

## Perspectives in Practice

# Evidence-Based Practice Recommendations for Nutrition-Related Management of Children and Adults with Cystic Fibrosis and Pancreatic Insufficiency: Results of a Systematic Review

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**ABSTRACT**

The Cystic Fibrosis Foundation established a process of systematic review of evidence to inform the development of clinical care guidelines and encourage evidence-based practice. The Subcommittee on Growth and Nutrition reviewed the evidence in two areas: energy intake and dosing for pancreatic enzyme replacement therapy. Evidence-based recommendations are presented here. Also, an ad hoc working group conducted a review of the literature and performed new analyses using the Cystic Fibrosis Foundation Patient Registry to update the recommendations for growth and weight-status monitoring. These Registry data-based recommendations are presented.

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Optimization of growth and nutritional status is essential for effective treatment of individuals with cystic fibrosis (CF). According to the 2005 CF Foundation Patient Registry Report (1) 23% of children are below the 10th percentile weight-for-age and sex and 22% of adults (aged 18 to 30 years) are underweight with a body mass index (BMI) <18.5 (2). Therefore, nutritional and growth status monitoring and management are vital to CF health care. Achieving and maintaining normal weight for adults and normal patterns of growth for children with CF requires management of gastrointestinal and pulmonary symptoms, nutrient and energy intakes, and psychosocial and financial issues. Malnutrition results from a discrepancy between energy and micronutrient requirements and food intake modified by malabsorption (3,4).

Currently the clinical guidelines for nutrition management for individuals with CF are consensus-based. For children, these 2002 guidelines (5) provide recommendations for identifying individuals at-risk for and those in nutrition failure, utilizing weight, stature, and weight-for-stature anthropometric measurements and associated reference standards. However, in clinical practice, this approach was difficult to use and often resulted in inconsistent patient nutritional risk classifications. The use of percent ideal body weight was especially problematic. For adults, nutrition screening status and treatment recommendations are presented in the 2004 CF Adult Care Consensus Report (6). Although the efficacy of pancreatic enzyme replacement therapy (PERT) to improve fat absorption due to pancreatic insufficiency (PI) is supported by the evidence base, recommendations for the PERT dose for patients are consensus-based (5,7). Seeking to encourage evidence-based practice, the CF Foundation set out to determine whether the consensus recommendations have evidence-based support and whether energy intake and PERT dosing recommendations could be updated based on the evidence currently available. The CF Foundation established the Clinical Practice Guidelines Growth and Nutrition Subcommittee of experts in the related disciplines. The Subcommittee developed a series of questions related to energy intake and PERT for children and adults with CF and PI. A systematic review of evidence was conducted to inform the guideline development process. Four specific questions were addressed:

- What is the evidence of a relationship between energy intake and nutritional and growth status? For this report, nutritional and growth status included weight, stature, and weight-for-stature.
- What is the evidence that nutritional and growth status is associated with health outcomes?
- What is the evidence for an association between the dose of PERT and the coefficient of fat absorption (CFA), and nutritional and growth status?
- What is the evidence for the effect of using generic rather than name brand PERT on the CFA and on nutritional and growth status?

In addition, the Subcommittee recognized the need to revise the recommendations for growth and weight monitoring. Therefore, the Subcommittee established the Ad Hoc Working Group to complete a review of the literature, conduct new analyses using the 2005 CF Foundation Patient Registry (1), and prepare a report with CF Foundation Patient Registry data-based recommendations. In this review process it is important to note that when evidence-based recommendations could not be made, it indicated that the needed studies have not been conducted, and, thus, there was insufficient evidence to make a recommendation. The Working Group recommendations were reviewed and approved by the Subcommittee and are presented as part of this report.

## METHODS

Investigators at Johns Hopkins University conducted a systematic review in spring 2005 to assist the Subcommittee in making recommendations. English-language articles published from January 1988 to February 2005 reporting studies addressing the questions were identified for review. Searches were conducted in PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, PASCAL, Allied and Complementary Medicine, and Agricultural On-line Access. Bibliographies of eligible articles and review articles were also examined. Two reviewers screened each article at the abstract and then full-text level for eligibility. A total of 1,008 publications were reviewed and resulted in 57 eligible publications addressing questions pertaining to energy intake and 10 eligible publications for PERT. Evidence tables were created and a report drafted for the Subcommittee to use to develop recommendations. The evidence base for each recommendation was graded using the system developed by the US Preventive Services Task Force (8) as described in Figures 1 and 2. The Subcommittee carefully considered the evidence identified and prepared the report of the evidence-based finding.

### Evidence Summary and Recommendations for Clinical Care

Each question selected for evidence-based review is presented and followed by a brief summary of the findings. Overall evidence for each of the four questions was rated as fair and the estimate of net benefit was moderate (8).

**What Is the Evidence of a Relationship Between Energy Intake and Nutritional Status?** The Subcommittee found good evidence from prospective and retrospective cohort studies, includ-

- The USPSTF strongly recommends that clinicians provide [the service] to eligible patients. The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.
- The USPSTF recommends that clinicians provide [the service] to eligible patients. The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.
- The USPSTF makes no recommendation for or against routine provision of [the service]. The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.
- The USPSTF recommends against routinely providing [the service] to asymptomatic patients. The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.
  - The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. Evidence that [the service] is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

**Figure 1.** US Preventive Services Task Force (USPSTF) evidence grades for evidence-based recommendations. The USPSTF grades its recommendations based on the strength of evidence and magnitude of net benefit (benefits minus harms).

ing within-subject design and randomized clinical trials, that higher energy intake resulted in improved weight gain. Evidence was lacking that demonstrated higher energy intake resulted in improved stature (9-28).

**Recommendation.** For children older than age 2 years and adults, the CF Foundation recommends energy intakes greater than the standard for the general population to support weight maintenance in adults and weight gain at an age-appropriate rate in children. Improved weight status has been found at intakes ranging from 110% to 200% of energy needs for the healthy population of similar age, sex, and size. (B recommendation)

To achieve energy intakes of 110% to 200% of requirements for the healthy population, the CF Foundation makes the following recommendations for patients with CF:

**Recommendation.** For children aged 1 to 12 years with growth deficits, the CF Foundation recommends that intensive treatment with behavioral intervention in conjunction with nutrition counseling be used to promote weight gain. (B recommendation)

**Recommendation.** For children with growth deficits and adults with weight deficits, the CF Foundation recommends the use of nutritional supplements (oral and enteral) in addition to usual dietary intake to improve the rate of weight gain. (B recommendation)

For children aged 13 years and older with growth deficits and for adults with weight deficits, the CF Foundation has insufficient evidence to make a recommendation regarding intensive treatment with behavioral intervention in conjunction with nutrition counseling to promote weight gain.

Strength of overall evidence of effectiveness	Estimate of Net Benefit			
	Substantial	Moderate	Small	Zero/negative
Good <sup>a</sup>	A <sup>b</sup>	B <sup>c</sup>	C <sup>d</sup>	D <sup>e</sup>
Fair <sup>f</sup>	B	B	C	D
Poor <sup>g</sup>	I <sup>h</sup>	I	I	I

<sup>a</sup>Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.  
<sup>b</sup>The USPSTF found good evidence that the service improves important health outcomes and concludes that benefits substantially outweigh harms.  
<sup>c</sup>The USPSTF found at least fair evidence that the service improves important health outcomes and concludes that benefits outweigh harms.  
<sup>d</sup>The USPSTF found at least fair evidence that the service can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.  
<sup>e</sup>The USPSTF found at least fair evidence that the service is ineffective or that harms outweigh benefits.  
<sup>f</sup>Evidence is sufficient to determine effects on health outcomes, but the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes limits the strength of the evidence.  
<sup>g</sup>Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information in important health outcomes.  
<sup>h</sup>The USPSTF concludes that evidence that the service is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

**Figure 2.** A grade for the quality of the overall evidence for a service is determined by the US Preventive Services Task Force (USPSTF) based on the strength of overall evidence and an estimate of net benefit. These grades were used by the Cystic Fibrosis Foundation Subcommittee on Growth and Nutrition to make evidence-based recommendations for the management of cystic fibrosis in children and adults, and by an ad hoc working group to update the recommendation for growth and weight status monitoring.

**What Is the Evidence that Nutritional and Growth Status Is Associated with Health Outcomes?** The Subcommittee found good evidence from population-based studies that normal ranges of weight-for-age, height-for-age, and weight-for-height percentiles were associated with better pulmonary function as indicated by the percent predicted forced expiratory volume in 1 second (FEV<sub>1</sub>) and survival for adults and children (9,11-14,16-18,20,26-55).

**Recommendation.** For children, the CF Foundation recommends maintenance of normal ranges of weight- and stature-for-age, because normal growth status was associated with better FEV<sub>1</sub> and survival. (B recommendation)

**Recommendation.** For adults, the CF Foundation recommends maintenance of normal weight-for-height because this was associated with better FEV<sub>1</sub> and survival. (B recommendation)

For children and adults with nutritional deficits, the CF Foundation has insufficient evidence to make a recommendation about the relationship between improved rate of weight gain following nutritional interventions and improved FEV<sub>1</sub>.

**What Is the Association Between the Dose of PERT and CFA and the Dose of PERT and Growth?** For this review, the CF Foundation was interested in determining whether a

**Average stature** For children in the 25th to 75th percentile height-for-age range, there was little difference in the classification outcome between methods.

**Shorter stature** For children in the <25th percentile height-for-age range, about 3.5 times more shorter children were classified as underweight.

- <90% IBW=7% underweight individuals
- <15th percentile BMI=26% underweight individuals

**Taller stature** For children in the >75th percentile height-for-age range, about 3.5 times fewer taller children were classified as underweight using the BMI percentile method.

- <90% IBW=48% underweight individuals
- <15th percentile BMI=14% underweight individuals

**Figure 3.** Effect of change to classifying underweight status using the body mass index (BMI) percentile method in individuals with cystic fibrosis aged 2 to 20 years compared to using the percent ideal body weight (%IBW) method. Modified with permission from reference 70.

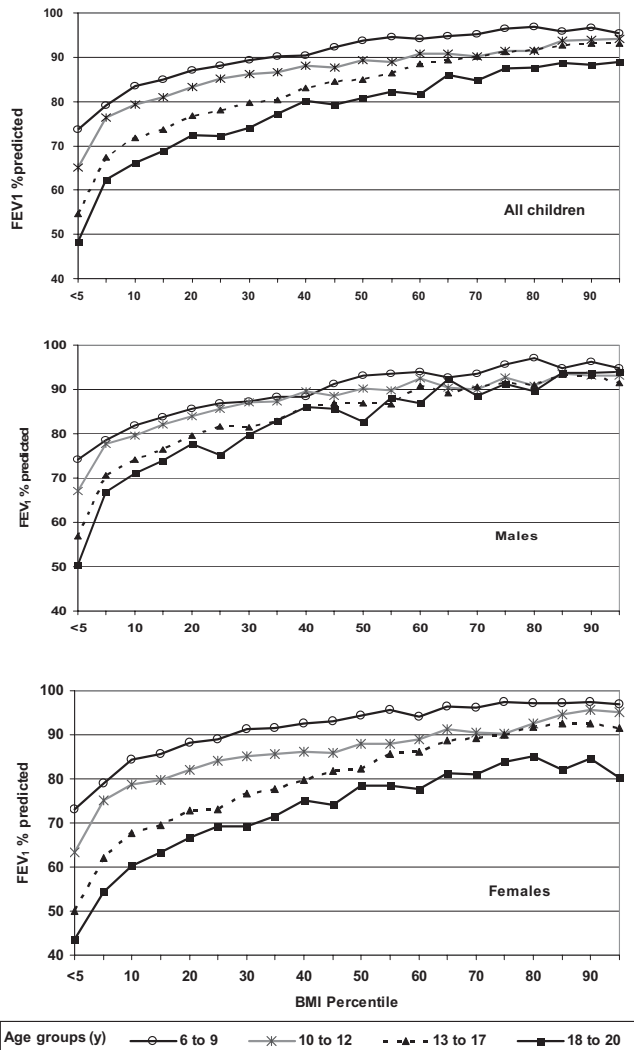
dose-response association exists between PERT and CFA and/or growth. Therefore, only evidence from publications directly comparing different doses of pancreatic enzymes was included. Articles reporting pancreatic enzyme doses compared to placebo were not included because PERT efficacy is well established. There were no studies on PERT dosing in relation to the macronutrient content (ie, fat, protein, and carbohydrate) of typical diets as study protocols require a high-fat diet for the CFA methodology. Using these criteria there was insufficient evidence to make a recommendation regarding the association of specific PERT dosing and CFA or growth (56-62). In a limited number of individuals, decreasing PERT from higher levels to levels within the current recommended dosing ranges as defined in the consensus conference (5) was associated with either an improvement or no adverse effect on weight status (63-65).

**Recommendation.** For children and adults, the CF Foundation has insufficient evidence to amend the existing guidelines regarding PERT dosing and the CFA or growth response, and, therefore, recommends that the current consensus-based guidelines be used for care (7). These include: 500 to 2,500 units lipase per kilogram body weight per meal; or <10,000 units lipase per kilogram body weight per day; or <4,000 units lipase per gram dietary fat per day.

**What Is the Effect of Using Generic Compared to Name-Brand Pancreatic Enzyme Preparations on CFA and Growth?** There was insufficient evidence to support efficacy of generic pancreatic enzyme preparations (61).

**Recommendation.** For children and adults, the CF Foundation has insufficient evidence to make a recommendation about the efficacy of generic pancreatic enzyme preparations and, therefore, recommends the use of proprietary pancreatic enzyme preparations for PERT.

The absence of evidence-based recommendations highlights the need for well-designed studies of both PERT preparations and dosing and important clinical outcome variables.

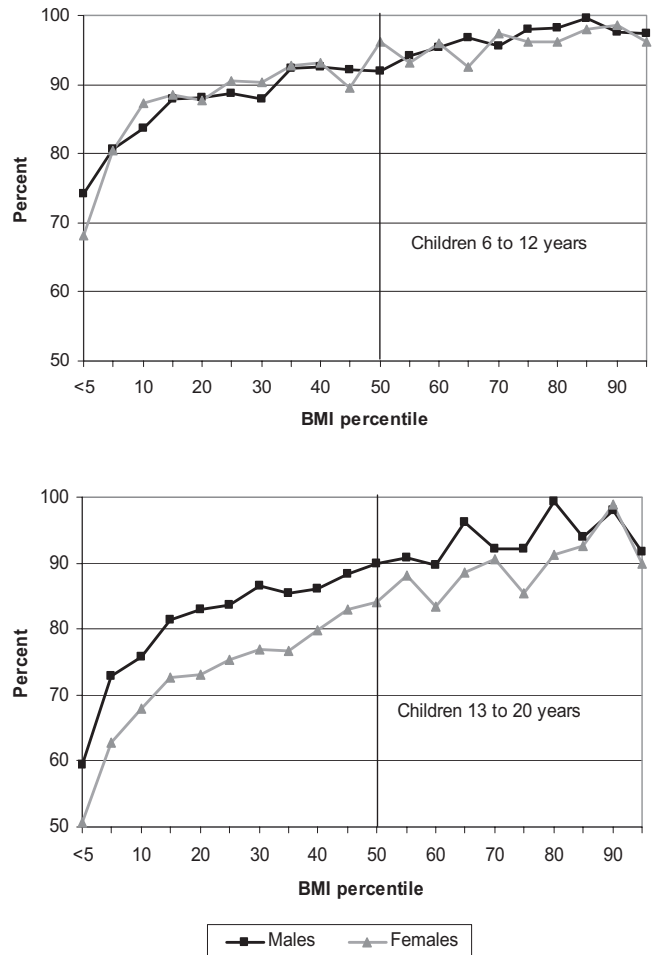


**Figure 4.** Associations of body mass index (BMI) percentile and percent predicted forced expiratory volume in 1 second (FEV<sub>1</sub>) for children (n=9,878) with cystic fibrosis and pancreatic insufficiency by age and sex group, from the 2005 Cystic Fibrosis Foundation Patient Registry. Percent predicted FEV<sub>1</sub> estimated from Wang and colleagues (68) and Hankinson and colleagues (69).

**RECOMMENDATIONS FOR CLINICAL CARE**

**New Analysis for Growth and Weight Monitoring in CF Care**

The Working Group commissioned new analyses from the CF Foundation Patient Registry, reviewed the related literature, and prepared a report with recommendations for monitoring weight in adults and for monitoring growth in children. The 2005 CF Foundation Patient Registry included data from approximately 22,700 patients from 117 CF centers and 48 affiliated programs in the United States, and represents about 75% of the patient population. Each center and affiliate has institutional review board approval to obtain patient- and center-specific clinical data. New analyses were conducted to determine the association of the percent predicted FEV<sub>1</sub> with weight-for-stature status in individuals with CF and PI. The BMI percen-

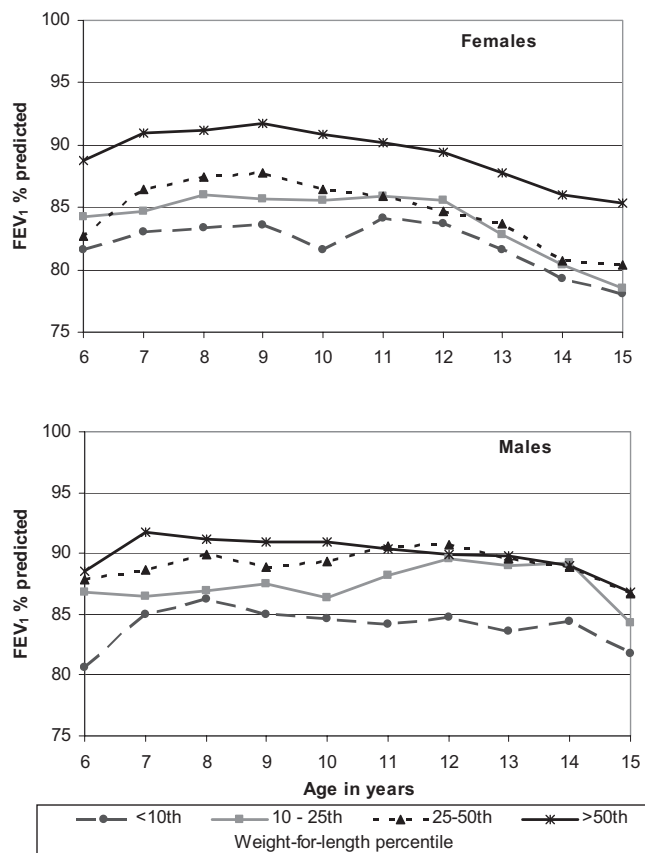


**Figure 5.** Associations of body mass index (BMI) percentile and percent predicted forced expiratory volume in 1 second (FEV<sub>1</sub>) for all children aged 6 to 12 years (n=4,753) and 13 to 20 years (n=5,125) with cystic fibrosis and pancreatic insufficiency by age and by sex, from the 1994 to 2003 Cystic Fibrosis Foundation Patient Registry. Percent predicted FEV<sub>1</sub> estimated from Wang and colleagues (68) and Hankinson and colleagues (69).

tile was the indicator for children aged 6 to 20 years (66), and BMI was the indicator in adults defined as >20 years of age (67). Analyses for children were conducted using the Wang and colleagues (68) pulmonary function reference standard and the Hankinson and colleagues (69) equations were used for adolescents and adults.

**Assessment Method.** The CF care provider community and the Subcommittee recognize the difficulty of using the percent ideal body weight (%IBW) method for weight-for-stature assessments in the clinical setting. In 2005, Zhang and Lai (70) reported a comparison of %IBW and BMI percentile methods using the CF Foundation Patient Registry population (Figure 3). The BMI percentile method was shown to be more sensitive to changes in percent predicted FEV<sub>1</sub> and had a stronger association to percent predicted FEV<sub>1</sub> than %IBW.



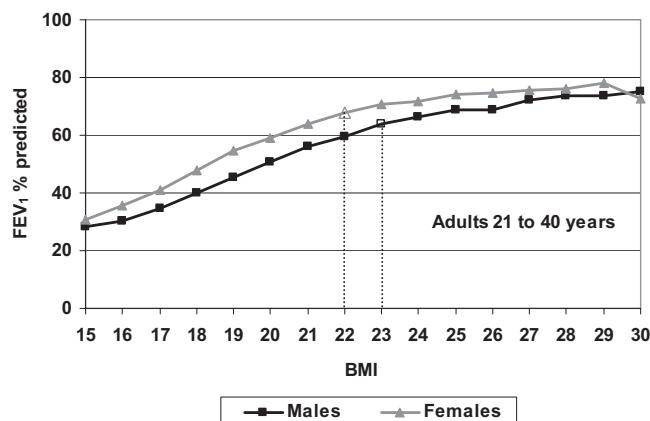


**Figure 6.** Associations in children aged 6 to 15 years (n=4,553) with cystic fibrosis and pancreatic insufficiency of forced expiratory volume in 1 second (FEV<sub>1</sub>) by weight-for-length percentile cohorts classified at age 2 years. Percent predicted FEV<sub>1</sub> estimated from Wang and colleagues (68).

**Recommendation.** For all individuals with CF, the CF Foundation recommends that the age-appropriate BMI method be used to assess weight and height, and that the %IBW method of assessment be discontinued. (Registry data-based recommendation).

**Growth Monitoring in Children.** Figure 4 shows the percent predicted FEV<sub>1</sub> and BMI percentile association in children and adolescents with CF and PI aged 6 to 20 years by birth cohort and by sex based on the 2005 CF Foundation Patient Registry data set. Better FEV<sub>1</sub> status at about 80% predicted or above was associated with BMI percentiles at the 50th percentile and higher. Improving weight-for-stature as indicated by BMI percentile was demonstrated during the past decade. Figure 5 shows these data by sex and separately for two age groups: 6 to 12 years and 13 to 20 years. The BMI 50th percentile reference point is highlighted in each Figure.

**Recommendation.** For children and adolescents aged 2 to 20 years, the CF Foundation recommends that weight-for-stature assessment use the BMI percentile method, and that children and adolescents maintain a BMI at or above the 50th percentile. (Registry data-based recommendation).



**Figure 7.** Associations of body mass index (BMI) and percent predicted forced expiratory volume in 1 second (FEV<sub>1</sub>) for adults aged 21 to 40 years (n=10,585) with cystic fibrosis and pancreatic insufficiency, from the 1994 to 2003 Cystic Fibrosis Foundation Patient Registry. Percent predicted FEV<sub>1</sub> estimated from Hankinson and colleagues (68).

Figure 6 shows the percent predicted FEV<sub>1</sub> and weight-for-length associations for 6- to 15-year-old children with CF and PI based on their cohort status for weight-for-length at age 2 years. These analyses demonstrate the effect of optimizing growth in weight and length following CF diagnosis in patients diagnosed before age 2 years.

**Recommendation.** For children diagnosed before age 2 years, the CF Foundation recommends that children reach a weight-for-length status of ≥50th percentile by age 2 years. (Registry data-based recommendation).

**Weight Monitoring for Adults.** Similar analyses were conducted for adults with CF and PI using CF Foundation Patient Registry data from 1994 to 2003. Figure 7 shows the association of BMI and FEV<sub>1</sub> in adults, and demonstrates that better lung function was associated with higher BMI in both men and women. An FEV<sub>1</sub> ≥60% predicted was associated with a BMI of 22 in women and 23 in men. For the group of adults, there was no evidence of decreased FEV<sub>1</sub> with BMI up to 29. The sample of adults with BMI >29 was small and analyses were not conducted in this BMI range.

**Recommendation.** For adults aged 20 years and older, the CF Foundation recommends that weight-for-stature assessment use the BMI method, and that women maintain a BMI at or above 22, and men maintain a BMI at or above 23. (Registry data-based recommendation).

**Unintentional Weight Loss in Adults.** The effect of unintentional weight loss on pulmonary status or survival in adults with CF and PI has not been directly investigated. The review of limited related literature and of CF Foundation Patient Registry analyses was uninformative.

**Recommendation.** For adults aged 20 years and older, the CF Foundation recommends that unintentional weight loss be avoided. When encountered in patient care, unintentional weight loss should be evaluated in the context of the patient's usual weight and health status. (Consensus-based recommendation)

	Children birth to <2 y	Children 2 to 20 y	Adults >20 y
<b>Evidence-based recommendations</b>			
Routine energy intake as indicated for age and sex (9-28)	Not reviewed <sup>a</sup>	110% to 200% standards for healthy population	110% to 200% standards for healthy population
Combined behavioral and nutrition intervention indicated for weight gain (12,13,22,24)	Recommended for children aged 1 to 2 y	Recommended for age 2 to 12 y; insufficient evidence for age 13 to 20 y <sup>a</sup>	Insufficient evidence for adults <sup>a</sup>
Nutritional supplementation (oral and enteral) intervention indicated for weight gain (9,17,18,21,23,26-28)	Not reviewed <sup>a</sup>	Recommended	Recommended
Optimal ranges of weight-for-age and stature-for-age for children and weight-for-height for adults are indicated to support better FEV <sub>1</sub> <sup>b</sup> and survival (9,11,12-14,17,18,20,26-55)	Not reviewed <sup>a</sup>	Recommended	Recommended
Nongeneric, proprietary pancreatic enzyme preparations are required to ensure efficacy in treating cystic fibrosis-related pancreatic insufficiency <sup>c</sup> (61)	Recommended	Recommended	Recommended
<b>Registry data-based recommendations</b>			
Discontinue use of percent ideal body weight method and incorporate age-appropriate method of assessment of weight-for-stature	Weight-for-length percentile recommended	BMI <sup>d</sup> percentiles recommended	BMI recommended
Maintain growth status for children and weight-for-height status for adults within recommended ranges to support better FEV <sub>1</sub> status	Weight-for-length ≥50th percentile recommended	BMI ≥50th percentile recommended	Woman: BMI ≥22 Man: BMI ≥23
Avoid unintentional weight loss to support better FEV <sub>1</sub> status in adults	—	—	Recommended
After early diagnosis, establish a weight-for-length status of ≥50th percentile by age 2 y to support better FEV <sub>1</sub> status during childhood	Recommended	—	—
<sup>a</sup> If a topic was not reviewed or reviewed and found to have insufficient evidence to make a recommendation, then previous recommendations for children (3) and adults (4) are used for clinical care. <sup>b</sup> FEV <sub>1</sub> =forced expiratory volume in 1 second. <sup>c</sup> Current recommendations for dose of pancreatic enzymes are 500 to 2,500 units lipase per kilogram body weight per meal, or <10,000 units lipase per kilogram body weight per day, or <4,000 units lipase per gram of dietary fat per day. <sup>d</sup> BMI=body mass index.			

**Figure 8.** Summary of recommendations of the Cystic Fibrosis Foundation Subcommittee on Growth and Nutrition and Ad Hoc Working Group for energy intake, pancreatic enzyme replacement therapy, and growth and weight status monitoring in children and adults with cystic fibrosis.

### Current Center-Specific Status

The 2005 center-specific CF Foundation Patient Registry data for BMI percentile for all children by sex, and BMI for all adults by sex was reviewed. This included the 117 CF centers and 48 affiliate programs in the United States. For girls and boys with CF and PI, the all-center median BMI percentile was at the 44th percentile with a 16 to 73 range for girls and 18 to 67 range for boys. Further analyses of the 2005 data found that 43% of girls and 44% of boys in the United States met the recommendation for a BMI ≥50th percentile. When the 2005 adult CF and PI data were examined, the all-center median BMI was 21 (range 18 to 24) for women and 22 (range 19 to 24) for men. Overall, 32% of

women and 35% of men in the United States met the recommendation for a BMI ≥22 or 23, respectively.

### CONCLUSIONS

These guidelines offer evidence-based recommendations for the increased energy intake required to support growth and development for children and weight maintenance in adults with CF and PI, and for improving weight and growth patterns when indicated. Finally, Registry data-based recommendations for the use of BMI for adults and BMI percentile for children for monitoring growth and weight status are provided. Desirable growth patterns in children and weight status in adults were

defined based on the relationship between nutritional and growth status as assessed by BMI percentile or BMI and FEV<sub>1</sub> as the indicator of CF-related lung disease. In cases where insufficient evidence was cited for an evidence-based recommendation, the previously published CF Foundation Pediatric and Adult Consensus Statements continue to provide recommendations for nutrition care (5,6) and the consensus statement on the use of pancreatic enzymes (7) continues to provide recommendations for dosing. Our recommendations are summarized in Figure 8.

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