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**Title: Validation of paediatric health-related quality of life instruments for primary ciliary dyskinesia (QOL-PCD)**

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**Running head**

Validated PCD paediatric quality of life measures

**Summary Conflict of Interest Statement**

All other authors wish to declare that they have no competing interests.

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**Contributors**

MWL, SDD, ALQ and JSL had the concept for this study. All authors contributed to the study design. JSL and LB managed the conduct of the study and analysed the data. CH, MWL, SDD and JSL recruited patients for the study.LB, MWL, SDD, ALQ and JSL discussed the analysed data and agreed the resultant QOL-PCD questionnaires. LB and JSL drafted the manuscript. All authors contributed to iterations and approved the final document. JSL is accountable for the accuracy and integrity of the data.

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Parts of this work have been presented at the European Respiratory Society meeting in Paris (September 2018)

**Abstract**

***Rationale***

Having developed the first disease-specific, health-related quality of life (QOL) instruments for children with primary ciliary dyskinesia (PCD), we aimed to assess the psychometric performance of QOL-PCD Child, Adolescent and Parent Proxy versions in terms of reliability and validity across cross-cultural settings caring for patients with this rare disease.

***Methods***

Children (n=71), adolescents (n=85) and parents (n=68) from multiple centers in the UK and North America completed age-appropriate QOL-PCD and generic QOL measures: PedsQL, COPD assessment test (CAT), and SNOT-20. Thirteen children and 13 parents and 17 adolescents repeated QOL-PCD 10–14 days later to assess test-retest reliability. Multitrait analysis evaluated how the items loaded to hypothesised scales: Physical, Emotional & Social Functioning, Treatment Burden, Role, Vitality, Upper & Lower Respiratory Symptoms, and Ears & Hearing Symptoms. Examination of item-to-total correlations led to removal of 3, 5 and 6 items respectively in the prototype Child, Adolescent and Parent Proxy versions; the validated measures now comprise between 34-38 items.

***Results***

The QOL-PCD scales had good internal consistency; Cronbach's α for QOL-PCD Parent-Proxy ranged 0.62-0.86. Test–retest reliability demonstrated stability across all scales; for example QOL-PCD Adolescent intraclass correlation coefficients ranged 0.71-0.89. Significant relationships were found between QOL-PCD scales and similar constructs on generic questionnaires, for example, QOL-PCD Adolescent Lower Respiratory Symptoms and the CAT score (r=0.64, p<0.01); weaker correlations were found between different constructs.

***Conclusion***

Age-specific QOL-PCD demonstrated good internal consistency, test–retest reliability, and validity. QOL-PCD offers promising outcome measures for multi-center clinical trials, as well as monitoring symptoms, functioning and QOL during routine care.

**Key words:**

Primary ciliary dyskinesia, health-related quality of life, patient-reported outcome measure

**Validation of paediatric health-related quality of life instruments for primary ciliary dyskinesia (QOL-PCD)**

**Introduction**

Primary ciliary dyskinesia (PCD) is a rare heterogeneous genetic disease characterised by impaired mucociliary clearance caused by abnormal ciliary function ([1](#_ENREF_1)). Symptoms typically begin in the first few days of life with unexplained neonatal respiratory distress ([2](#_ENREF_2), [3](#_ENREF_3)). Patients continue to have daily wet cough and recurrent upper and lower respiratory tract infections throughout childhood ([3](#_ENREF_3)). Lung function is reduced by early childhood and continues to decline with age ([4-6](#_ENREF_4)). Recurrent infections lead to bronchiectasis in many children ([7](#_ENREF_7)) and in virtually all adults. Upper airway and ear disease is common; hearing loss can lead to speech delay and impaired learning if not identified and managed during early childhood ([8-10](#_ENREF_8)).

Monitoring disease progression and evaluating new treatments for PCD patients are chal ([6](#_ENREF_6))lenging due to the lack of validated disease-specific outcome measures. Outcome measures used to assess disease severity include spirometry ([4](#_ENREF_4)), chest computed tomography ([7](#_ENREF_7), [11](#_ENREF_11)), magnetic resonance imaging ([12](#_ENREF_12)), audiology and lung clearance index ([13-16](#_ENREF_13)). These physiological and radiological measures all have limitations in terms of their sensitivity or feasibility to monitor disease progression. To date, there have been no medications approved by regulatory bodies to treat PCD ([17](#_ENREF_17)). Disease-specific HRQoL questionnaires provide an in-depth picture of the day-to-day concerns of patients with the ability to capture changes in HRQoL that may occur as a result of clinical exacerbations or therapeutic treatment ([18](#_ENREF_18)). The use of patient-reported outcome measures in clinical trials is recognised by the FDA and EMA to measure the impact of the disease on the patient's daily physical symptoms and emotional functioning ([19](#_ENREF_19), [20](#_ENREF_20)).

Prototypes of the QOL-PCD measures for children (aged 6-12 years), adolescents (aged 13-17 years) and parent proxy (child 6-12 years) were developed using rigorous qualitative methods and following the procedures recommended by the FDA guidance on patient-reported outcome measures i.e. conceptual frameworks were generated following literature review, focus groups (expert clinicians and patients/parents) and open-ended interviews with children, adolescents and parents of young patients ([20](#_ENREF_20)). Content validity, clinical relevance score and cognitive testing using these prototypes supported QOL-PCD concepts, items and scale options ([21](#_ENREF_21)).

This study aimed to assess the performance of these three QOL-PCD measures through psychometric analysis to test for reliability and validity ([19-21](#_ENREF_19)). The QOL-PCD measures are the first validated disease-specific patient reported outcome measures for the paediatric population with this rare disease. These instruments were developed and validated through extensive international collaborate efforts to enable their use as outcomes in multi-center international clinical trials to determine the impact of medications or non-pharmacological interventions.

**Materials and Methods**

***Population and study design***

We recruited participants from the UK, US, Ireland and Canada. Children (aged 6-12 years), adolescents (aged 13-17 years) and parents of children (aged 6-12 years) with a PCD diagnosis were eligible to participate. Recruitment was conducted when patients attended PCD diagnostic centres for their clinic appointments. The study was also advertised through social media forums of the PCD Foundation in North America and PCD Support Group in the UK. Participants from the UK were included if diagnosed at one of the national diagnostic centres based on their clinical phenotype and a combination of nasal nitric oxide, high-speed video analysis of ciliary function and assessment of ciliary ultrastructure by electron microscopy ([22](#_ENREF_22), [23](#_ENREF_23)). Participants from North American were included if diagnosed at a specialised PCD research centre, based on a compatible clinical phenotype plus defect in ciliary ultrastructure and/or identification of biallelic disease-causing mutations in one of the PCD genes. Participants were required to speak English fluently.

***Measurements***

Participants (parents for children aged 6-12 years) were provided with a unique study number and a link to the online survey. Parents of more than one young child with PCD, completed a separate measure for each child. No identifiable information was collected, and the data were captured on a server of University of Southampton. Participants completed age-appropriate QOL-PCD prototypes before any clinical consultation or procedures. The QOL-PCD prototypes contained the following numbers of items and hypothesised scales: 1) Child version (37 items, 7 scales); 2) parent proxy version (41 items, 9 scales); and 3) adolescent version (43 items, 7 scales).

The first time QOL-PCD was completed, participants also completed age-appropriate generic HRQoL questionnaires: Pediatric Quality of Life Inventory (PedsQL), respiratory specific quality of life measures i.e. COPD assessment test (CAT), and measures focusing on rhinosinus symptoms: Sino-Nasal Outcome Test 20 (SNOT-20) and the Sinus and Nasal Quality of Life Survey (SN-5). Further details of these instruments are outlined in the Supplementary materials. The participants’ physician provided clinical data (e.g. FEV1 % predicted).

***Statistical Analysis***

We used equations developed by Bonett (2002)([24](#_ENREF_24)) to estimate the number of participants needed to establish Cronbach’s alpha (internal consistency) for each age-specific version. This formula utilized parameters for precision, number of items and level of reliability. For an average of 5 items per scale, we required 59 participants for each age-version to yield an alpha coefficient of 0.70 with 95% confidence. Once the measures were complete, recoding was carried out and each item was summed to generate a scale score and then standardized; scores range from 0 to 100, with higher scores indicating better outcome.

To look for floor and ceiling effects, we assessed the distribution of responses for each item and each scale. We considered floor and ceiling effects, using <15% of participants as the threshold for the highest and lowest scores for a scale ([25](#_ENREF_25)). To test the extent to which items correlate with their hypothesised versus competing scales, we conducted multitrait analysis; this type of analysis was developed for smaller samples for which factor analysis is not appropriate. We required item-to-scale correlations ≥0.40 with the intended scale and lower correlations with competing scales ([26](#_ENREF_26), [27](#_ENREF_27)). We analysed data using SPSS (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). P <0.05 was considered significant.

*Reliability:* We assessed internal consistency of the QOL-PCD scales using Cronbach’s α values (values 0 to 1; >0.70 indicates good internal consistency). To increase the efficiency of the instrument, if removal of an item led to higher Cronbach’s α, it was omitted from the scale. During a series of teleconferences, taking reliability and clinical relevance into consideration, multitrait analyses led to the QOL-PCD measures being shortened by removing redundant items.

A subgroup of stable patients completed the QOL-PCD a second time after 10–14 days. They were required to be stable, based on no change in symptoms or change in medication. We assessed test–retest reliability using intraclass correlation coefficients (ICC). An ICC>0.60 indicates good stability and an ICC >0.75 indicates excellent stability.

*Validity:* We predicted that QOL-PCD scales would have moderate Spearman’s correlations (>0.30) with generic scales (PedsQL, SNOT-20, CAT) measuring similar constructs (convergent validity). We hypothesised small or weak correlations (<0.30) with scales measuring different constructs (divergent validity).

To investigate construct validity (i.e. the extent to which the scales measures what it is expected to measure: health-related quality of life), we tested the scales against *a priori* hypotheses. For patients who have grown *Pseudomonas aeruginosa*, we predicted Physical Functioning and Upper and Lower Respiratory Symptoms would be associated with a lower/worse score. For FEV1 % predicted, we hypothesised Physical Functioning and Lower Respiratory Symptoms scores would be more closely associated than Upper Respiratory Scores. For gender, we *a priori* examined differences in Social Functioning and Emotional Functioning scores. Using Cohen's guidelines for the interpretation of correlation coefficients, correlations between 0.50 and 1.00 were strong, correlations between 0.30 and 0.50 were moderate, correlations between 0.10 and 0.30 were small and correlations <0.10 were weak ([28](#_ENREF_28)).

***Ethical approval***

The study was approved by the National Research Ethics Service, UK (UK 07/Q1702/109), the Research Ethics Board at the Hospital for Sick Children in Toronto, Canada and the Institutional Review Boards at the University of North Carolina, Chapel Hill. Consent was obtained prior to participation.

**Results**

We recruited 71 children, 85 adolescents and 68 parents between June 2014 and February 2017. Participant characteristics are shown in Table 1.

### *Development of scales*

Multitrait analysis generated seven scales in the child version, nine in the adolescent version, and nine in the parent proxy version. All three questionnaires included the following scales: Physical Functioning, Emotional Functioning, Social Functioning, Treatment Burden, Upper Respiratory Symptoms, Lower Respiratory Symptoms and Ears & Hearing Symptoms. The parent proxy version had additional scales including Health Perception and Eating & Weight. The adolescent’s version had additional scales of Vitality and Role Functioning.

Examination of the distribution of responses to items and the multitrait analyses led us to remove questions which were redundant, not strongly endorsed or did not correlate strongly with its designated scale; 3 items were removed from the child version (Supplementary materials Table 1), 6 items from the parent proxy measure (Supplementary materials Table 3) and 5 items from the adolescent version (Supplementary materials Table 5). The final QOL-PCD versions (versions 2.0) comprise 34 items on 7 scales in the child version, 35 items and 9 scales in the parent proxy version and 38 items on 9 scales in the adolescent version. These new versions underwent further psychometric analysis.

All items had item-to-scale correlations ≥0.40 with their intended scales and lower correlations with competing scales (Table 2). There was only one exception in the child version where one correlation was <0.40; Q27 ‘You had liquid coming out of your ears’ had a correlation of 0.35; this item was maintained on clinical grounds (Supplementary materials Table 2). No floor effects were reported for any of the measures; ceiling effects were observed in each measure for the Physical Functioning scale (child 28%, adolescent 31%, parent-proxy 22%) and Ears and Hearing Symptoms scale (child 17%, adolescent 43%, parent-proxy 26%). In the child and parent proxy measures, the Social Functioning scale had >15% of participants scoring the highest values (child 19%, parent proxy 32%). While ceiling effects were not reported in the adolescent Social Functioning scale (5%), a high percentage had the highest values for Treatment Burden (24%) and Role Functioning (31%).

***Reliability: internal consistency and test–retest reliability***

The QOL-PCD scales had moderate to good internal consistency; scales for the QOL-PCD Child version ranged from 0.60-0.78, QOL-PCD Adolescent ranged 0.70-0.90, and QOL-PCD Parent-Proxy ranged from 0.62-0.86. Thirteen children, 17 adolescents and 13 parents repeated QOL-PCD after 10–14 days, providing evidence of stability across all scales in the QOL-PCD Child (ICC 0.54 to 0.90), and excellent stability was found across QOL-PCD Adolescent scales (0.71 to 0.89). In the QOL-PCD Parent Proxy, good stability was reported across 7 of the 9 scales; poor ICC was found in 2 scales: emotional functioning (ICC 0.33) and health perception (ICC 0.44) (Table 3).

As predicted, associations were found between the QOL-PCD Adolescent Upper Respiratory Symptoms and the SNOT-20 score (r=0.61, p<0.01) and the SN-5 (r=0.471, p<0.01) (Table 4). Correlations were found between QOL-PCD Adolescent Lower Respiratory Symptoms and CAT score (r=0.64, p<0.01) and the QOL-PCD Parent Proxy Lower Respiratory Symptoms and CAT score (r=0.71, p<0.01). As hypothesised, we found correlations between PedsQL Physical Functioning and QOL-PCD Physical Functioning scales for each age-version (QOL-PCD Child r=0.53, p<0.01; QOL-PCD Adolescent r=0.84, p<0.01; Parent-proxy r=0.56, p<0.01).

In contrast, weaker relationships were generally found between the QOL-PCD scale scores and generic questionnaires that measured dissimilar constructs (divergent validity) (Table 4). For example, Upper Respiratory Symptoms of the QOL-PCD Child correlated weakly with School Functioning (r=0.001, p>0.05) on the PedsQL; Ears and Hearing Symptoms of the QOL-PCD Parent-Proxy correlated weakly with Emotional Functioning of the PedsQL (r=0.243, p>0.05).

***Validity***

We predicted that patients with FEV1 % predicted >70 would have better Physical Functioning, and Upper and Lower Respiratory Symptoms scores than those with lower lung function. Overall, scores were higher (better) for those with an FEV1 % predicted ≥70, however significance was only reached in QOL-PCD Adolescent for Physical Functioning (Adolescents with FEV1 <70% predicted: 72 (SD 25.7) and FEV1 ≥70% predicted: 85 (SD 20.8) p= 0.041).

For patients who grew *Pseudomonas aeruginosa*, as predicted, lower scores were found across Upper and Lower Respiratory Symptoms scales however statistical significance was not reached across scales for any of the measures. For example, the Parent-Proxy Upper Respiratory Symptoms score for patients with *Pseudomonas aeruginosa was* 59 (SD 22.1) and for patients without *Pseudomonas aeruginosa* was 49 (SD 26.3), p=0.358.

We predicted patients with siblings with PCD would report lower Treatment Burden than those without an affected sibling, because therapeutic intervention is more ‘normal’ within the home. Higher scores (less treatment burden) were reported for each measure; statistical significance was reached in the QOL-PCD Child measure (Children without siblings: 53 (SD 24.2) and children with siblings: 66.3 (SD 23.0) p= 0.049).

We had predicted gender differences in the QOL-PCD Emotional Functioning scales. Young boys had a significantly lower Emotional Functioning score than girls (69 compared to 77, p=0.031). For the QOL-PCD Adolescents and Parent-proxy measures, boys had higher Emotional Functioning scores than girls (not significant). There was no significant difference between boys and girls across the measures for Social Functioning and Treatment Burden. (Table 5)

**Discussion**

This study shows that health-related quality of life measures (QOL-PCD) for children, adolescents and parents of young children are valid disease-specific instruments for patients with PCD. Psychometric testing confirmed QOL-PCD are robust, reliable and valid measures in children and adolescents. These measures have cross-cultural equivalence in English-speaking countries having been developed and validated in the UK, Ireland, Canada and the USA ([21](#_ENREF_21)). QOL-PCD adult version has previously been validated ([29](#_ENREF_29), [30](#_ENREF_30)).

To date, few studies have reported the psychological and social burden of PCD ([21](#_ENREF_21), [29-33](#_ENREF_29)). Qualitative studies have shown the emotional impact of PCD, with prominent themes arising including anger and frustration on account of the constant symptoms, treatment burden and anxiety about their future health ([31](#_ENREF_31)). Feelings of embarrassment were attributed to the need to cough, expectorate sputum or blow nose in social settings ([32](#_ENREF_32), [34](#_ENREF_34)). In the absence of disease-specific questionnaires, researchers have used generic HRQoL measures to investigate the psycho-social impact of PCD including the Wechsler Intelligence Scale for Children, the Child Behaviour Check-List questionnaire, St George's Respiratory Questionnaire, Leicester Cough Questionnaire, and Medical Outcomes Study Short Form 36 ([35-38](#_ENREF_35)). These studies indicated that PCD children were more likely than peers to be withdrawn, experience anxiety or depression, and internalise problems ([39](#_ENREF_39)); they have also highlighted the need for a disease specific HRQoL measure for PCD([35](#_ENREF_35)).

We recruited 71 children, 68 parents and 85 adolescents with PCD from centres in North America, Ireland and the UK. This collaborative effort was required to recruit sufficient participants with this rare disease (estimated prevalence 1:15,000).

Since the number of patients with PCD in each age-group were limited, we used multitrait analyses to develop the scales, which have been advocated for smaller study populations rather than exploratory factor analysis which require >200 patients. The multitrait analysis supported the conceptual foundations of the scales. Assessment of the item-scale relationships endorsed the conceptual underpinnings of the scales, and a majority of the QOL-PCD scales were shown to have strong internal consistency and good to excellent test-retest reliability.

We found no floor effects and a minimum of ceiling effects in the scales overall, suggesting that the items cover a broad range of functioning, thereby allowing for differentiation among patients. The QOL-PCD scales were sensitive to differences in HRQoL that occur with disease severity as measured by FEV1 <70% predicted, and past growth of *Pseudomonas aeruginosa*. As predicted, there were also differences in responses according to gender and to having an affected sibling. The population size was powered for analyses of internal consistency. Lack of statistically significant associations between disease severity and scales may reflect small numbers of PCD children with FEV1 <70% predicted or *Pseudomonas* infections. Again, meta-analyses from future studies will contribute to more robust analyses for this rare disease.

The QOL-PCD scales correlated with a generic HRQoL measure PedsQL on scales assessing similar constructs. Convergent validity was also confirmed between scales of the QOL-PCD and generic versions measuring the same construct (CAT, SN-5, SNOT-20). Divergent validity was less clear; this could be due to the general nature of the generic questionnaires. Comparison of QOL-PCD with generic measures has limitations. This has been highlighted in a number of studies that have assessed HRQoL in patients with PCD by using generic measures, such as the St George Respiratory Questionnaire ([35-38](#_ENREF_35), [40](#_ENREF_40), [41](#_ENREF_41)), Cystic Fibrosis Questionnaire ([40](#_ENREF_40)), Leicester Cough Questionnaire ([35](#_ENREF_35)), Sino-Nasal Outcome Test-22([40](#_ENREF_40)), and Medical Outcomes Study Short Form-36 ([38](#_ENREF_38), [39](#_ENREF_39), [41](#_ENREF_41)). These studies indicated that generic measures lack sensitivity to the specific concerns of patients with PCD; this could limit our assessment of convergent and divergent validity ([41](#_ENREF_41)).

The QOL-PCD have already been translated into Danish, Dutch, German (developed and linguistically validated for Germany and Switzerland), Greek, French, Spanish (European), Portuguese (Brazilian) and Turkish; translations are progressing in Arabic, Spanish (Latin America), Hebrew, Italian and Norwegian. Each of these translation have followed a protocol-led process of forward and back translation followed by cognitive testing; teleconferences were held at each stage of the process chaired by the authors of this study. This international approach is important for a rare disease, providing outcome measures for multinational clinical trials.

The QOL-PCD measures is now being used as outcome measures in a clinical trial of azithromycin prophylaxis in PCD ([42](#_ENREF_42)), and a trial of VX-371 and Ivacaftor (<https://clinicaltrials.gov/ct2/show/NCT02871778>); findings from these studies will allow us to assess the responsiveness of the measures to treatment, and estimates of the minimal clinically important difference score.

**Conclusion**

QOL-PCD (Child, Adolescent and Parent-proxy) are ready for use in clinical trials to assess the impact of medications or non-pharmacological interventions. It will also be used to monitor the natural course and progression of the disease in terms of its effects on physical, emotional, role and social functioning. The measures have already been translated into a number of languages, facilitating international collaboration for clinical research.

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