Measurement of quality of life in cystic fibrosis
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Considerable progress has been made over the past 2 decades in defining and measuring health-related quality of life (QOL), and there is a growing recognition that these measures provide unique information about the impact of a chronic illness and its treatment. For patients with cystic fibrosis (CF), health-related QOL measures enable researchers and clinicians to determine the effects of clinical interventions on several aspects of daily living (psychological, emotional, social) that are not reflected in typical health indicators, eg, pulmonary functioning scores. Three types of health-related QOL measures have been developed: 1) utility measures, 2) health profiles, and 3) disease-specific measures. The purpose of each type of health-related QOL measure is described, and its application to patients with CF is reviewed. Although important descriptive information has been obtained from utility measures, eg, the Quality of Well-Being Scale, and health profiles, eg, the Nottingham Health Profile, both of these instruments have serious limitations. Disease-specific measures, similar to those developed for children and adults with asthma, seem to hold the greatest promise for advancing our understanding of the impact of CF on daily life and for evaluating the effectiveness of new clinical interventions. The Cystic Fibrosis Questionnaire is the only published disease-specific measure of health-related QOL for children, adolescents, and adults with CF. Its psychometric properties are briefly reviewed, and directions for future research are suggested.

There is increasing recognition that measures of health-related quality of life (QOL) provide unique information about the impact of an illness and its treatment. Although conventional measures of physical functioning are essential, they do not adequately capture the broader impact of a disease on the patient’s physical, psychological, and social functioning. This may be particularly true for chronic diseases, eg, cystic fibrosis (CF) and asthma, in which an important goal of treatment is to improve patient well-being [1*].

Two decades ago, the World Health Organization defined health as “a state of complete physical and social well being, not just the absence of disease” [2], and since that time, tremendous progress has been made in defining and measuring health-related QOL. Although health-related QOL was initially viewed as vague and difficult to define, a consensus has emerged that health-related QOL: 1) is a multidimensional construct, including several core dimensions (eg, physical functioning and symptoms, psychological and emotional state, and social relationships); 2) should be patient rather than physician centered; and 3) reflects the individual’s subjective evaluation of his or her daily functioning and psychological well-being [3,4]. Schipper et al. [5] wrote that “quality of life in clinical medicine represents the functional effects of an illness and its consequent therapy upon a patient, as perceived by the patient.” It is important to note that although emphasis is placed on the patient’s subjective perceptions, rigorous standards of measurement development and psychometric analysis may still be applied to QOL measures. The systematic development of QOL measures developed by Juniper et al. [6–8] for children and adults with asthma stands as an excellent example of the generation of reliable and valid measures of health-related QOL.

Why measure health-related quality of life in patients with cystic fibrosis?
For several reasons, QOL should be evaluated in children and adults with CF. First, as our understanding of the pathophysiology of CF has advanced, new and intensive therapies have emerged that hold promise for both prolonging and increasing the QOL of patients with CF. For example, new drug treatments, eg, rhDNase, have been evaluated in a series of short-term safety and efficacy trials, with some indication of improvement in pulmonary functioning and QOL [9,10]. Although positive changes in forced expiratory volume in 1 second (FEV₁) are considered the essential indicators of clinical effectiveness, improvements in how patients feel and

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Abbreviations

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<th>Abbreviation</th>
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<td>CF</td>
<td>cystic fibrosis</td>
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<td>CFQ</td>
<td>Cystic Fibrosis Questionnaire</td>
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<td>FEF</td>
<td>forced expiratory flow</td>
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<td>QOL</td>
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<td>QWB</td>
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function on a daily basis are also important to measure. For chronic diseases in particular, some treatments may yield benefits in activities of daily living that are not reflected in conventional medical outcomes. Further, the patient’s perception of improved functioning may be an important factor in promoting adherence to complex and time-consuming treatment regimens [11,12].

Second, measures of QOL provide information on the impact of the illness and its treatment that may be more meaningful to patients with CF and their families than conventional medical indices. For example, anecdotal reports from our nutrition intervention study, aimed at increasing calorie intake and weight gain in young children with CF, indicated that the children’s increased energy level and ability to participate in sports were as exciting for families as the improved weight and height percentiles [13]. These changes in activity levels were meaningful behaviors that both the children and families could observe.

Finally, the assessment of health-related QOL is an additional parameter that may be used to evaluate the effectiveness of various treatments. Many of the new therapies being introduced for CF patients (e.g., rhDNase and lung transplantation) are expensive and require large expenditures of health care resources. QOL data may be useful for comparing the benefits of different treatments and their cost-effectiveness to inform health care policy [14–16]. In a recent review of outcome measures for clinical trials in patients with CF, the Consensus Group recommended that QOL measures be incorporated into phase 3 clinical trials for both children and adults with CF [17].

Approaches to measuring health-related quality of life

Health-related QOL is typically measured by having the patient or parent (in the case of younger children) complete a questionnaire. Three major types of health-related QOL measures have been developed: 1) utility measures, 2) health profiles, and 3) disease-specific instruments. These approaches reflect the different conceptual models and purposes that underlie the development of items and response formats [18]. Each type of health-related QOL measure is briefly described, and its application and utility for patients with CF is reviewed.

Utility measures

The utility model is derived from economic decision theory and is used to compare alternative treatments or assess the impact of different diseases. Utility measures yield a single value that reflects overall QOL, with 1 representing perfect health and 0 representing death. This approach has several strengths, including its weighting of societal preferences for various symptoms and functional states (e.g., general tiredness and limitations in major role activity) and its usefulness for generating data on the cost-effectiveness of clinical interventions [15]. Limitations of this approach include uncertain applicability to children and adolescents, the absence of information on different aspects of QOL, and a potential lack of sensitivity to clinically meaningful changes in airway disease [19].

Several utility measures of QOL have been developed, including the Quality of Well-Being (QWB) Scale [20,21], the Karnofsky Performance Status [22], and the Euroqol Visual Analogue Scale [23]. The QWB is the most widely used utility measure of health-related QOL and has been applied to several chronic diseases, including CF, arthritis, and AIDS [15]. Scores on the QWB are obtained by first classifying respondents into levels of functioning on the Mobility, Physical Activity, and Social Activity scales, and then having patients indicate the symptoms or problems that have bothered them most over the past few days (Symptom/Problem Complex). These limitations and symptoms yield point deductions from 1 (perfect health) that are weighted by preferences derived from large-scale population surveys [15]. Orenstein et al. [20] were the first to use the QWB with patients with CF, and since that time, three additional studies have used the QWB with this population [21,24,25].

In their initial study, the QWB was administered to 44 patients with CF, ranging in age from 7 to 36 years, with parents completing the measure for children under 10 years of age [20]. As a step toward establishing construct validity, the authors proposed that the QWB scale would be significantly correlated with both pulmonary function tests and exercise capacity (peak oxygen uptake). As predicted, higher QWB scores were obtained by patients with better lung function (r=0.41–0.55) and greater exercise tolerance (r=0.58). Although these data provided some support for the validity of the QWB, the patients in this study were generally more severely ill, with an average FEV1 of 66.5% predicted.

In a subsequent longitudinal study, Orenstein et al. examined the sensitivity of the QWB scale to changes in QOL following antibiotic treatment for a pulmonary exacerbation [21]. In this case, respondents were directed to answer the questions on the QWB for the 3 days before and directly following treatment, and these scores were averaged. The majority of the 28 patients demonstrated improved pulmonary functioning and obtained higher QWB scores after 2 weeks of oral ciprofloxacin treatment. Furthermore, the changes in pulmonary functioning, other than for peak expiratory flow rate, were significantly correlated with the changes on the QWB scale (rs=0.40–0.50). Although these results are encouraging, efforts to replicate them by other investigators have not been completely successful [24] (Munzenberger et al., Unpublished data).

In a study currently under review, Munzenberger et al. (Unpublished data) administered the QWB to 20 patients
with CF, ranging in age from 9 to 20 years, who were being admitted for an acute pulmonary exacerbation. The QWB was completed using the 6 days before admission and immediately following discharge. After completing a 2-week minimum course of intravenous tobramycin and ceftazidime, significant changes were detected in pulmonary function tests and the QWB scores. Concurrent correlations between the QWB and forced vital capacity (FVC) were significant ($r=0.48$), but the correlations between the QWB and FEV$_1$ and forced expiratory flow ($\text{FEF}_{25-75}$) were marginal ($r=0.36-0.35$). Unlike the previous study, no significant associations were found between changes on the QWB and changes in pulmonary functioning. These patients also tended to have significant pulmonary disease, with high rates of mortality at the 12-month follow-up. The authors noted that much of the association between the QWB and pulmonary function test scores could be attributed to the weightings on the Symptom/Problem Complexes rather than the scores derived from the Mobility, Physical Activity, or Social Activity scales. This raises a question about the extent to which the QWB scale is able to capture the multidimensional aspects of QOL as opposed to the physical symptoms associated with the disease.

To answer questions about the validity of the QWB for children and adolescents with CF, Czyzewski et al. [24] administered the QWB to 35 adolescents with CF and 199 caregivers. In contrast to previous results, the QWB scores did not correlate significantly with pulmonary function tests ($\text{FEV}_1$, FVC, and $\text{FEF}_{25-75}$), and low correlations were obtained between the QWB and National Institutes of Health Health Status scores ($r=0.22-0.29$). One explanation for this lack of association is that these patients had relatively mild disease (mean $\text{FEV}_1 = 81$) compared with the earlier samples, and that a ceiling effect on the QWB attenuated its relationship with other health indicators. This suggests that the QWB may be less sensitive to changes in QOL for patients who are healthier. The correspondence between adolescent and caregiver report for the same 5-day period was also modest, ($r=0.23-0.55$), indicating that the results may differ by respondent. Rather than relying on parental reports of a child or adolescent’s QOL, measures that are developmentally appropriate and valid for children and teens should be developed.

In sum, evidence to support the validity and clinical utility of the QWB is mixed. On the positive side, the QWB has demonstrated some evidence of construct validity, particularly with patients who are more severely ill. Strongest relationships have been found between the summary QWB score and measures of pulmonary functioning and symptoms. Because the QWB is a generic measure, it can be used to compare the impact of different diseases on health-related QOL and the effects of different treatments within a disease group. Although this is a strength, the generic nature of the instrument and its unitary score make it difficult to determine which aspects of daily functioning are most affected by the illness and which have responded to treatment. The other serious limitation is its uncertain applicability to children and adolescents. Because both the weighting schemes and interview methods were developed with adults, it is not clear whether they are meaningful or valid for younger populations. It should also be noted that the QWB does not evaluate psychological or emotional functioning, two core dimensions of the health-related QOL construct.

**Health profiles**

Health profiles are generic instruments that assess important dimensions of health-related QOL for a wide range of diseases and disease states. Because they are designed for use with a variety of populations, their items must be general and broad based. The advantages of health profiles are their quick and easy administration and their generation of separate scores for different domains (e.g., energy, emotional reactions, and social isolation). Several health profiles have been developed and tested, including the Sickness Impact Profile [25], the SF-36 [26], and the Nottingham Health Profile (NHP) [27]. Three important concerns have been raised about health profiles: 1) because they must be applicable to a variety of diseases, they may not measure specific and important dimensions of functioning for any one condition, 2) they may not be responsive to small but important changes resulting from a clinical intervention, and 3) few health profiles have been developed and validated for use with children and adolescents [28,29]; see the Child Health Questionnaire for an exception [30].

The NHP has been used in several studies to assess health-related QOL in patients with CF. It consists of two parts: Part 1 is made up of 38 statements to which a “yes” or “no” response is calculated for six scales (i.e., energy, pain, emotional reactions, sleep, social isolation, and physical mobility), and Part 2 asks whether the patient’s current state of health is causing problems in any of seven areas of daily living (i.e., working life, looking after home, social life, home/family relationships, sex life, interest/hobbies, and holidays).

Three studies have used the NHP to assess QOL following lung transplantation [31–33]. In the earliest study, the NHP scores were compared for 13 CF patients awaiting a transplant and 37 CF patients who were not transplanted [31]. Before transplantation, no significant differences in QOL scores existed between the two groups as measured by the NHP. At 3 to 6 months following transplantation, improvement was shown for the transplanted group on all six dimensions of Part 1 of the NHP, but only physical mobility and energy reached statistical significance. On Part 2 of the NHP, significantly lower (better) scores were reported for five of the seven areas (i.e., looking after home, social life, sex life, hobbies, and holidays).
Similar results were found in an update of this study with a larger sample [32]. Thirty-one patients who received a heart-lung transplant completed the NHP before and 3 to 6 months following transplantation. Significant improvements were found on all scales in Part 1 of the NHP except pain, and on most areas of daily living in Part 2. Although these studies suggest that the NHP is able to detect changes in QOL following transplantation, selection biases compromised both studies because many patients either failed to complete the questionnaire or died before its completion. In addition, for those patients who survived the initial surgery, the intervention was likely to produce the greatest benefit. Whether the NHP is sensitive to changes resulting from less dramatic clinical interventions, eg, new antibiotics, is not clear.

More recently, Congleton et al. [34] conducted a cross-sectional study of the NHP with 240 clinically stable CF patients. Interestingly, the generic NHP was supplemented with six questions that related specifically to CF symptoms and treatment (eg, degree of breathlessness and time spent doing treatment). Compared with published norms for the NHP, males with CF reported lower QOL scores in the areas of energy, pain, and social isolation, whereas females with CF reported poorer QOL in the areas of pain, emotion, and sleep. Significant but modest correlations were obtained between the scores in Part 1 of the NHP and several health indicators, including FEV1; strong associations were also found between the NHP and the six CF-specific questions. Although these results provide some evidence for the validity of the NHP, the mean scores indicated that the QOL of patients with CF was similar to that of persons with minor, nonacute conditions, eg, varicose veins and inguinal hernias. This problem is most likely caused by the general nature of the questions contained in the NHP and their lack of focus on the specific difficulties faced by these patients [35]. Similar concerns have been raised about other generic health profiles, eg, the Sickness Impact Profile and the SF-36 [29].

Generic health profiles are most useful as discriminative instruments, indicating how the QOL of individuals with CF differs from healthy populations or those with a different chronic illness. In contrast to utility measures, they also provide some information about the areas of functioning that are most affected by the disease; however, because the items tend to be broad based and general, they are less useful as evaluative instruments that are designed to detect and quantify the effects of clinical interventions. In addition, these health profiles have not been developed or validated with children and adolescents.

Disease-specific measures

Disease-specific measures of health-related QOL are designed to assess the symptoms and areas of functioning that are most important to patients with a particular disease. They provide information that is maximally relevant to the clinician and are sensitive to the small but important changes in health-related QOL that result from new treatments. Efforts to develop disease-specific measures of health-related QOL have gained momentum in the past 5 years as researchers have recognized that generic instruments (both utility measures and health profiles) are not sufficiently responsive to the effects of clinical interventions [6,18] and as health-related QOL instruments have become a more standard part of clinical trials. Furthermore, tremendous progress has been made in the development of disease-specific measures for children and adults with asthma [7,37], and systematic guidelines have been established for developing and validating disease-specific measures [8].

More than 10 years ago, the National Institutes of Health sponsored a workshop on the psychological and behavioral aspects of CF, recommending that disease-specific measures of health-related QOL be developed and incorporated alongside conventional health outcomes [36]. This was particularly timely because it predated the discovery of the gene for CF and the development of several new treatments; however, despite these recommendations and recent advances in treatment, efforts to develop CF-specific measures of QOL have just begun.

To date, the work of Henry et al. [38,39,40,41] in France represents the only published effort to develop disease-specific QOL measures for patients with CF. One important advantage of this work is its life span approach, which when completed will yield CF-specific measures of health-related QOL for school-aged children, parents of school-aged children, and teenagers and adults. Initial item development began with 44 interviews with young children with CF aged 6 to 13 years and their parents, and adolescents and adults with CF. From these interviews and extensive reviews of the literature, five generic domains of health-related QOL were identified: physical symptoms, role functioning (eg, school or job), psychological and emotional functioning, energy/fatigue, and social functioning. In addition, four domains specific to CF were measured: eating disturbances, body image, embarrassment caused by symptoms, and treatment burden. Three initial CQFs were developed, one for children aged 8 to 13 years (20 items), one for parents of young children (81 items), and one for patients 14 years of age or older (90 items) [38].

In the item-reduction phase, 534 questionnaires were completed at 24 hospital sites, with patients varying in disease severity as measured by the Shwachman score. Descriptive statistics and factor analyses provided support for the initial scale structure, and the psychometric properties of the three questionnaires were very good. For example, item-total correlations for each scale were higher than 0.40, and internal consistency coefficients exceeded 0.70. Test-retest correlations with 25 stable patients
showed good reproducibility (r=0.95), and preliminary validity data indicated that the CFQ scores successfully differentiated among illness severity groups. Based on these analyses, nine additional items were added to the CFQ-Child Version, the CFQ-Parent Version was reduced to 44 items, and the CFQ 14+ was reduced to 48 items [39,40*].

Because of an increasing number of multinational clinical trials and improved communication between researchers and clinicians in different parts of the world, it has become important to develop health-related QOL instruments that are cross-culturally valid [41,42]. Substantial interest has been generated in the CFQ, and it is currently being translated and evaluated in three countries: Germany, Spain, and the United States. In the United States, forward and backward translations were recently completed by two independent translators, and cognitive interviews are being conducted to assess comprehension of the items, use of the response categories, and convergence between children and parents [43*]. The sensitivity of the CFQ to changes in health-related QOL is also being evaluated in longitudinal, clinical trials.

Development of reliable and valid disease-specific measures of health-related QOL for children, adolescents, and adults with CF is greatly needed. The primary disadvantage of disease-specific measures is that they preclude comparisons across diseases. However, in contrast to both utility measures and health profiles, disease-specific instruments provide a level of specificity that is useful for clinicians and is likely to be maximally sensitive to the effects of new treatments. Based on the results of the item-development phase and initial psychometric analyses, the CFQ seems to hold considerable promise as a disease-specific measure for CF. Other disease-specific measures are currently in development, with published reports expected soon (Tullis, personal communication).

Conclusions
There is substantial recognition that measures of health-related QOL provide important information about the impact of chronic illness and the benefits of treatment. Over the past 2 decades, significant progress has been made in the development of reliable and valid measures of QOL, and a great deal has been learned about their predictive and clinical utility. Different types of measures of health-related QOL have been developed, and decisions about which measure to use should be governed by the purpose of the assessment. Researchers often recommend that both a generic and disease-specific instrument be administered because they provide different types of information; however, because of time constraints and limited resources, this is not always possible. In general, for studies of cost utility and cost-effectiveness, utility measures have the greatest empirical support. For comparisons of health-related QOL across different chronic conditions, generic measures should be used, and of these, health profiles have the advantage of providing information about levels of functioning in different domains. Finally, for the purposes of evaluating changes in patient functioning over time or the effects of new pharmacologic or behavioral interventions, disease-specific measures are likely to be most clinically relevant and sensitive to change [12]. Disease-specific measures are currently being developed for CF, and efforts should be made to include these measures in future studies.

As research on QOL measurement in CF moves forward, several methodologic issues need to be addressed. What is the correspondence between parent and child responses to health-related QOL measures? If disease-specific measures, eg, the CFQ, are used, which respondent’s scores are most strongly correlated with indicators of pulmonary functioning, and whose report is most predictive of change? Although perfect agreement between parents and children is not expected, it will be important to determine the areas in which discrepancies are likely to occur (school functioning) and how to interpret these different perceptions.

Another interpretation issue that requires further research is determining the minimal important change on a health-related QOL measure that is meaningful. For example, on the CFQ, what does an improvement of 5 points mean? In clinical trials, in which health-related QOL instruments are now being commonly used as outcomes, a statistically significant change may not necessarily be clinically meaningful for the patient. A variety of methods have been proposed for estimating the minimal important difference [44], and efforts to establish this clinically significant difference have been successful in other disease-specific measures, eg, the Asthma Quality of Life Questionnaire [45]. To address these complex measurement issues, additional studies with large samples of children and adults with CF, and researchers committed to the process of instrument development, will be needed.

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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• Of special interest
** Of outstanding interest
This article provides a good overview of the purpose and significance of quality of life measures for medical populations.


Initial psychometric data on the Cystic Fibrosis Quality of Life Questionnaire for children. This is the first published report of a CF-specific measure of QOL for this disease. Preliminary reliability and validity data are promising.


44. Report on the US translation of the CFIQ for children, parents, and adolescents/young adults with CF. Preliminary cognitive testing data indicate that the measure holds promise as a CF-specific tool.
