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Title: Validation of the Parent-Proxy Version of the Pediatric Charcot-Marie-Tooth Disease Quality of Life Instrument for children aged 0-7 years

Running Title: Validation of the pCMT-QOL (0-7 years parent-proxy)

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ABSTRACT

Objective: To evaluate the parent-proxy version of the pediatric Charcot Marie Tooth specific quality of life (pCMT-QOL) outcome instrument for children aged 7 or younger with CMT. We have previously developed and validated the direct-report pCMT-QOL for children aged 8-18 years and a parent proxy version of the instrument for children 8-18 years old. There is currently no CMT-QOL outcome measure for children aged 0-7 years old.

Methods: Testing was conducted in parents or caregivers of children aged 0-7 years old with CMT evaluated at participating INC sites from the USA, United Kingdom, and Australia. The development of the instrument was iterative, involving identification of relevant domains, item pool generation, prospective pilot testing and clinical assessments, structured focus group interviews and psychometric testing. The parent-proxy instrument was validated rigorously by examining previously identified domains and undergoing psychometric tests for children aged 0-7.

Results: The parent-proxy pCMT-QOL working versions were administered to 128 parents/caregivers of children aged 0-7 years old between 2010 and 2016. The resulting data underwent rigorous psychometric analysis, including factor analysis, internal consistency, and convergent validity, and longitudinal analysis to develop the final parent-proxy version of the pCMT-QOL outcome measure for children aged 0-7 years old.

Conclusions: The parent-proxy version of the pCMT-QOL outcome measure, known as the pCMT-QOL (0-7 years parent-proxy) is a valid and sensitive proxy measure of health-related QOL for children aged 0-7 years with CMT.

INTRODUCTION

Charcot-Marie-Tooth disease (CMT) is the most common heritable neuromuscular disease afflicting 1:2500 individuals [1]. CMT is genetically heterogeneous, caused by pathogenic variants in >100 genes [2]. CMT is subdivided based on nerve conduction velocities and inheritance patterns into autosomal dominant demyelinating (CMT1) or axonal (CMT2) forms, X-linked forms (CMTX) and autosomal recessive demyelinating (CMT4) or axonal (ARCMT2) forms. All CMT subtypes are progressive, causing increasing disability throughout a person's lifetime, though rates of progression differ. Progressive impairment correlates with axonal degeneration, even in demyelinating forms [3]. Promising therapies are under development for CMT including antisense oligonucleotides[4], small interfering RNA[5] and viral vector delivered gene replacement [6]. Ideally, preventing and reversing axonal damage is likely to be more successful if started early. Symptoms typically begin in childhood for most forms of CMT [7]. Therefore, effective therapies will ultimately be most effective if initiated in early childhood when axonal degeneration is mild.

Clinical trial readiness and natural history studies in CMT require clinical outcome assessments (COA) to quantify disease progression. The CMT Pediatric Scale (CMTPedS) and CMT Infant Toddler Scale (CMTInf) were developed as functional outcome instruments to measure physical impairment in children, infants and toddlers with CMT. We have also used the Patient-Reported Outcomes Measurement System (PROMIS) to develop a patient-reported-outcome (PRO) measure for health-related quality of life (QOL) in children aged 8-18 years with CMT (pCMT-QOL) [8, 9]. Recently, we tested a parent-proxy version of pCMT-QOL for this age group and determined that parents scored in both physical and mental domains of pCMT-QOL similarly as their affected children, although parents slightly overestimated the impact of CMT on their child compared to the child themselves [10]. However, there remains no instrument to measure QOL in children with CMT under the age of 8 years. To address this need we validated our parent-proxy

version of the pCMT-QOL outcome measure for children aged 0-7 years old. These results are presented in the current manuscript.

METHODS

Standard Protocol Approvals, Registrations, and Patient Consents

The protocol was approved and monitored by the institutional ethics review board at Wayne State University and the University of Michigan. Samples used for pilot testing have been previously described [8]. The parents of 128 children with CMT aged 0-7 years old, seen in the prospective, natural history study in children with CMT were recruited for the parent-proxy version development and validation (clinicaltrials.gov identifier NCT01193075) from 2010-2016, at the following sites of the Inherited Neuropathies Consortium: USA- Wayne State University; University of Michigan; University of Iowa; Stanford University; Johns Hopkins University; University of Rochester; Children's Hospital of Philadelphia; Hospital of the University of Pennsylvania; and Nemours Children's Hospital; United Kingdom- UCL Institutes of Child Health and Neurology, London, UK; Australia- University of Sydney & Children's Hospital, Sydney, Australia. Ethics approval from all institutions for all studies and written informed consent from parents of all participants were obtained.

Statistical Analysis

The iterative process to define the construct, generate the item pool, and pilot testing has been previously described; the pilot testing was done on the parents of the 31 children with CMT ages 4-17 referenced in the original paper [8]. The resulting parent-proxy working version of the pCMT-QOL outcome measure for children aged 0-7 years old was administered prospectively to parents or primary caregivers (both henceforth referred to as parents) of children seen at the participating

sites of the Inherited Neuropathies Consortium. The version underwent psychometric testing, including internal consistency, convergent validity, and IRT modeling, to develop the final parent-proxy version of the pCMT-QOL outcome measure for children aged 0-7 years old. The statistical software used for the analyses were SAS version 9.4 (SAS Institute Inc., Cary, NC) and Mplus version 8.4 (Muthén & Muthén, Los Angeles, CA). Specific analyses are detailed below.

Final version and scoring: The final 57-item parent proxy version of the pCMT-QOL outcome measure for children aged 0-7 years old, known as the 'pCMT-QOL (0-7 years parent-proxy)', was virtually identical to both the direct-report and parent-proxy version of the pCMT-QOL outcome measures for children aged 8-18 years old (Table 1). Questions 37 and 38 in the 8-18 version, previously addressing concerns of the child worrying about their future health and concerns about dependency, were replaced by questions about behavior and the ability to follow directions in the 0-7 version, as these were determined to be more age appropriate. All items are reverse scored such that lower scores indicate higher QOL and higher scores indicate worse QOL. Individual domain scores, Physical Composite Domain Score, Mental Composite Domain Score and Total Score for the parent-proxy version were calculated and standardized identically to the direct-report and parent-proxy 8-18 score. All scores were calculated for individuals with non-missing values for at least half of the items in each domain. For those with half or more missing values (including those with "I don't know" responses), the scores were set as missing. Each score was calculated in two steps for those with more than half of the scores available in the domain. In step 1, the weighted sum of all items in the domain was calculated, with the weights derived from the mean Likert response of each question from the main dataset. At step 2, the weighted sum was transformed to a 0-100 scale as a percentage of the maximum possible value, with a score of 100 representing the most severe QOL and a score of 0 representing the best QOL. If there were missing items and the number of missing items was smaller than half, then we only used the non-missing items in the calculations. We were unable to compare the parent-proxy

forms to those completed by the children aged 0-7 years old because the children were not old enough to complete the instrument themselves. Nevertheless, because the scores from the parent-proxy version of the pCMT-QOL for children aged 8-18 tightly correlated with the direct-report pCMT-QOL scores for children aged 8-18, we believe the parent-proxy version for children aged 0-7 years old should accurately measure both physical and mental factors in this younger age group.

Internal consistency and convergent validity: Cronbach's alpha coefficient was calculated to evaluate the internal consistency within each domain. Convergent validity was determined by calculating the Spearman's Rank Correlation between the parent-proxy version of the pCMT-QOL for children aged 0-7 years old and the established scores such as CHQ Physical Summary Score, CHQ Psychosocial Summary Score [11-14], CMTPeds [15], and CMT Exam Score (CMTES)[16] when appropriate.

Known group comparisons: Two-sample t tests were used to compare groups defined by the child's gender, disease severity characterized by child's CMTPedS [17] and child's CMT genetic subtype (CMT1A vs. all others).

Longitudinal analysis: longitudinal analysis in the 0-7 years old group were performed, when possible, on annual visits following the baseline visit. Longitudinal responsiveness was assessed by calculating the Pearson correlation coefficient for the 1-year change in proxy Total pCMT-QOL Score with the 1-year change in version 2 CMTES score [16] . CMTPedS, initially published in 2012[15], was not available for most patients who underwent longitudinal analysis in this series.

RESULTS:

Internal Consistency

To have the parent-proxy version retain consistency with the child version of the pCMT-QOL measure, the factor analysis from the original paper [8] was used to assign the items to the

previously identified six unidimensional domains (Table 1). Standardized Cronbach alpha coefficients for the items per domain were high, reflecting good internal consistency.

Parents' Assessment Scores

Overall parents assessed Physical Composite Scores (mean of 39.5) higher than Mental Composite Scores (23.5) for their children though there was a wide range in the individual domain scores; the physical domain scores ranged from 4 to 86 and 0 to 80 for the mental domain scores, depending on the child (Table 2).

Convergent Validity

The Spearman Correlation Coefficients, shown in Table 3, showed several significant correlations. The strongest inverse correlations were between the CHQ Physical Summary Score and the Physical Composite Domain score and the Total pCMT-QOL Score of the parent-proxy version of the pCMT-QOL for children aged 0-7. The Mental Composite Domain Score of the parent-proxy measure was also highly inversely correlated with the CHQ Psychosocial Summary Score. Of note, in the CHQ measure, higher scores indicate better QOL, converse to the pCMT-QOL where higher scores indicate worse QOL. The Physical Composite Domain Score and the Total pCMT-QOL score of the parent-proxy measure correlated modestly but significantly with the CMTPedS, a validated pediatric physical function outcome measure used in CMT (Table 3).

Breakdown between ages 5-7 and ages 0-4

Although most children do not begin reading or completing tasks in school until five years of age, more than 50% of parents responded to questions on these issues in our study; therefore, these questions were not removed from consideration. However, we recognized that children 4 years of age and younger had usually not begun reading or attending elementary school and that their parents were unlikely to have responded to questions regarding reading or completing projects. Therefore, we elected to separate the overall cohort into two groups: 0-4 years old and 5-7 years old. We then determined the percentage of parents in each group addressing the questions related to reading and task completement (questions 43, 45, 47, 49, 50). As predicted, we found

that a low percentage (<50%) of the parents in the 0-4 years old group responded to this set of questions whereas the majority of parents of the 5-7 years old group did respond. Because questions not answered are considered "missing" and do not enter the calculations of the total scores, these questions did not enter into the overall scoring for most of the 0-4 years old group whereas they did enter into the scoring for most 5-7 years old children. The overall missing rate for all items was 5.52%, and the missing rate for the 0-4 group and 5-7 group was 9.37% and 2.99%, respectively. With the low missing rate and high data quality, none of the children were excluded from the calculation due to missing values. Physical scores were available for all 113 children. Additionally, only one child from each age group had missing overall and mental scores, although their physical scores were available.

To determine whether differences related to missing items may have altered parent perception of their children, we compared the parent assessment scores for the 0-4 to the 5-7 years old group (Tables 2 and 4). Although the Physical Function Doman Score and the Physical Composite Domain Score was higher in the younger children (Table 2), the pCMT-QOL individual domain scores and Composite and Total Scores were generally similar for the two age groups (Table 2) with no statistically significant differences (Table 4).

We next investigated how results from the 0-4 years old group correlated with the CHQ Physical Summary Score and the CHQ Psychosocial Summary scores and the CMT PedS scale, recognizing that CMTPedS has only been validated for children 4 years of age and older [15]. Overall, the correlations were similar by age in terms of magnitude, direction and significance; the only divergent correlations were weaker / less significant correlations with the CHQ Psychosocial Summary score in the 0-4 age group (Table 3).

Known Group Validation

Differences in parent-proxy version of the pCMT-QOL for children 0-7 years old by gender, age, CMT subtypes and severity are shown in Table 4. Significant differences in QOL scores were noted by gender: higher (worse) Physical Composite Domain Score in females (43.4 vs 36.9, p = 0.029), and higher (worse) Mental Composite Domain Score in males (27.2 vs 17.9, p = 0.0004). . The Total Score was virtually identical for males and females. No other significant differences were seen by age or CMT subtypes. As expected, children with moderate or severe CMT had worse Total, Physical Composite Domain and Mental Composite Domain Scores than children with mild CMT.

Longitudinal analysis

Fourteen parents out of 113 performed assessments at both baseline and year 1, 16 parents performed assessments at baseline and year 2, but only 2 parents performed repeat assessments at baseline and year 4. Longitudinal responsiveness, was assessed by calculating the Pearson correlation coefficient for the 1-year change in proxy Total pCMT-QOL Score with the 1-year change in CMTES score, was moderate at 0.398 (p = 0.159). Interpreting this data is limited by the fact that the CMTES is usually not considered valid for children < 10 years of age because of the subjectivity of several of the components [18].

Supplemental Information

The Parent-Proxy version for children 0-7 instrument is included as Appendix 1. The Excel file containing the means scores necessary for scoring is attached as Appendix 2.

DISCUSSION

We have rigorously validated our disease-specific parent-proxy version of the pCMT-QOL PRO for young children aged 0-7 years old. Parents perceived that CMT had a clear impact on the QOL of the younger children, similar to their perception in the parent-proxy version for older children [19] . This perception was apparent, even in milder cases. For example, CMT1A, the most common form of CMT, is generally considered to have a relatively mild phenotype, particularly in

young children [20]. However, the Total Score for 0-7 year old children with CMT1A was 33, demonstrating that the CMT was impacting the QOL even for this "mild" CMT, at this young age. Moreover, this Total score of 33 is similar to the Total Score identified by parents for their 8-18 year old children [19], suggesting that the parents' overall perception of the effects of CMT1A on their child's QOL was not changing significantly throughout childhood. Results were similar for the non-CMT1A 0-7 patients: the Total Score was 36 for the 0-7 group and 35 for the 8-18 group [6].

Other similarities between the 0-7 and 8-18 proxy groups included the parents' perception that physical domains were more affected than mental domains in their children. Specifically, in the 0-7 age children, the Physical Composite Domain Scores were 37 for CMT1A and 43 for non-CMT1A whereas the Mental Composite Domain Scores were only 24 for both CMT1A and non-CMT1A children. Taken together these data demonstrate that parents of very young children detect impairment from CMT, that the impairment is noticeable more in physical than in mental domains and is observed in milder as well as more severe forms of CMT. For the 8-18 age group, the Physical Composite Domain scores were 37 and 41 for CMT1A and non-CMT1A while the Mental Composite Domain Scores were 28 and 25 for the two groups respectively. Therefore, the parents' perception that the impact on QOL of the physical aspects is more severe than the mental aspects of the disease also remains relatively constant throughout childhood.

While physical challenges with CMT are known there is scant data on factors affecting mental health in children with CMT. We identified nine items on the Mental Composite Scores that the parents scored with a high (worst) average score (Supplements 1&2). These items included having to read something several times, reading slower than other children and being frustrated with reading or writing. Parents also provided high scores on questions related to following directions, trouble paying attention, trouble completing tasks or finding it hard to concentrate. We

suspect that these issues were related to the young age of the children rather than being specific for CMT The one question that we considered to be CMT specific was “Your child seems frustrated because of their CMT.”

Parents perceived females to be more impaired in physical functions and less impaired in mental functions in the 7 and under group, which is again similar to their perceptions in the 8-18 age group, though the differences were not as pronounced in the 8-18 group [19]. Females scoring themselves in the 8-18 age group also scored their physical impairment more pronounced than boys [8]. Thus, our data suggests that parents’ evaluations are accurately matching those of their female children, at least in the 8-18 age group. As studies have not shown more severe disease in females compared to males with CMT, there must be factors other than severity that causes both female children and their parents to score their physical QOL worse than males.

A potential explanation for gender differences could depend on whether the mother or father of the child completed the questionnaire, and whether this parent also had CMT. We did not assess parental CMT status but recognize that personal perception may have an impact on their proxy-score. However, CMT can be due to de novo mutations and are not always inherited; no significant outliers were seen amongst the parent proxy scores to suggest that parental CMT status might impact their assessment of their child’s CMT. It would also be challenging to accurately obtain this information because in many cases both parents were present at their child’s visit and both parents collaborated to fill out the instrument. We also don’t know if the affected parent was the mother or father. We do recognize that these are important questions going forward and hope to investigate these issues in future studies with this parent proxy instrument.

Correlating parent-proxy QOL scores with other standardized CMT assessments was difficult for the 0-7 age group, due to the lack of other validated COA data this age group, particularly for

children 4 years of age and younger. For example, the CMTPedS functional instrument is only validated for children ages 4 and older [15]. We were able to demonstrate a correlation between CMTPedS, with the physical QOL score (correlation coefficient=0.44) but not the mental QOL score (-0.01), as might be expected. The CMT infant toddler scale (CMTInfS) has been validated for children less than 4 years; however, it was only published in 2018 [21] and was not available between 2010 and 2016 as a concurrent assessment for this QOL measure validation study. The CMTES, as mentioned, is only considered valid for most children over 10 years of age and can be quite variable for children < 7 due to the subjectivity of many of the queries[18]. Thus future correlative studies with CMTInfS and CMTPedS will be particularly informative for 'pCMT-QOL (0-7 years parent-proxy'). Moreover, correlations studies with CMTInfS and CMTPedS may enable incorporating additional more specific items for young children in pCMT-QOL (0-7 years parent-proxy) in the future.

An additional limitation of the current study is that many of the subjects had CMT1A (58) compared to all other subtypes (32) and only five of 49 children had moderate to severe impairment based on their CMTES scores (Table 4). We again recognize that future studies correlating pCMT-QOL (0-7 years parent-proxy) with CMTInfS and CMTPedS in young children with additional genetic subtypes and severity levels will be important to perform to enable both natural history studies and clinical trials.

The parent-proxy version of the pCMT-QOL outcome measure for children aged 0-7 years old does contain questions that were not applicable to children 0-4 years old, pertaining to reading and writing. Far less than 50% of parents of children ages 0-4 did leave those items blank. Our known group validation analyses, however, indicate that there is no significant difference in the Total Score, Physical Composite Domain Score and the Mental Composite Domain Score by age (0-4 vs 5-7), as were correlations with other pediatric outcome measures including the CHQ and

CMTPedS scales, indicating that all items can be retained in the final outcome measure. A limitation was our inability to compare the parent-proxy scores with scores from the children themselves, which we had been able to do with the 8-18 year age group. Our pilot testing [5] had shown that children under the age of 7 are not able to interpret and complete the questions in the pCMT-QOL outcome measure. Nevertheless, parent-proxy scores were similar for children 0-4, 5-7 and 8-18 age groups, suggesting that the parent-proxy assessment is valid even for the youngest age group of 0-7.

We did attempt longitudinal analysis in the 0-7 years old group but believe the sample size was too small to draw definitive conclusions. Only 14 parents out of 113 performed assessments at both baseline and year 1, 16 parents performed assessments at baseline and year 2, but only 2 parents performed repeat assessments at baseline and year 4. Longitudinal responsiveness, assessed by calculating the Pearson correlation coefficient for the 1-year change in proxy Total pCMT-QOL Score with the 1-year change in the CMTES was moderate. The average PGIC score at year 1 fell midway between the “no change” (score=3) and “a little better” (score =2) values on the PGIC scale. The proxy Total pCMT-QOL score was fairly stable, as shown in the Results section. The conclusion was similar to the previous studies on both direct-report [8] and parent-proxy pCMT-QOL scores for the 8-18 group; with the even smaller sample size for the 0-7 group, our ability to draw conclusions with more confidence was even more limited [10].

In summary, we believe that the parent-proxy version of the pCMT-QOL outcome measure for children aged 0-7 years old can serve as a valid PRO measure of QOL in young children with CMT, particularly when combined with data that will emerge from the CMTInfS and CMTPedS in this age group. Importantly, the parent-proxy pCMT-QOL for children aged 0-7 years old does not require a clinic visit to be completed. As instruments such as the CMTInfS are also being developed for remote usage, it will be increasingly possible to evaluate young children remotely

both with functional and patient reported outcome measures, expanding the potential to perform natural history studies and clinical trials for children with limited access to established CMT clinics.

Conflict of Interest Statement:

MES has consulted with Applied Therapeutics, DTx Pharma, Alnylam, Inflectis, Passage Biosci, Swan Bio and Neurogene. MMR has served on a steering committee for Eidos Therapeutics, and consulted for Akcea, Alnylam, Applied Therapeutics, Augustine Therapeutics and Inflectis. RF has nothing to disclose. JB has nothing to declare. TTW, FM, EM, and TE have nothing to disclose. All companies listed are developing products they hope will be used in clinical trials and treatment for various forms of inherited neuropathies. SR is currently employed by Janssen Pharmaceutical Companies though she was on the faculty of the University of Michigan at the time the study was performed.

Data Availability Statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contribution Statement:

TTW, MES and SR contributed to the conception and design of the study. RF, CES, SMEF, JB, MMR, FM, EM, TE and MES contributed to the drafting of the text and evaluation of subjects

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Table 1: Internal Consistency of the Domains of the pCMT-QOL (0-7 years parent-proxy) Outcome Measure for Children Ages 0-7

Domain	Number of variables	Themes of Items pertaining to Domain	Standardized Cronbach alpha
Physical: Symptoms	12	Parent perception of the child's physical fatigue/weakness, pain, sleep, tremor, cramps	0.89
Physical: Function	10	Parent perception of the child's physical ADLs, upper extremity and lower extremity functions, balance	0.87
Physical: Social Activities	7	Parent perception of the child's physical activities with peers and adults	0.78
Mental: Feelings	10	Parent perception of the child's experiences of stigma, anxiety/fear, depression, stress	0.85
Mental: Cognition	10	Parent perception of the child's perceived cognitive function	0.94
Mental: Social Skills	8	Parent perception of the child's self-esteem, emotional bonding with peers and adults	0.82

ADLs: activities of daily living

Table 2: Individual Domain Scores, Composite Domain Scores, and Total Score: pCMT-QOL (0-7 years parent-proxy) for children 0-4 and 5-7 years old

Variable	Mean Parent-Proxy Version Score (n, SD)	Minimum Score	Maximum Score
Physical Domain Symptoms	0-7 yo: 36.7 (113, 16.2) 0-4 yo: 36.7 (45, 17.3) 5-7 yo: 36.6 (68, 15.6)	4.9 9.8 4.9	93.2 93.2 77.1
Physical Domain Function	0-7 yo: 42.0 (113, 20.5) 0-4: 49.1 (45, 21.1) 5-7: 37.4 (68, 18.9)	0 4.5 0	96.6 96.6 83.7
Physical Domain Social Activities	0-7 yo: 39.2 (111, 19.5) 0-4: 38.6 (44, 20.4) 5-7: 39.6 (67, 19.0)	0 0 0	80.2 75.8 80.2
Mental Domain Feelings	0-7 yo: 20.8 (111, 14.7) 0-4: 17.8 (44, 13.4) 5-7: 22.8 (67, 15.2)	0 0 0	72.2 53.4 72.2
Mental Domain Cognition	0-7 yo: 28.4 (102, 21.3) 0-4: 25.4 (36, 17.6) 5-7: 30.1 (66, 23.1)	0 0 0	94.3 68.8 94.3
Mental Domain Social Skills	0-7 yo: 18.7 (112, 12.4) 0-4: 17.8 (45, 11.1) 5-7: 19.4 (67, 13.2)	0 0 0	64.7 49.6 64.7
Physical Composite Domain Score	0-7 yo: 39.5 (113, 15.5) 0-4: 42.3 (45, 15.4) 5-7: 37.6 (68, 15.4)	4.1 7.1 4.1	86.5 86.5 80.2
Mental Composite Domain Score	0-7 yo: 23.5 (111, 14.4) 0-4: 21.0 (44, 11.4)	0 0	80.1 50.2

	5-7: 25.2 (67, 16.0)	0	80.1
Total Score	0-7 yo: 33.5 (111, 12.7) 0-4: 34.6 (44, 11.6) 5-7: 32.8 (67, 13.5)	3.4 5.9 3.4	80.1 63.2 80.1

Table 3: Convergent Validity: Spearman's Rank Correlations between pCMT-QOL (0-7 years parent-proxy) and Standard CMT Assessments

	Total pCMT-QOL Score	Physical Composite Domain Score	Mental Composite Domain Score
CHQ Physical Summary Score	-0.72, $p < 0.0001$*	-0.86, $p < 0.0001$*	-0.14, $p = 0.3002$
Age 0-4	-1, $p < 0.0001$*	-0.94, $p < 0.0048$*	0.09, $p = 0.8717$
Age 5-7	-0.69, $p < 0.0001$*	-0.85, $p < 0.0001$*	-0.14, $p = 0.3063$
CHQ Psychosocial Summary Score	-0.39, $p = 0.0022$*	-0.12, $p = 0.3538$	-0.64, $p < 0.0001$*
Age 0-4	-0.77, $p = 0.0724$	-0.71, $p = 0.1108$	-0.37, $p = 0.4685$
Age 5-7	-0.35, $p = 0.0106$*	-0.06, $p = 0.6531$	-0.66, $p < 0.0001$*
CMTPedS	0.36, $p = 0.0004$*	0.44, $p < 0.0001$*	-0.01, $p = 0.9003$
Age 0-4	0.37, $p = 0.0424$*	0.49, $p = 0.0044$*	-0.16, $p = 0.3954$
Age 5-7	0.35, $p = 0.0060$*	0.41, $p = 0.0010$*	0.04, $p = 0.7547$

*$p < 0.05$; uncorrected for multiple testing

Table 4: Known Group Validation with pCMT-QOL (0-7 years parent-proxy)

		Total Score		Physical Composite Domain Score		Mental Composite Domain Score	
		Mean (SD)	p value	Mean (SD)	p value	Mean (SD)	p value
Gender	Male (n=68)	33.28 (12.66)	0.829	36.90 (13.94)	0.029*	27.18 (15.21)	0.0004*
	Female (n=45)	33.82 (13.01)		43.35 (16.98)		17.94 (11.20)	
Age	0-4 (n=45)	34.59 (11.60)	0.468	42.26 (15.34)	0.119	20.98 (11.38)	0.109
	5-7 (n=68)	32.78 (13.48)		37.62 (15.40)		25.18 (16.00)	
CMT subtypes	1A (n=58)	32.09 (12.23)	0.182	37.05 (15.44)	0.094	23.72 (13.42)	0.943
	Other types (n=32)	35.86 (13.23)		42.72 (14.74)		23.96 (17.86)	
CMTES	Mild (n=44)	31.01 (11.71)	0.047*	35.89 (14.16)	0.013*	22.93 (14.42)	0.978
	Moderate/Severe (n=5)	42.18 (10.51)		52.90 (11.12)		23.11 (11.47)	

*$p < 0.05$; uncorrected for multiple testing