic and antiserotonergic properties) and megestrol acetate (a progesterone derivative) to be used in the CF population to improve weight gain.

However, the long-term efficacy of these medications is unknown. This Cochrane analysis evaluated studies in which these two specific appetite stimulants were compared to placebo or a control group, with at least one month's duration of medication use. Although 108 potential studies were identified initially, most studies were excluded because appetite stimulants were used for conditions other than CF, or medications were used in animal studies. Only three studies (all randomized, controlled trials) fit criteria for evaluating appetite stimulant use in children and adults with CF. One study had a crossover design, while the other two had a parallel design. Additionally, one study was limited to children with CF, while the other two studies combined pediatric and adult patients with CF. All studies were placebo-controlled, with one study evaluating cyproheptadine hydrochloride and two studies evaluating megestrol acetate.

The appetite of study subjects improved in two studies, while one study noted a change in dietary intake. Two studies noted that body weight improved on study medication and one study (using megestrol acetate) noted a significant improvement of forced expiratory volume in one second percent predicted ( $FEV_1\%_{\text{predicted}}$ ) at 2, 3, and 6 months ( $P < .04$ ). Two studies noted an improvement in quality of life (QOL) associated with less fatigue. When these three studies were combined, appetite stimulant use was significantly associated with increased mean weight at three months (3 kg, 95% CI 0.92 to 5.08) and six months (3.8kg, 95% CI 1.27 to 6.33). Weight z-score for all studies showed a significant improvement at three months, as well (0.61, 95% CI 0.29 to 0.93). The studies did not have enough information to determine a change in body composition, such as changes in fat mass. Side effects were minimal. Fatigue was reported in some patients taking cyproheptadine hydrochloride, while megestrol acetate was associated with a significant decrease in morning cortisol levels (although no loss of bone mineral density was noted during the study duration of megestrol acetate use).

The authors of this Cochrane review state that few high-quality trials addressing appetite stimulant use are available. Randomization of study subjects to medication or placebo was poorly explained in the three included studies, and risk of bias was graded as "moderate." Appetite stimulant use may be helpful in improving weight gain in the short-term care in individuals with CF; however, long-term outcomes are unknown.

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#### STATEMENT OF NEED

Based on a review of the current literature, including national and regional measures, detailed conversations with expert educators at Johns Hopkins, and a survey of potential program participants, this program will address the following core patient care gaps:

##### Disease-Modifying Therapies

- Clinicians need guidance in understanding how new findings describing CFTR-modifying therapies may improve their treatment of patients with cystic fibrosis.
- Incomplete clinician awareness of genotype/phenotype correlations in non-pulmonary targets of CFTR-modifying therapies may limit their ability to provide optimal patient care.

##### Nutrition

- Clinicians lack effective guidance to increase caloric intake in patients who are nutritionally compromised.
- Clinicians do not fully understand how to manage the complexities of pancreatic enzyme replacement therapy to achieve optimal results in their patients.

##### *Pseudomonas Aeruginosa*

- Clinicians have unanswered questions about *P. aeruginosa* eradication in asymptomatic patients with positive cultures.
- New data and new choices for selecting initial inhaled anti-pseudomonal agents have created confusion.
- Conflicting data about pulmonary exacerbations has led to incorrect clinical assumptions and inappropriate treatment regimens.

This activity is supported by educational grants from AbbVie, Gilead Sciences, Inc, and Vertex Pharmaceuticals Incorporated.

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