Development and Validation of the Cystic Fibrosis Questionnaire in the United States*

A Health-Related Quality-of-Life Measure for Cystic Fibrosis

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Background: **The Cystic Fibrosis Questionnaire (CFQ) is a disease-specific instrument that measures health-related quality of life (HRQOL) for adolescents and adults with cystic fibrosis (CF) ≥ 14 years, consisting of 44 items on 12 generic and disease-specific scales. Versions of the CFQ are also available for children with CF and their parents. This study evaluated the psychometric properties of the CFQ in a national study at 18 CF centers in the United States.**
Participants: **The CFQ-teen/adult was administered to 212 patients with CF ranging in age from 14 to 53 years. Test-retest reliability was assessed in a subset of patients over a 10- to 14-day interval.**
Results: **Multitrait analysis indicated a majority of items (95%) correlated more highly with their intended scale than a competing scale, supporting the conceptual model. Internal consistency coefficients indicated the CFQ scales had good reliability (Cronbach $\alpha = 0.67$ to 0.94), and test-retest stability was acceptable ($rs = 0.45$ to 0.90). Validity was demonstrated by examining relationships between the CFQ, age, pulmonary function, and body mass index. As expected, the CFQ was inversely correlated with age, with older adults reporting lower CFQ scores than younger adults, better nutritional status was positively correlated with several weight-related scales, and the measure differentiated between individuals with varying levels of disease severity. Strong associations were also found between the CFQ and similar scales on the Short Form-36 Health Questionnaire, a well-known generic HRQOL measure.**
Conclusions: **The results demonstrated that the CFQ-teen/adult is a reliable and valid measure of HRQOL for individuals with CF. It may be utilized in clinical trials to assess the effects of new therapies, to document the progression of disease, and to inform clinical practice.**
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Key words: adolescents and adults; cystic fibrosis; disease specific; health-related quality of life; psychometric validation

Abbreviations: CF = cystic fibrosis; CFQ = Cystic Fibrosis Questionnaire; HRQOL = health-related quality of life; SF-36 = Short Form-36 Health Questionnaire

Substantial progress has been made over the past 2 decades in defining and measuring health-related quality of life (HRQOL), with a consensus among experts that HRQOL is multidimensional and should include four core domains: (1) disease state and physical symptoms, (2) functional status, (3) psychological and emotional state, and (4) social functioning.[1] In addition, HRQOL assessments are patient centered and should reflect the individual's subjective evaluation of his or her daily functioning and well-being. Rigorous standards for the development and psychometric evaluation of HRQOL measures have been published, and efforts to develop reliable

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and valid measures of HRQOL have been highly successful, particularly in adult populations.[2–3]

Research on HRQOL has flourished as a result of advances in medical technology and treatment, the growing prevalence of chronic illnesses in adult and pediatric populations, and the need to reduce health-care costs. Although conventional measures of physical functioning are essential, they do not capture the broader impact of a disease on the patient's physical, social, and emotional functioning.[4] HRQOL measures are used for several purposes: (1) as primary or secondary outcomes in clinical trials, (2) to describe the impact of an illness on a patient's daily functioning, (3) to evaluate new pharmaceutical and surgical interventions, (4) to aid in clinical decision making, and (5) to estimate the costs and benefits of medical interventions.[5–7] Reliable and valid measures of HRQOL for several chronic conditions, such as asthma and cancer, are now widely used.[2,8] The purpose of the current study was to conduct a psychometric evaluation of a new, disease-specific HRQOL measure for cystic fibrosis (CF), the Cystic Fibrosis Questionnaire (CFQ).[9]

Development of a well-validated HRQOL measure for CF is important for several reasons. First, discovery of the genetic defect for CF in 1989 led to dramatic advances in our understanding of the pathophysiology of this chronic illness, which in turn has led to the development of new medications and treatments.[10] These treatments have shown promise for extending life span and improving quality of life. Both recombinant human deoxyribonuclease and inhaled antibiotics have been shown to positively impact FEV_1 percentage of predicted and HRQOL.[11–12] However, in the absence of a well-validated measure of HRQOL, these studies have relied on *ad hoc* items that make it difficult to determine how these new treatments affect functioning in the four core HRQOL domains.

Measures of HRQOL are also important for identifying the benefits of new treatments that are not reflected in conventional health indexes, such as pulmonary functioning. For example, after controlling for changes in pulmonary functioning for patients with CF in the Tobramycin Solution for Inhalation trial,[12] additional variance remained unaccounted for, suggesting the possibility of improvements in other areas of functioning, such as energy level. These patient-reported outcomes are now routinely included in US Food and Drug Administration-approved clinical trials, and this information can be added to the label if it meets certain measurement and statistical criteria.[13] Thus, HRQOL data may play an important role in decision making between health-care providers and patients.

Over 15 years ago, the National Institutes of Health sponsored a conference on the behavioral and psychological aspects of CF and recommended the development of a disease-specific measure of HRQOL to be included along with other health outcomes.[14] More recently, a consensus conference reviewed the use of HRQOL measures in clinical trials with CF patients and again recommended that validated measures of HRQOL be incorporated into phase 3 clinical trials for both adults and children.[15] Only one other disease-specific HRQOL measure for CF, the Cystic Fibrosis Quality of Life Questionnaire, has been published for patients in the United Kingdom.[16] However, this measure does not have parallel forms available for children with CF, who make up the majority of the patient population.

To date, most studies of HRQOL in patients with CF have utilized generic measures, such as the Quality of Well-being Scale and the Short Form-36 Health Questionnaire (SF-36),[3,17] which include general items of physical, social, and emotional functioning that can be rated by patients with a variety of medical conditions. Results from these studies have indicated that generic measures are not sensitive to the specific concerns of patients with CF,[18–20] which limits their ability to quantify the benefits of new treatments (*eg*, lung transplantation, new medications) or the natural progression of the disease (*eg*, treatment of pulmonary exacerbations).[4,21]

The CFQ is a newly developed, disease-specific HRQOL measure for individuals with CF, with developmentally appropriate versions for children aged 6 to 13 years (CFQ-child), parents of children with CF aged 6 to 13 years (CFQ-parent), and adolescents and adults with CF $\geq$ 14 years old (CFQ-teen/adult).[9,22] The CFQ was originally developed in France,[23] and all three versions recently underwent independent forward and backward translations, followed by a two-phase cognitive testing procedure in the United States.[24] The set of instruments has been developed to encompass general domains of HRQOL: physical functioning, role functioning, vitality, health perceptions, emotional functioning, and social functioning, as well as domains specific to CF: body image, eating disturbances, treatment burden, and respiratory and digestive symptoms.

This study presents data from the national psychometric validation of the English CFQ-teen/adult version at 18 CF centers across the United States. The primary objective of the study was to assess the reliability and validity of the CFQ. Specifically, item-level analyses were conducted to examine item to scale correlations, ceiling and floor effects, internal consistencies, and test-retest reliability. Convergent and discriminant validity was also evaluated by

testing hypotheses related to age, disease severity, and nutritional status, and by examining associations between the CFQ and a generic measure of HRQOL (*ie*, the SF-36).

Materials and Methods

Participants

Participants were 212 adolescents and adults with a confirmed diagnosis of CF, ranging in age from 14 to 53 years. The mean age of participants was 23.0 years (SD, 8.1), and a similar number of male (49%) and female (51%) patients were enrolled. Disease severity was classified using the Knudson equations[25] for FEV_1 percentage of predicted. A wide range of disease severity was documented, with FEV_1 percentage of predicted scores ranging from 17 to 130%. FEV_1 percentage of predicted was missing for six participants. Average FEV_1 percentage of predicted for the sample was 65.2% (SD, 25.2), with 44.2% of the sample classified as having mild disease, 34.4% classified as having moderate disease, and 21.4% classified as having severe disease (n = 44).[26] In order to evaluate test-retest reliability, a subset of participants (n = 21) at three study sites returned for a second visit 10 to 14 days later to complete the CFQ. This sample did not differ significantly from the larger sample: mean age of this subgroup was 23.1 years (SD, 4.1), mean FEV_1 percentage of predicted was 59.8% (SD, 22.6), and 47.6% were male (n = 10) and 52.4% were female (n = 11) patients.

Procedures

To obtain a geographically representative sample, participants were recruited from 18 CF centers across the United States. Written informed consent and assent was obtained from all participants according to the procedures specified by the relevant institutional review boards. Patients were enrolled in this study during a routine clinic visit that was not associated with an acute illness or pulmonary exacerbation. All of the measures, including the CFQ, were administered prior to a physical examination or other laboratory procedures (*eg*, pulmonary function tests) in order to obtain an unbiased perception of HRQOL. Basic demographic (*eg*, age, gender) and medical information (*ie*, pulmonary functioning, body mass index) was collected, followed by completion of two HRQOL measures, the CFQ-teen/adult version and the SF-36,[3] a generic HRQOL instrument. Each HRQOL instrument took approximately 15 min to complete.

Measures

CFQ-Teen/Adult: The CFQ-teen/adult measure[9] evaluated in this study consisted of 44 items across 12 scales (Table 1). Response choices generally included ratings of frequency and difficulty on a 4-point scale (1 = always to 4 = never; 1 = a lot of difficulty to 4 = no difficulty) or true/false responses (1 = very true to 4 = very false). Scores were standardized on a 0- to 100-point scale, with higher scores representing better quality of life.

SF-36: The SF-36 is a brief, generic health status measure consisting of 36 questions that yield eight health status scales: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.[3] Items are rated with respect to the individual's experience over the past 7 days. Scores range from 0 to 100, with higher scores indicating better quality of life and functioning. The SF-36 has been shown to be both reliable and valid, with internal consistency coefficients exceeding 0.70 for all scales.[27]

Results

Preliminary Tests of the French CFQ

To test the fit between the items and scales identified in the French CFQ, a multitrait analysis was conducted (revised Multitrait/Multi-item Analysis Program[28]). This analysis assessed the extent to which items correlated with their hypothesized scale vs a competing scale. Psychometric guidelines suggest that item-to-scale correlations should be ≥ 0.40 with the intended scale and should correlate much lower with competing scales, after accounting for the SE of measure (item discriminant validity).[29–30] The results generally supported the French model, with item-scale correlations > 0.40, with the exception of one social ("feel comfortable sleeping away"), one

Table 1—*CFQ-Teen/Adult Scales*

QOL Dimensions	Items, No.	Sample Items
Physical functioning	8	Physical 2: Walking as fast as others
Role	2	Role 37: How often were you absent from school/work during the last 2 wk because of your illness or treatments?
Vitality	4	Role 9: You felt tired
Emotional functioning	5	Emotion 12: You felt worried
Social	5	Social 29: I get together with my friends a lot
Body image	3	Body 23: I think I am too thin
Eating disturbances	3	Eating 21: I have to force myself to eat
Treatment burden	2	Treatment 16: Compared to 3 mo ago, how much time do you currently spend on your treatment?
Health perceptions	3	Health 33: I feel healthy
Weight	1	Weight 39: Have you had trouble gaining weight?
Respiratory symptoms	6	Respiratory 45: Have you had trouble breathing?
Digestive symptoms	2	Digestive 48: Have you had abdominal pain?
Total	44	

marginalization ("people ask me annoying questions"), and one health perception item ("compared to 3 months ago, how you feel about your health?"). These poorly performing items were deleted. This left only two items on this scale that correlated highly with the social functioning scale ($\alpha = 0.45$ and $\alpha = 0.41$). Thus, combining the marginalization and social scales made both conceptual and psychometric sense. The final social functioning scale had five items.

Item-Level Analyses of the English CFQ

Two types of item-level analyses were conducted on the US national validation data. First, items were subjected to a multitrait analysis (revised Multitrait/Multi-item Analysis Program[28]) to evaluate item-to-scale relationships.[30] Next, floor and ceiling effects were identified for each scale.

As can be seen in Table 2, a large percentage of items correlated highly with their intended scale;

Table 2—*Multitrait Analysis: CFQ-Teen/Adult (n = 208)*

Items	Physical	Role	Vitality	Emotion	Social	Body Image	Eating	Treatment Burden	Health	Weight	Respiratory	Digestion
Physical 1	0.82†	0.53	0.62	0.48	0.56	0.31	0.44	0.34	0.62	0.28	0.52	0.18
Physical 2	0.83†	0.52	0.58	0.43	0.57	0.29	0.45	0.26	0.61	0.25	0.45	0.18
Physical 3	0.81†	0.57	0.59	0.48	0.56	0.37	0.43	0.21	0.56	0.30	0.45	0.14
Physical 4	0.75†	0.50	0.55	0.42	0.51	0.24	0.35	0.17	0.53	0.20	0.41	0.17
Physical 5	0.84†	0.50	0.57	0.41	0.56	0.25	0.44	0.28	0.59	0.27	0.48	0.13
Physical 13	0.74†	0.54	0.61	0.45	0.57	0.29	0.43	0.21	0.61	0.33	0.43	0.20
Physical 19	0.68†	0.44	0.55	0.44	0.54	0.36	0.39	0.34	0.57	0.32	0.50	0.21
Physical 20	0.77†	0.50	0.55	0.46	0.59	0.38	0.39	0.27	0.66	0.26	0.48	0.15
Role 37	0.55	0.82†	0.35	0.38	0.45	0.20	0.26	0.21	0.48	0.22	0.35	0.22
Role 38	0.62	0.82†	0.44	0.43	0.47	0.24	0.34	0.25	0.50	0.16	0.38	0.20
Vitality 6	0.60	0.38	0.66†	0.45	0.46	0.25	0.39	0.25	0.60	0.26	0.48	0.21
Vitality 9	0.56	0.33	0.73†	0.42	0.37	0.23	0.30	0.24	0.44	0.28	0.47	0.27
Vitality 10	0.52	0.31	0.66†	0.39	0.41	0.16	0.30	0.18	0.46	0.22	0.37	0.10
Vitality 11	0.61	0.36	0.75†	0.49	0.46	0.27	0.33	0.28	0.49	0.27	0.48	0.22
Emotion 7	0.36	0.20	0.44	0.55†	0.44	0.08	0.31	0.28	0.31	0.01	0.26	0.20
Emotion 8	0.42	0.38	0.48	0.68†	0.48	0.26	0.34	0.38	0.42	0.28	0.24	0.31
Emotion 12	0.35	0.27	0.42	0.63†	0.34	0.16	0.33	0.27	0.33	0.14	0.20	0.29
Emotion 32	0.36	0.31	0.32	0.68†	0.52	0.37	0.37	0.27	0.48	0.21	0.31	0.31
Emotion 34	0.52	0.42	0.40	0.56†	0.54	0.40	0.35	0.28	0.60	0.25	0.35	0.19
Social 22	0.66§	0.49	0.47	0.46	0.45†	0.31	0.33	0.31	0.53	0.24	0.39	0.19
Social 28	0.44	0.28	0.36	0.46	0.53†	0.37	0.24	0.28	0.49	0.22	0.35	0.20
Social 29	0.44	0.37	0.39	0.41	0.46†	0.18	0.32	0.11	0.42	0.15	0.28	0.20
Social 30	0.42	0.26	0.37	0.47	0.46†	0.34	0.33	0.25	0.46	0.22	0.48	0.19
Social 31	0.31	0.27	0.15	0.29	0.46†	0.15	0.31	0.04	0.30	− 0.02	0.17	0.12
Body 23	0.27	0.17	0.19	0.16	0.19	0.51†	0.32	0.05	0.33	0.66§	0.30	0.06
Body 24	0.33	0.21	0.21	0.27	0.40	0.61†	0.37	0.11	0.44	0.38	0.22	0.21
Body 25	0.32	0.18	0.28	0.49	0.41	0.60†	0.37	0.09	0.48	0.28	0.25	0.26
Eating 14	0.43	0.27	0.33	0.32	0.39	0.29	0.70†	0.08	0.38	0.19	0.32	0.17
Eating 21	0.44	0.27	0.34	0.44	0.44	0.41	0.77†	0.13	0.39	0.34	0.28	0.16
Eating 49	0.46	0.31	0.38	0.40	0.37	0.43	0.76†	0.07	0.42	0.35	0.36	0.35
Treatment 15	0.36§	0.31§	0.30§	0.44§	0.35§	0.17	0.14	0.10†‡	0.40§	0.19	0.28§	0.22
Treatment 16	0.10	0.05	0.12	0.12	0.09	− 0.02	0.02	0.10†‡	0.11	− 0.03	0.15	− 0.03
Health 17	0.56	0.34	0.49	0.36	0.44	0.41	0.28	0.23	0.65†	0.36	0.49	0.13
Health 33	0.63	0.41	0.57	0.48	0.58	0.40	0.39	0.24	0.65†	0.35	0.57	0.23
Health 35	0.61	0.52	0.46	0.59	0.59	0.47	0.43	0.37	0.61†	0.32	0.47	0.27
Weight 39	0.33	0.20	0.31	0.24	0.24	0.56	0.34	0.11	0.40	†	0.38	0.12
Respiratory 40	0.37	0.24	0.39	0.30	0.32	0.31	0.29	0.21	0.50	0.37	0.66†	0.26
Respiratory 41	0.39	0.26	0.36	0.23	0.34	0.25	0.26	0.14	0.42	0.29	0.73†	0.20
Respiratory 42	0.41	0.29	0.33	0.25	0.35	0.20	0.24	0.19	0.44	0.34	0.68†	0.15
Respiratory 44	0.33	0.29	0.42	0.30	0.37	0.18	0.12	0.27	0.40	0.17	0.54†	0.20
Respiratory 45	0.63	0.40	0.58	0.38	0.49	0.28	0.38	0.31	0.59	0.25	0.52†	0.28
Respiratory 46	0.40	0.26	0.36	0.21	0.38	0.19	0.31	0.21	0.35	0.22	0.55†	0.34
Digestion 47	0.10	0.15	0.11	0.28	0.23	0.20	0.19	0.09	0.17	0.06	0.27	0.50†
Digestion 48	0.25	0.23	0.31	0.28	0.23	0.16	0.26	0.13	0.28	0.14	0.27	0.50†

*SE = 0.07.

†Item-scale correlation corrected for overlap (relevant item removed from its scale for correlation).

‡Less than desirable item internal consistency: item-scale correlation is < 0.4.

§Less than desirable item discriminant validity: item correlation with competing scale is significantly higher than its correlation with its own scale.

95% of the item-scale correlations (corrected for overlap) were ≥ 0.40. In addition, 83% of the items correlated at least two SEs greater with their hypothesized than competing scales. However, low item-scale correlations were observed for the treatment burden scale, on which the two items correlated only minimally with their intended scale (*rs* = 0.10). Subsequently, modifications were made to the wording of these items to reduce their retrospective nature, and an additional item was added to the treatment burden scale.

An analysis of floor and ceiling effects indicated that a majority of scales elicited responses in the mid-range. Minimal floor effects were found for the role and weight scales, with 13.9% and 20.2% of respondents endorsing low functioning on these scales, respectively. Ceiling effects were also observed on these scales, with 42.8% of respondents endorsing high values. Ceiling effects were also found for eating disturbances (60.6%), body image (28.8%), and physical scale (19.7%), with respondents scoring at the upper end of the range.

Scale-Level Reliability

Two scale-level analyses were conducted: (1) calculations of the internal consistency or reliability of each scale, and (2) test-retest reliability. First, scale-level reliability was calculated using Cronbach α. As can be seen in Table 3, the reliability coefficients ranged from $r = 0.18$ to 0.94, with a majority of the coefficients > 0.70. Only two domains fell below that cutoff: the Cronbach α for digestion was 0.67 and for treatment burden was 0.18.

Test-retest reliability was calculated on a subsample of medically stable patients who returned 10 to 14 days later (n = 21). Intraclass correlations provided evidence of stability for most domains, with stability coefficients ranging from 0.45 to 0.90 (Table 3). Lower stability was found for vitality, social functioning, and treatment burden.

Construct Validity

Several hypotheses were tested to establish the validity of the CFQ. First, because CF is a deteriorating medical condition, a strong correlation was expected between age and CFQ scores, with higher HRQOL reported by adolescents vs adults. This hypothesis was supported with inverse relationships found between age and the physical, role, vitality, emotion, social, eating, health perceptions, and respiratory scales (*rs* = − 0.17 to − 0.36, $p < 0.05$). Next, respondents were classified into three age groups (adolescents, age 14 to 17 years, n = 68; young adult, age 18 to 25 years, n = 66; and adult, age > 25 years, n = 74), and their scores were compared using a multivariate analysis of variance. As expected, younger individuals with CF reported higher quality of life than older individuals on most dimensions (Hotelling $T^2 = 0.30$, F [22,388] = 2.60, $p < 0.001$). No age-related differences were found on the eating disturbances, treatment burden, and digestion scales. Significant associations were also found between the CFQ weight-related domains and nutritional status, with positive relationships obtained between the body image, eating disturbances, and weight domains and body mass index scores (Table 4).

Differences in HRQOL were also expected as a function of current disease severity. The sample was divided into three disease severity levels (mild = FEV_1 percentage of predicted ≥ 70%, n = 91; moderate =

Table 3—*Reliabilities and Test-Retest Reliabilities on the CFQ-Teen/Adult*

Scale	Cronbach α	Intraclass Correlations (n = 21)
Physical	0.94	0.72*
Role	0.90	0.84*
Vitality	0.85	0.49†
Emotion	0.81	0.83*
Social	0.71	0.45‡
Body image	0.74	0.82*
Eating	0.85	0.77*
Treatment burden	0.18	0.45‡
Health perceptions	0.78	0.75*
Respiratory	0.84	0.90*
Digestive	0.67	0.65*
Weight§		0.63*

*p < 0.001.
†p < 0.01.
‡p < 0.05.
§Scale contains only one item.

Table 4—*Correlations Between CFQ Domains and Health Status Variables*

Domains	Age	FEV_1 % predicted	Body Mass Index
Physical	− 0.36*	0.42*	0.11
Role	− 0.26*	0.28*	0.10
Vitality	− 0.26*	0.26*	0.07
Emotion	− 0.23*	0.28*	0.09
Social	− 0.30*	0.33*	0.02
Body image	− 0.13	0.38*	0.38*
Eating	− 0.17†	0.23*	0.16†
Treatment burden	− 0.07	0.11	− 0.02
Health perceptions	− 0.22*	0.45*	0.14†
Respiratory	− 0.19*	0.39*	0.11
Digestive	− 0.07	0.03	− 0.00
Weight	− 0.03	0.35*	0.47*

*p < 0.01.
†p < 0.05.

FEV_1 percentage of predicted ≥ 40%, n = 71; and severe = FEV_1 percentage of predicted < 40%, n = 44) based on pulmonary functioning scores measured at the time of the CFQ assessment. A multivariate analysis of variance indicated significant differences in CFQ scores by disease severity (Hotelling $T^2 = 0.44$, F [22,384] = 3.84, $p < 001$). Individuals with less severe disease reported higher scores on all of the CFQ scales except for digestion, compared to individuals with more severe disease (Fig 1). Thus, the CFQ successfully differentiated between those with mild, moderate, and severe disease.

Convergent and Discriminant Validity With the SF-36

Convergent validity was tested by examining correlations between similar domains on the CFQ and SF-36. Strong associations were found between the CFQ and SF-36 on the following domains: physical ($r = 0.81$, $p < 0.01$), health perceptions/general health ($r = 0.79$, $p < 0.01$), vitality ($r = 0.84$, $p < 0.01$), role/role-physical ($r = 0.73$, $p < 0.01$), emotional functioning/mental health ($r = 0.74$, $p < 0.01$), and social ($r = 0.57$, $p < 0.01$). In contrast, discriminant validity was assessed by examining relationships between scales on the CFQ and SF-36 that were not measuring similar constructs. For example, the digestion and role scales on the CFQ were only moderately correlated with the SF-36 general health and mental health scales ($rs = 0.19$ to 0.42).

Discussion

Results of this national study at 18 CF centers across the United States indicated that the CFQ is a reliable and valid measure of HRQOL for adolescents and adults with CF. In terms of both internal consistency coefficients and relationship to lung function, it is similar if not stronger than psychometric data presented for the American version of the St. George's Respiratory Questionnaire.[31] Analysis of the item-scale relationships demonstrated support for the conceptual underpinnings of the scales, and a majority of the CFQ scales were shown to have strong internal consistency and adequate test-retest reliability. The CFQ was sensitive to the differences in HRQOL that are expected to occur with age, disease severity, and nutritional status, and it was significantly correlated with a well-respected generic HROQL measure on scales assessing similar constructs. Finally, evidence from two clinical trials[32–33] also suggests that the CFQ is responsive to the

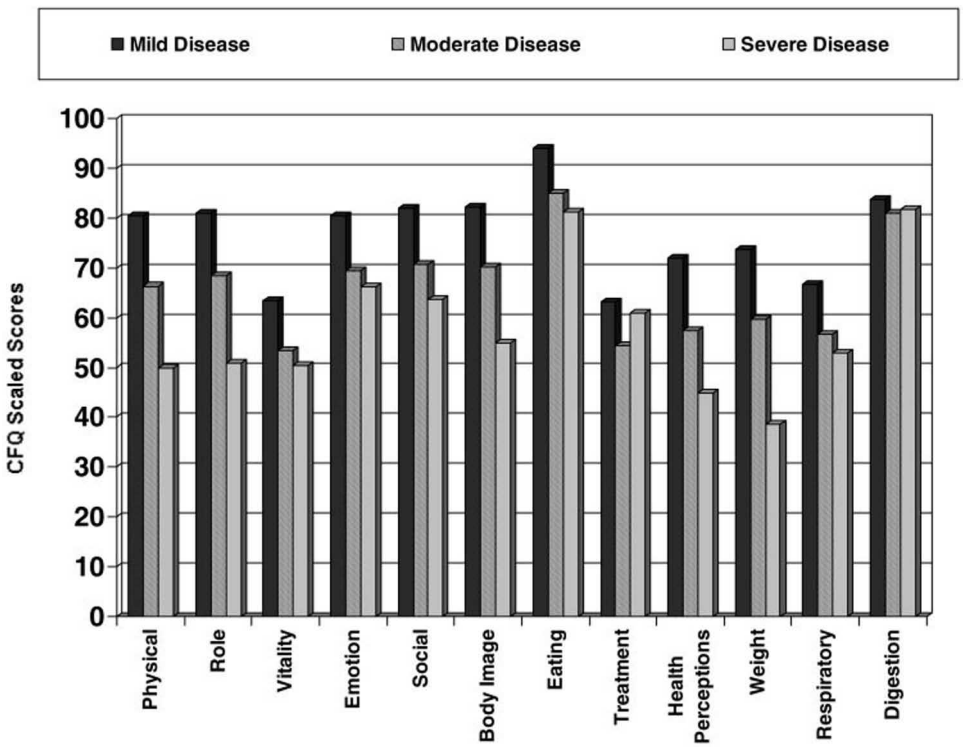

Figure 1. CFQ scores categorized by disease severity according to pulmonary functioning tests, as measured by FEV_1 percentage of predicted. Significant differences were found for all CFQ scales, except digestion.

effects of new medications and antibiotic treatments of pulmonary exacerbations.

In an effort to improve the internal consistency of the treatment burden and digestion scales, both of which had only two items, new items have been added to these scales (treatment burden: "How difficult is it for you to do your treatments [including medications] each day?; digestion: "Have you had problems with gas?"). An analysis of these additional items in two studies[34,35] indicates that the scale-level reliability has been improved (average $\alpha > 0.70$). Ceiling effects were also noted on the eating disturbances, role functioning, and weight scales. This is a common problem for HRQOL measures[18,20] that can be addressed by using item-response theory techniques to generate more difficult items.[36,37] We have recently added more items to the role functioning scale, which may remedy this problem.

Increases in the life span of individuals with CF, as well as the development of new medications, have highlighted the importance of measuring HRQOL using a disease-specific instrument. Thus, the CFQ has a number of potential applications and is currently ready to be used for research purposes. First, it can be used in clinical trials as a secondary outcome to assess the benefits of new medications and treatments from the patient's perspective. Second, it can be used to understand the natural course and progression of the disease in terms of its effects on several domains, including role, social, and emotional functioning. It may also illuminate the mechanisms associated with differential survival. For example, there are well-documented gender differences in morbidity and mortality for male and female CF patients.[38,39] Studies[40–42] using the CFQ have found significant gender differences on the body image and weight scales, suggesting that female CF patients are more satisfied with their "thinness" and weight than male CF patients, although this is clearly detrimental to their health. Finally, the CFQ can be used as a clinical tool in annual visits to provide a broader assessment of the individual's functioning and to identify problem areas that require intervention. Computerized versions of the CFQ are now available that permit patients to complete the measure in clinic, with real-time scoring and interpretation. The CFQ is currently being used in a national, Web-based data entry system for the Epidemiologic Study of Cystic Fibrosis II. This database includes $> 20{,}000$ patients at 203 CF centers.[42] Patients complete the CFQ at their annual visit with comparisons to normative information based on age and gender. These data can then be used to generate a patient profile for that clinic visit or to examine changes in quality of life over the course of a year.

There are several important directions for future research in quality-of-life measurement for individuals with CF. As the CFQ is used more commonly in research and clinical contexts, it will be important to determine the minimal clinically important difference score.[43] This will facilitate interpretation of the clinical significance of observed changes in CFQ scores. In addition, because adults with CF are now living much longer, we are developing an adult-focused module that includes items related to job satisfaction, intimate relationships, and having children.[44] There are an increasing number of clinical trials being conducted internationally, and this requires conceptually and linguistically equivalent translations of the CFQ. In addition to the French version, the CFQ has now been translated into German, Dutch, Italian, and Portuguese, and we are currently completing the cognitive testing phase of the Spanish translation.[45,46] The CFQ, scoring information, software program, and manual are available by request from the authors (e-mail: aquittner@miami.edu).

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References

1 Spilker B. Introduction. In: Spilker B, ed. Quality of life and pharmacoeconomics in clinical trials. 2nd ed. Philadelphia, PA: Lippincott-Ravenm, 1996; 1–10
2 Juniper E, Guyatt G, Ferrie P, et al. Measuring quality of life in asthma. Am Rev Respir Dis 1993; 147:832–838
3 Ware J, Sherbourne C. The MOS 36-item short-form health survey: conceptual framework and item selection. Med Care 1992; 30:473–481
4 Quittner AL. Measurement of quality of life in cystic fibrosis. Curr Opin Pulm Med 1998; 4:326–331
5 Gold MR, Franks P, McCoy KI, et al. Toward consistency in cost-utility analyses: using national measures to create condition-specific values. Med Care 1998; 36:775–777
6 Kaplan RM. Health outcome models for policy analysis. Health Psychol 1989; 8:723–735
7 Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled,

double-blind trial. JAMA 1998; 280:1490–1496
8 Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85:365–376
9 Quittner AL, Buu A, Watrous M, et al. The Cystic Fibrosis Questionnaire (CFQ): user's manual. Washington, DC: Cystic Fibrosis Foundation, 2000
10 Griesenback U, Geddes DM, Alton EW. Advances in cystic fibrosis gene therapy. Curr Opin Pulm Med 2004; 10:542–546
11 Ramsey BW, Pepe MS, Quan JM, et al, for the Cystic Fibrosis Inhaled Tobramycin Study Group. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. N Engl J Med 1999; 340:23–30
12 Quittner AL, Buu A. Effects of tobramycin solution for inhalation on global ratings of quality of life in patients with cystic fibrosis and *Pseudomonas aeruginosa* infection. Pediatr Pulmonol 2002; 33:269–276
13 Willke RJ, Burke LB, Erickson P. Measuring treatment impact: a review of patient-reported outcomes and other efficacy endpoints in approved product labels. Control Clin Trials 2004; 25:535–552
14 Eigen H, Clark N, Wolle J. NHLBI Workshop summary: clinical behavioral aspects of cystic fibrosis; directions for future work. Am Rev Respir Dis 1987; 136:1509–1513
15 Ramsey B, Boat T. Outcome measures for clinical trials in cystic fibrosis. J Pediatr 1994; 124:177–192
16 Gee L, Abbott J, Conway SP, et al. Development of a disease specific health related quality of life measure for adults and adolescents with cystic fibrosis. Thorax 2000; 55:946–954
17 Kaplan R, Anderson J, Wu A, et al. The Quality of Well-being Scale. Med Care 1989; 27:S27–S43
18 Czyzewski D, Mariotto M, Bartholomew K, et al. Measurement of quality of well-being in a child and adolescent cystic fibrosis population. Med Care 1994; 23:965–972
19 Britto MT, Kotagal UR, Hornung RW, et al. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. Chest 2002; 121:64–72
20 Munzenberger PJ, Van Wagnen CA, Abdulhamid I, et al. Quality of life as a treatment outcome in patients with cystic fibrosis. Pharmacotherapy 1999; 19:393–398
21 Tullis DE, Guyatt GH. Quality of life in cystic fibrosis. Pharmacoeconomics 1995; 8:23–33
22 Modi AC, Quittner AL. Validation of a disease-specific measure of health-related quality of life for children with cystic fibrosis. J Pediatr Psychol 2003; 28:535–545
23 Henry B, Aussage P, Grosskopf C, et al. Development of the Cystic Fibrosis Questionnaire (CFQ) for assessing quality of life in pediatric and adult patients. Qual Life Res 2003; 12:63–76
24 Quittner AL, Sweeny S, Watrous M, et al. Translation and linguistic validation of a disease-specific quality of life measure for cystic fibrosis. J Pediatr Psychol 2000; 25:403–414
25 Knudson RJ, Slatin RC, Lebowitz MD, et al. The maximal expiratory flow-volume curve. Am Rev Respir Dis 1976; 113:587–600
26 Taussig LM. Advances in cystic fibrosis: bring the bench to the bedside. Eur J Pediatr 1995; 54:S9–S10
27 McHorney CA, Ware JE, Raczek AE. The MOS 36-item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993; 31:247–263
28 Ware JE, Harris WJ, Gandek B, et al. MAP-R for Windows: Multitrait/Multi-item Analysis Program-Revised user's guide. Boston, MA: Health Assessment Lab, 1997
29 Campbell DT, Fiske DW. Convergent and discriminant validation by the multitrait-multimethod matrix. Psychol Bull 1959; 56:81–105
30 Hays RD, Hayashi T. Beyond internal consistency reliability: rationale and user's guide for Multitrait Analysis Program on the microcomputer. Behav Res Methods Instrum Comput 1990; 22:167–175
31 Barr JT, Schumacher GE, Freeman S, et al. American translation, modification, and validation of the St. George's Respiratory Questionnaire. Clin Ther 2000; 22:1121–1145
32 Quittner AL, Stack C, Modi AC, et al. Evaluation of health-related quality of life before and after antibiotic treatment of a pulmonary exacerbation in children and adolescents with cystic fibrosis [abstract]. Pediatr Pulmonol Suppl 2002; 24: 350
33 Saiman L, Marshall B, Mayer-Hamblett N, et al. A multicenter, randomized, placebo controlled, double-blind trial of azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa.* JAMA 2003; 290:1749–1756
34 Davis MA, Ray M, Modi AC, et al. Evaluation of health-related quality of life in participants of the Florida Abilities Adult Cystic Fibrosis Program (ACFP) [abstract]. Pediatr Pulmonol Suppl 2001; 22:349
35 Davis MA, Quittner AL, Ray M, et al. Longitudinal changes in health-related quality of life for adults in the statewide cystic fibrosis program [abstract]. Pediatr Pulmonol 2002; 34(suppl):350
36 McHorney CA. Generic health measurement: past accomplishments and a measurement paradigm for the 21st century. Ann Intern Med 1997; 127:743–750
37 Revicki DA, Cella DF. Health status assessment for the twenty-first century: item response theory, item banking and computer adaptive testing. Qual Life Res 1997; 6:595–600
38 Davis PB. The gender gap in cystic fibrosis survival. J Gender Spec Med 1999; 2:47–51
39 O'Connor GT, Quinton HB, Kahn R, et al. Case-mix adjustment for evaluation of mortality in cystic fibrosis. Pediatr Pulmonol 2002; 33:99–105
40 Quittner AL, Modi AC, Davis MA. Gender differences in HRQOL among patients with CF: a life span perspective [abstract]. J Cystic Fibrosis 2002; 1:S75
41 Quittner AL, Buu A, Davis MA, et al. Application of factor analysis and random effects modeling to examine gender differences in HRQOL [abstract]. Qual Life Res 2002; 11:661
42 Quittner AL. Examination of quality of life scores in ESCF II: The impact of age, disease severity, and gender [abstract]. Pediatr Pulmonol Suppl 2004; 38:355
43 Wright JG. The minimal important difference: who's to say what is important? J Clin Epidemiol 1996; 49:1221–1222
44 Quittner AL, Davis MA, Ray M, et al. Evaluation of changes in health-related quality of life for participants in the adult cystic fibrosis program [abstract]. J Cystic Fibrosis 2002; 1:S171
45 Quittner AL, Zapata C, Landon C. Spanish translation of the Cystic Fibrosis Questionnaire: preliminary results of the cognitive testing phase [abstract]. Pediatr Pulmonol Suppl 2002; 24:350
46 Klijn PH, Nieuwenhuis M, van Stel H, et al. Validation of the Dutch pediatric cystic fibrosis quality of life questionnaire. J Cystic Fibrosis 2003; 3:29–36