# Development and Validation of the Pediatric Charcot–Marie–Tooth Disease Quality of Life Outcome Measure

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**Objective:** Charcot–Marie–Tooth disease (CMT) reduces health-related quality of life (QOL), especially in children. Defining QOL in pediatric CMT can help physicians monitor disease burden clinically and in trials. We identified items pertaining to QOL in children with CMT and conducted validation studies to develop a pediatric CMT-specific QOL outcome measure (pCMT-QOL).

**Methods:** Development and validation of the pCMT-QOL patient-reported outcome measure were iterative, involving identifying relevant domains, item pool generation, prospective pilot testing and clinical assessments, structured focus-group interviews, and psychometric testing. Testing was conducted in children with CMT seen at participating sites from the USA, United Kingdom, and Australia.

**Results:** We conducted systematic literature reviews and analysis of generic QOL measures to identify 6 domains relevant to QOL in children with CMT. Sixty items corresponding to those domains were developed de novo, or identified from literature review and CMT-specific modification of items from the pediatric Neuro-QOL measures. The draft version underwent prospective feasibility and face content validity assessments to develop a working version of the pCMT-QOL measure. From 2010 to 2016, the pCMT-QOL working version was administered to 398 children aged 8 to 18 years seen at the participating study sites of the Inherited Neuropathies Consortium. The resulting data underwent rigorous psychometric analysis, including factor analysis, test–retest reliability, internal consistency, convergent validity, item response theory analysis, and longitudinal analysis, to develop the final pCMT-QOL patient-reported outcome measure.

**Interpretation:** The pCMT-QOL patient-reported outcome measure is a reliable, valid, and sensitive measure of health-related QOL for children with CMT.

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Charcot–Marie–Tooth disease (CMT) is the most common inherited neurodegenerative disorder, affecting 1 in 2,500 individuals,[1] with no disease-modifying treatment. Previous therapeutic discoveries in CMT[2–4] led to several clinical trials[5–7]; although unsuccessful, these trials gave rise to an international collaboration to study the natural history of CMT[8] and validate new outcome measures for future trials.[9–12] Pediatric trials are especially in focus, as signs and symptoms can progress throughout childhood in CMT and many children become dependent on assistive devices by early adulthood.[13–16] Therefore, there is an urgent need for validated outcome measures for pediatric CMT trials, including patient-reported outcome (PRO) measures to assess disease burden. Health-

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related quality of life (QOL), a specific type of PRO, is an important outcome to assess in pediatric CMT trials, as it is significantly reduced in children with CMT.[17,18] However, generic health-related QOL outcome measures are unsuitable for clinical trials, as they lack specificity[19,20] and sensitivity[5,21] to disease-related changes, and there is no disease-specific health-related QOL outcome measure for children with CMT. The objective of this study was to build, and rigorously validate through prospective studies, a pediatric CMT health-related QOL (pCMT-QOL) PRO measure for use in trials.

## Patients and 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. Three different samples were used for different aspects of the study. Group 1 (n = 31) participants were recruited from Wayne State University for the pilot testing of the pCMT-QOL PRO measure. Group 2 (n = 398) participants were recruited through the prospective, natural history study in children with CMT (ClinicalTrials.gov identifier NCT01193075) from 2010 to 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; Australia—University of Sydney & Children's Hospital, Sydney. Group 3 (n = 13) participants were recruited from the University of Iowa for test–retest validation. Ethics approval from all institutions for all studies and written informed assent/consent from all children and their families were obtained.

### Statistical Analysis

The development and validation of the pCMT-QOL PRO measure was an iterative process, as recommended by US Food and Drug Administration guidance.[22,23] The details of the conceptual framework (Fig 1) are provided below.

***Defining the Construct.*** We identified domains that are pertinent to the health-related QOL of a CMT patient through (1) systematic literature review; and (2) analysis of common domains in existing pediatric QOL measures and the 36-item Short-Form Health Survey (SF-36), a gold-standard adult generic QOL measure.

***Generation of the Item Pool.*** For the domains identified through the above process, a literature review was conducted to identify items pertaining to pediatric CMT health-related QOL; remaining items were developed de novo and through CMT-specific modification of select items from the pediatric Neuro-QOL measures, which in turn were developed and evaluated with National Institutes of Health funding.[24] The items were edited for clarity and then underwent patient and expert review[25] to develop a draft version of the pCMT-QOL PRO measure.

***Pilot Testing.*** We prospectively administered the draft version of the pCMT-QOL in 31 children with CMT aged 4 to 17 years (Group 1), followed by structured focus-group interviews and clinical assessments to assess feasibility and face validity, and developed a working version of the pCMT-QOL PRO measure.

***Psychometric Testing.*** From 2010 to 2016, the working version of the pCMT-QOL was also administered prospectively to 398 children seen at the participating sites of the Inherited Neuropathies Consortium (Group 2) for further psychometric testing, including internal consistency, convergent validity, and item response theory (IRT) modeling, to develop the final pCMT-QOL PRO measure. The working version of the pCMT-QOL PRO measure was also prospectively administered to 13 children with CMT (Group 3) to assess test–retest reliability. Validated assessments used for the analyses included the generic Child Health Questionnaire (CHQ), considered a gold standard in pediatric quality of life research,[26–29] and validated CMT clinical outcome assessments (COAs), including the CMT Neuropathy Score (CMTNS) version 2, a validated composite outcome measure in CMT,[11] the CMT Examination Score (CMTES), a subset of the CMTNS without nerve conduction studies that has been validated as a standalone outcome measure in CMT,[12] and the CMT Pediatric Scale (CMTPedS),[10] the validated functional outcome measure in pediatric CMT. The statistical software used for the analyses was Stata-IC 12.1 (StataCorp, College Station, TX), SAS version 9.4 (SAS Institute, Cary, NC), and Mplus version 8.4 (Muthén & Muthén, Los Angeles, CA). Specific analyses are detailed below.

***Descriptive Statistics.*** The study sample was characterized with descriptive statistics such as mean, standard deviations (SDs), median, and range.

***Test–Retest Reliability.*** Thirteen children were administered the working version of the pCMT-QOL twice

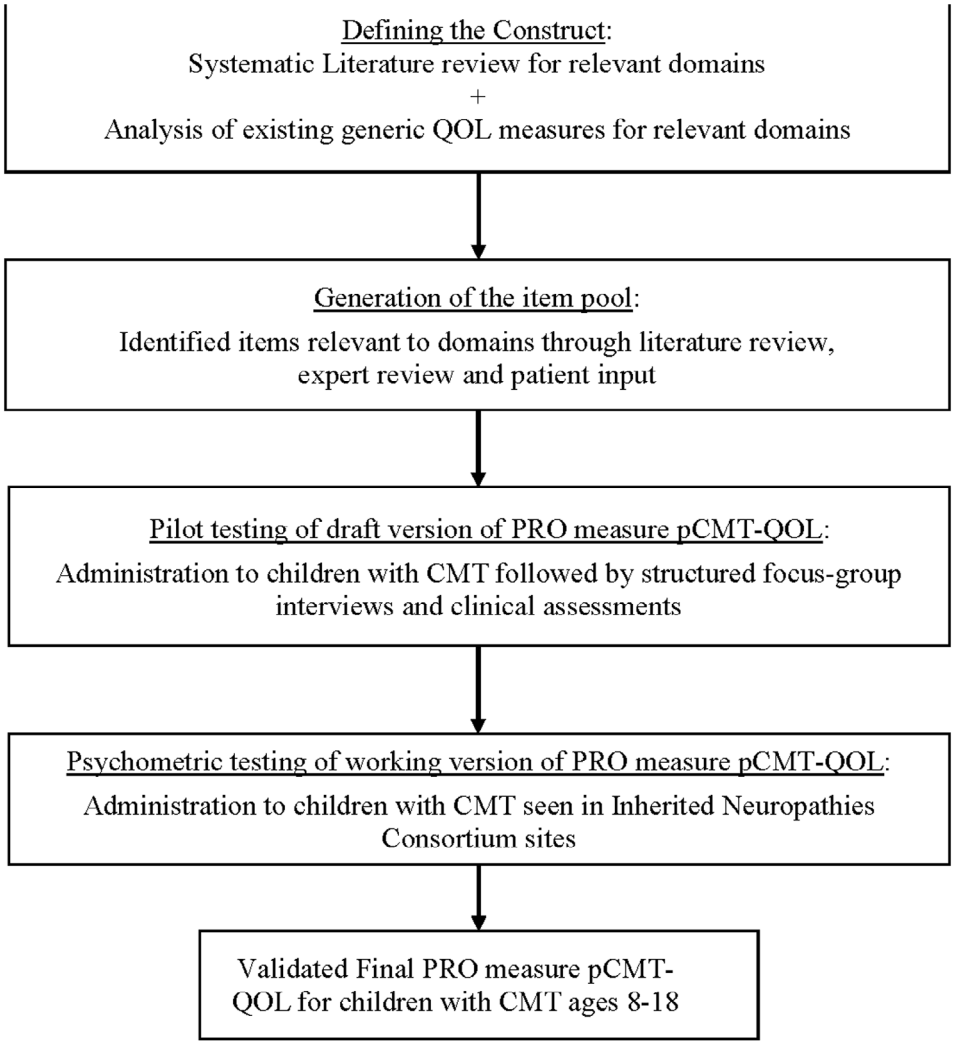


**FIGURE: Conceptual framework for pCMT-QOL development and validation. CMT = Charcot–Marie–Tooth disease; PRO = patient-reported outcome; QOL = quality of life.**

within a 7-week period, the first provided in clinic, and the second mailed to their home. Intraclass correlation coefficients (ICCs) were used to quantify the test–retest reliability of the pCMT-QOL; individual items with low ICCs were discarded, depending on content analysis.

***Factor Analysis and IRT Analysis.*** The construct validity of the 6-domain working version of the pCMT-QOL was assessed via exploratory factor analysis (EFA), with iterated principal axis factoring as the extraction method, and varimax as the rotation method. Questions with significant factor loadings (>0.30) were assigned to a domain, whereas those with cross-loadings or factor loadings < 0.30 were considered for transfer to a more appropriate domain. Confirmatory factor analysis (CFA) was performed to determine construct validity of the domains. IRT analysis using graded response models (GRM) was used to verify the unidimensionality of each domain.

***Final Version and Scoring.*** The final version of the pCMT-QOL PRO measure was developed, and domain, composite, and total scores were calculated and transformed to a 0–100 scale, with a higher score indicating worse QOL.

***Internal Consistency and Validity.*** Cronbach alpha coefficient was calculated to evaluate the internal consistency within each domain. Convergent validity was determined by calculating the Spearman rank correlation between the Total pCMT-QOL Score and validated outcome measures such as the CMTNS, CMTES, CHQ, and the CMTPeds, as well as the correlation between the pCMT-QOL Physical Composite Domain Score, the pCMT-QOL Mental Composite Domain Score, and the corresponding physical summary score and the psychosocial summary score of the CHQ.

***Known Group Comparisons.*** Two-sample *t* tests were used to compare groups defined by gender, worse disease severity characterized by CMTES >/= 10,[12] and CMT genetic diagnosis.

***Longitudinal Analysis.*** Longitudinal responsiveness was assessed by correlating changes in Total pCMT-QOL Score over time with changes to the CMTES and the 7-point Patient's Global Impression of Change (PGIC) scores (the latter ranging from 6 = "very much worse" to 3 = "no change" to 0 = "very much better"). The standardized response mean (SRM) for the Total pCMT-QOL Score over time was also calculated: SRM = mean change in scores over time / SD of change over time.

## Results

Results from specific steps of the iterative process were as follows.

### Defining the Construct

***Systematic Literature Review.*** We identified the following domains impacting QOL from CMT literature: psychosocial stressors,[30] physical disability, depression, pain,[31] ability to ambulate independently, toe and heel walk, bodily pain, strength of forearm/hand intrinsic muscles,[32] lower limb weakness, and leg cramps.[33]

***Analysis of Existing QOL Measures.*** We compared 3 existing pediatric QOL scales: the Pediatric Quality of Life Inventory,[34,35] the TNO-AZL Children's Quality of Life (TACQOL),[36] and the CHQ,[26–29] as well as 1 adult health status measure: the SF-36.[37–39] Common domains identified in these scales included physical complaints and functioning, activities of daily living, bodily pain, cognitive complaints and functioning, and social play (physical) versus social skills (mental). At the end of this process, 6 domains were identified as relevant to QOL in children with CMT, which could be further combined into 2 composite domains: physical and social (Table 1).

### Generation of the Item Pool

For the 6 domains, literature review identified leg cramps, tremor, agility, endurance, and ankle flexibility as items pertinent to pediatric CMT health-related QOL.[40] Sleep and fatigue were additional items identified as relevant to CMT patients.[41] Remaining items for the previously identified 6 domains were developed de novo and through CMT-specific modification of select items from the pediatric Neuro-QOL measures,[24] for a total of 60 items (10 items per domain). The items were edited for clarity (ease of reading, present tense, active voice) and then underwent expert review by 21 researchers and 2 patient representatives from Australia, Belgium, France, Germany, Italy, the Netherlands, Spain, the United Kingdom, and the USA at the 168th European NeuroMuscular Centre International Workshop[25] to develop a draft version of the pCMT-QOL PRO measure.

### Pilot Testing

We administered the draft version of the pCMT-QOL prospectively to 31 children aged 4 to 17 years with CMT, followed by structured focus-group interviews and CMTNS assessments, to assess feasibility and face content validity. Focus group characteristics and results are summarized in Table 2. The Physical Function Domain and Social Activities Domain of the pCMT-QOL PRO measure had an *r* of 0.70 and 0.51 with CMTNS scores, respectively, providing early content validity. The contents of the draft version were also well accepted by children per their interview responses. Children younger than 8 years had trouble understanding and completing the surveys on their own, and we therefore raised the minimum age for completing the pCMT-QOL PRO measure to 8 years, and increased the upper age limit to 18 years based on patient input. Varying response categories to the items proved confusing to children; therefore, all responses to questions were changed to a uniform 5-point Likert scale: (0 = never, 1 = almost never, 2 = sometimes, 3 = almost always/a lot of times, and 4 = always). Questions starting with "in the past 7 days" were problematic, especially if they referenced school activities and the child was being seen during holidays; therefore, these were changed to "lately." The final result was a working version of the pCMT-QOL PRO measure.

### Psychometric Testing

From 2010 to 2016, the pCMT-QOL working version was administered to 398 children seen at the participating study sites of the Inherited Neuropathies Consortium (Group 2). Of these, 358 had confirmed CMT; patient demographics and other characteristics are shown in Table 3.

***Test–Retest Reliability.*** Test–retest reliability of the working version of the pCMT-QOL was assessed by prospective administration to 13 children (Group 3). The measure was administered twice within a 7-week period; the first administration was in clinic, and the second was mailed to the child's home. Test–retest reliability for the overall measure was high (ICC = 0.92). Two items were eliminated for having an ICC < 0.65: "My CMT makes it hard to plan spontaneous trips" (ICC = 0.32) and "I have difficulty with my hobbies (ex. Playing video games) because of CMT" (ICC = 0.17). One additional item, "I

**TABLE 1. Conceptual Domains of the Pediatric CMT QOL Outcome Measure**

| Domain | Items Pertaining to Domain | Composite Domain | Complete Outcome Measure |
|---|---|---|---|
| Symptoms | Physical fatigue/weakness, pain, sleep, tremor, cramps | Physical | Pediatric CMT QOL outcome measure |
| Function | Physical ADLs, upper extremity and lower extremity functions, balance | | |
| Social Activities | Physical activities with peers and adults | | |
| Feelings | Stigma, anxiety/fear, depression, stress | Social | |
| Cognition | Perceived cognitive function | | |
| Social Skills | Self-esteem, emotional bonding with peers and adults | | |

ADL = activity of daily living; CMT = Charcot–Marie–Tooth disease; QOL = quality of life.

get easily frustrated with my reading or writing projects" (ICC = 0.54) was retained as relevant to pediatric CMT after content review.

***Factor Analysis and IRT Analysis.*** EFA was used to determine whether the remaining questions within each of the 6 domains measured a similar concept. The Kaiser–Meyer–Olkin value of 0.88 and the Tucker and Lewis reliability coefficient of 0.945 indicated good reliability. Bartlett test of sphericity showed a $p$ value < 0.0001, supporting factorability.[42] The factor analysis revealed 7 domains with eigenvalues > 1, explaining 83.5% of the total variance. After a careful examination of each question and loading values, the only item in the seventh domain (loading = 0.41) was transferred to the Symptoms Domain (loading = 0.34), resulting in the final 6 domains, which overlapped well with our original domains. The item "I have trouble falling asleep at night" was removed after content review, because it was not pertinent to the Cognition Domain assigned by EFA. CFA supported factor validity of the domains ($\chi^2/df$ ratio = 2.1 and root mean square error of approximation estimate = 0.0611 with 90% confidence interval = 0.0582–0.0640). IRT analysis using GRM for ordinal responses or rating scales supported the unidimensionality of each domain (first principal component explained >/= 50% of the variation).

**TABLE 2. Focus Group Characteristics and Results**

N = 31; 15 M and 16 F

84% Caucasian

Age range = 4–17 yr (mean age = 10, SD = 4)

Pearson correlation coefficients ($r$) between CMTNS and individual pCMT-QOL domain scores:
- CMTNS and Symptoms Domain: $r$ = 0.22
- CMTNS and Function Domain: $r$ = 0.70
- CMTNS and Social Activities Domain: $r$ = 0.51
- CMTNS and Feelings Domain: $r$ = 0.23
- CMTNS and Cognition Domain: $r$ = 0.35
- CMTNS and Social Skills Domain: $r$ = 0.05

Issues that needed immediate changes:
- Age groups (5–17 changed to 8–18 yr)
- Recall period ("in past 7 days" to "lately")

CMTNS = CMT Neuropathy Score; F = female; M = male; SD = standard deviation.

***Final Version and Scoring.*** The final version of the pCMT-QOL PRO measure is shown in Supplementary Table S1. All pCMT-QOL 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 pCMT-QOL Score were calculated and standardized as follows. All scores were calculated for individuals with nonmissing values for at least one half of the items in each domain. For those with half or more missing values, the scores were set as missing. The score was calculated in 2 steps for those with more than one half of the scores available. In Step 1, the weighted sum of all items 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

**TABLE 3. Patient Demographics and Characteristics**

| |
|---|
| n = 358 of 398 with CMT<br>Other diagnoses, excluded from analyses:<br>• HNPP: 4 (1%)<br>• HMN: 10 (2.5%)<br>• HSN: 8 (2.0%)<br>• Other: 5 (1.3%)<br>• Unknown: 13 (3.3%) |
| Confirmed genetic diagnosis: 272 of 358 (76%)<br>Most frequently confirmed CMT genetic diagnoses (n, % of 358):<br>• CMT1A: 183 (51.1%)<br>• CMT2A: 17 (4.7%)<br>• CMT1X: 12 (3.4%)<br>• CMT1B: 9 (2.5%)<br>• CMT4C: 9 (2.5%)<br>• CMT1E: 6 (1.7%) |
| Age range = 8–18 yr (median = 12)<br>Age (mean yr, SD) of most frequent subtypes:<br>• CMT1A (12, 3.1)<br>• CMT2A (13, 3.9)<br>• CMT1X (14, 3.1)<br>• CMT1B (12, 3.6)<br>• CMT4C (13, 2.9)<br>• CMT1E (11, 3.8) |
| Gender: M: 196 (54.8%) |
| Ethnicity: not of Hispanic, Latino, or Spanish origin: 295 (82.4%) |
| Race: Caucasian: 298 of 358 (83.2%)<br>Other races:<br>• African American: 9 (2.5%)<br>• Asian: 11 (3.1%)<br>• Multiple: 11 (3.1%)<br>• Unknown: 29 (8.1%) |

CMT = Charcot–Marie–Tooth disease; HMN = hereditary motor neuropathy; HNPP = hereditary neuropathy with liability to pressure palsies; HSN = hereditary sensory neuropathy; M = male; SD = standard deviation.

score of 0 representing the best QOL (of note, this is the opposite of the CHQ, where the higher the score, the better the QOL). The same algorithm was employed for each domain score, physical and mental summary measures, and the overall score. If there were missing items and the number of missing items was smaller than one half, then we only used the nonmissing items in the calculations. The mean individual domain scores, Physical Composite Domain Score, Mental Composite Domain Score, and Total pCMT-QOL Score in our study sample are provided in Table 4.

***Internal Consistency and Validity.*** To assess internal consistency, we calculated Cronbach alpha coefficients for the redistributed items per domain; this showed good internal consistency, with Cronbach alpha ranging from 0.78 to 0.90 for all 6 domains. Convergent validity as calculated by Spearman rank correlations is shown in Table 5. All correlations were highly significant, except for the CMTNS and the Mental Composite Domain Score. The strongest correlations were seen between the Total pCMT-QOL Score and the CHQ Physical Summary Score ($-0.61$, $p < 0.0001$), the Physical Composite Domain Score and the CHQ Physical Summary Score ($-0.67$, $p < 0.0001$), and the Mental Composite Domain Score and the CHQ Psychosocial Summary Score ($-0.51$, $p < 0.0001$).

***Known Group Comparisons.*** Differences in pCMT-QOL scores by gender, disease severity, and CMT genetic diagnoses using $t$ test are shown in Table 6. Significant differences in QOL scores were noted by disease severity (worse Total pCMT-QOL Score and Physical Composite Domain Score in children with more severe disease as characterized by CMTES >/= 10; no difference between severity types in Mental Composite Domain Score). Significant differences in QOL scores were also seen by gender (worse Total pCMT-QOL Score and Physical Composite Domain Score in females; no difference between genders in Mental Composite Domain Score). No difference in QOL scores was seen by genetically confirmed CMT1A (most common genotype seen) versus others. Furthermore, the correlation between Total pCMT-QOL Score in genetically confirmed CMT1A and age was nonsignificant at 0.032 ($p = 0.67$).

***Longitudinal Analysis.*** Over 5 years, of the 358 children with CMT, 57 had assessments at baseline and year 1, but the numbers decreased to only 5 children having repeat assessments from baseline to year 5. Longitudinal responsiveness, assessed by calculating the Pearson correlation coefficient for the 1-year change in Total pCMT-QOL Score with the 1-year change in CMTES score, was high at 0.57 ($p = 0.0008$). The average PGIC score at year 1 was 2.5, with a SD of 1.4, which falls midway between the "no change" (score = 3) and "a little better" (score = 2) values on the PGIC scale. Correspondingly, the Total pCMT-QOL Score was fairly stable over 1 year, with a mean difference of $-2.95$ in raw scores with an SD of 9 and an overall SRM of $-0.327$.

## Discussion

We have developed and rigorously validated a disease-specific, patient-reported health-related QOL outcome measure for children with CMT in this longitudinal study. The pCMT-QOL PRO measure can be used along with

**TABLE 4. Scores per Individual Domains, Composite Domains, and Total pCMT-QOL**

| Domain | n | Mean | SD | Minimum Score in Current Study Sample | Maximum Score in Current Study Sample |
|---|---|---|---|---|---|
| Symptoms | 355 | 33.5 | 17.2 | 0 | 84.7 |
| Function | 357 | 29.5 | 19.5 | 0 | 92.8 |
| Social Activities | 355 | 41.2 | 20.8 | 0 | 100 |
| Feeling | 356 | 28.4 | 22.7 | 0 | 100 |
| Cognition | 355 | 29.2 | 18.4 | 0 | 90.4 |
| Social Skills | 355 | 20.7 | 16.3 | 0 | 100 |
| Physical Composite Domain Score | 357 | 34.6 | 15.1 | 0 | 83.1 |
| Mental Composite Domain Score | 356 | 27.1 | 15.5 | 0 | 81.6 |
| Total pCMT-QOL Score | 357 | 30.9 | 13.6 | 2.4 | 68.3 |

SD = standard deviation.

the recently validated adult CMT-specific QOL instrument, the Charcot–Marie–Tooth Health Index,[43] to assess the QOL across all ages in patients with CMT.

It is important to note that our goal was not merely to show that QOL is impaired in CMT, but rather to systematically determine and quantify the factors that contribute to reduced QOL in children with CMT. The disease-specific pCMT-QOL PRO measure thus has important distinctions and advantages from generic QOL outcome measures; it includes items pertinent to pediatric CMT patients, which were modified and refined by prospective pilot testing prior to undergoing longitudinal validation. Furthermore, the specificity of the pCMT-QOL PRO measure will complement other validated CMT-specific COAs such as the CMTPedS,[10] the Rasch-modified CMTNS version 2,[11] the CMTES,[12] and other measures in development such as the CMT Functional Outcome Measure,[44] to fully capture the disease burden experienced by the child with CMT. The pCMT-QOL PRO measure can thus be used in a clinical setting or as a trial outcome measure to obtain the child's views on the comprehensive effectiveness of an intervention on their CMT.

People with CMT often have physical limitations that limit their ability to travel to centers of excellence and be evaluated for clinical trials. In addition, recent events such as the COVID-19 pandemic have made even more clear that there is an urgent need for trial outcome measures that do not require in-clinic visits and can be assessed remotely. Fortuitously, our study had included remote assessments of test–retest reliability, and our results show test–retest reliability of the pCMT-QOL PRO measure up to 7 weeks apart with remote administration.

**TABLE 5. Spearman Rank Correlations between pCMT-QOL and Other Standard CMT Assessments**

| | Total pCMT-QOL Score | Physical Composite Domain Score | Mental Composite Domain Score |
|---|---|---|---|
| CMTES | 0.36, $p < 0.0001$[a] | 0.43, $p < 0.0001$[a] | 0.19, $p = 0.0013$[a] |
| CMTNS | 0.36, $p = 0.0001$[a] | 0.39, $p < 0.0001$[a] | 0.18, $p = 0.0624$ |
| CHQ Physical Summary Score | −0.61, $p < 0.0001$[a] | −0.67, $p < 0.0001$[a] | −0.38, $p < 0.0001$[a] |
| CHQ Psychosocial Summary Score | −0.44, $p < 0.0001$[a] | −0.29, $p < 0.0001$[a] | −0.51, $p < 0.0001$[a] |
| CMTPedS | 0.37, $p < 0.0001$[a] | 0.47, $p < 0.0001$[a] | 0.16, $p = 0.0036$[a] |

[a] $p < 0.05$; uncorrected for multiple testing.
CHQ = Child Health Questionnaire; CMT = Charcot–Marie–Tooth disease; CMTES = CMT Examination Score; CMTNS = CMT Neuropathy Score; CMTPedS = CMT Pediatric Scale.

**TABLE 6. Known Group Comparisons by Gender, Disease Severity, and CMT Genetic Diagnosis for Total pCMT-QOL Score, and Physical and Mental Composite Domain Scores**

| Variable | n | Mean, SD | *t* Value, *p* |
|---|---|---|---|
| Total pCMT-QOL Score | | | |
| M | 195 | 29.4, 13.4 | 2.78, $p = 0.0058$[a] |
| F | 161 | 33.4, 13.5 | |
| CMTES mild | 231 | 29.1, 13.3 | 4.25, $p < 0.0001$[a] |
| CMTES moderate/severe | 42 | 38.5, 12.3 | |
| CMT1A | 182 | 31.3, 14.1 | −0.09, $p = 0.9255$ |
| CMT other genetic types | 88 | 31.1, 14.3 | |
| pCMT-QOL Physical Composite Domain Score | | | |
| M | 195 | 31.9, 14.6 | −3.79, $p = 0.0002$[a] |
| F | 162 | 37.8, 15.2 | |
| CMTES mild | 232 | 31.6, 14.3 | 5.53, $p < 0.0001$[a] |
| CMTES moderate/severe | 42 | 44.8, 13.4 | |
| CMT1A | 183 | 34.2, 15.3 | 1.05, $p = 0.2927$ |
| CMT other genetic types | 88 | 36.3, 16.3 | |
| pCMT-QOL Mental Composite Domain Score | | | |
| M | 195 | 26.4, 15.3 | −0.92, $p = 0.3571$ |
| F | 161 | 27.9, 15.7 | |
| CMTES mild | 231 | 26.1, 15.4 | 1.74, $p = 0.0830$ |
| CMTES moderate/severe | 42 | 30.6, 16.1 | |
| CMT1A | 182 | 27.7, 16.3 | −1.5, $p = 0.1343$ |
| CMT other genetic types | 88 | 24.6, 15.2 | |

[a] $p < 0.05$; uncorrected for multiple testing.
CMT = Charcot–Marie–Tooth disease; CMTES = CMT Examination Score; F = female; M = male; SD = standard deviation.

The known group comparisons in these children with CMT yielded several interesting results. Previous longitudinal studies have shown that the CMTES does worsen over time as the patient ages.[12] To assess whether QOL scores also correlate with age, we calculated the Pearson correlation between our Total pCMT-QOL Score in children with CMT1A and age; this was nonsignificant at 0.032 ($p = 0.67$). Of note, our longitudinal analysis showed a significant Pearson correlation coefficient of 0.57 ($p = 0.0008$) between the 1-year change in CMTES and Total pCMT-QOL Score. Taken together, these findings seem to suggest that although QOL correlates well with examination findings in CMT, age alone may not account for how QOL, as assessed by the pCMT-QOL PRO measure, changes over time. Further longitudinal studies are needed, given the significant attrition in numbers in our longitudinal group. Females had worse Total pCMT-QOL Score and Physical Composite Domain Score, but no significant difference was seen in the Mental Composite Doman Score. As studies have not shown more severe disease in females compared to males with CMT, there must be factors other than severity that causes females to score their physical signs worse than males. The pCMT-QOL PRO measure was able to statistically distinguish between mild and moderate/severe CMT, yet showed no significant difference in scores between CMT types, suggesting that QOL in pediatric CMT is not dependent on the underlying mechanism of the disease

but rather the overall disease severity. This association in particular would be important to track in future pediatric CMT trials, especially those that target the molecular and genetic basis of the disease. Recent scientific advances such as the development of antisense oligonucleotides to decrease PMP22 expression in CMT1A,[45] or gene replacement strategies to treat CMT1X[46] or CMT4,[47] make clinical trials directed at reversing the genetic and molecular causes of CMT realistic. These novel treatments are not directed at axonal repair, which causes much of the disability in patients, and are likely to be most effective when administered to children prior to the development of axonal degeneration and its consequences. However, because pediatric trials generally enroll children of varying ages and axonal loss, it would be pertinent to assess the impact of such root-cause treatments on the patient's overall QOL by disease severity.

There are some limitations in this study. Although our sample size is robust, the age ranges and means for the overall study group are skewed to younger patients, which may affect the QOL scores. There was significant attrition in the overall study group, such that only 5 of the original 358 children had repeat annual assessments from baseline to year 5. Although the Total pCMT-QOL Score stayed fairly stable over 1 year, we were able to show that the pCMT-QOL PRO measure was responsive to disease severity changes over time. This is important because it provides evidence that the pCMT-QOL PRO measure is not limited by the disability paradox that can be seen in chronic illness, in which QOL scores improve despite disease progression due to closer alignment between functional expectations and functional limitations.[48] Further research, including the analysis of pCMT-QOL scores through a prospective longitudinal drug trial, would allow for factor analysis to determine which items might be omitted to develop an abbreviated version of the pCMT-QOL, thus reducing patient burden in completing the measure, and making it more practical clinically. Although there was no significant difference in pCMT-QOL scores between the most common genotype (CMT1A) and all others, given the higher prevalence of CMT1A in this study, genotype-specific correlative studies must be conducted to ensure the suitability of this outcome measure for all CMT types. Finally, because our analyses showed that gender and severity are related to the pCMT-QOL, future pediatric CMT studies should further evaluate the influence of demographic and disease severity variables in QOL outcomes.

The pCMT-QOL PRO measure demonstrates robust psychometric properties overall. Together with the recently developed and validated CMT COAs, the pCMT-QOL PRO measure can thus be used as a measure of disease burden in the clinical setting, as well as an outcome measure in future pediatric CMT clinical trials.

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## Author Contributions

S.R., R.S.F., and M.E.S. contributed to the conception and design of the study; all authors contributed to data acquisition, analysis, and interpretation, and to drafting the text and preparing the figure.

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## Potential Conflicts of Interest

Nothing to report.

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