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Relationship Between Clinical Outcome Measures and Parent Proxy Reports of Health-related Quality of Life in Ambulatory Children with Duchenne Muscular Dystrophy

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Abstract

In Duchenne muscular dystrophy, data directly linking changes in clinical outcome measures to patient-perceived well-being are lacking. Our study evaluated the relationship between clinical outcome measures used in clinical trials of ambulatory Duchenne muscular dystrophy (Vignos functional grade, quantitative knee extension strength, timed functional performance measures, and gait velocity) and 2 health-related quality of life measures — the PODCI and PedsQL™ — in 52 ambulatory Duchenne muscular dystrophy subjects and 36 controls. Those with the disease showed significant decrements in parent proxy-reported health-related quality of life measures versus controls across all domains. The PODCI transfers/basic mobility, PODCI sports/physical function, and PedsQL™ physical functioning domains had significant associations with age (and hence disease progression), and traditional clinical outcome measures employed in clinical trials of ambulatory boys with Duchenne muscular dystrophy. Selected domains of the PODCI and generic PedsQL™ are potential patient-reported outcome measures for clinical trials in ambulatory individuals with the disease.

Keywords

Duchenne muscular dystrophy; clinical outcome measures; health related quality of life; clinical trials; PODCI; PedsQL

Introduction

While promising and novel therapeutic targets have emerged for muscular dystrophies and other neuromuscular diseases, significant barriers to the development of clinical trials in these diseases remain.¹ Crucial deficiencies include lack of a detailed understanding of the characteristics and natural history of specific neuromuscular diseases, lack of objective clinical outcome measures that are sufficiently sensitive to changes in disease course, and lack of data that directly link changes in clinical outcome measures to patient-perceived well-being.^{2–4} Health-related quality of life is a multidimensional construct, consisting at a minimum of physical, psychological (including emotional and cognitive), and social health

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dimensions delineated by the World Health Organization.^{5–6} It is thought to be the best representation of patient perceptions of the impact of an illness and its treatment on their own functioning and well being.^{5–6} There is an urgent need to develop practical and easily administered measures of health-related quality of life which are sensitive and responsive to changes produced by treatments in children with muscular dystrophies and other neuromuscular diseases across a range of ages and stages of disease severity.

Consumers, clinicians, researchers, the Food and Drug Administration, and industry have increasingly recognized the importance of *patient-reported outcome measures* in the determination of *clinically meaningful outcomes* and validation of clinical and surrogate endpoints for therapeutic trials.⁷ The FDA has strongly recommended inclusion of a patient-reported outcome measure such as a health-related quality of life assessment as an endpoint in all clinical trials.^{6,8} In recent years, health-related quality of life measurement has been increasingly used as an essential health outcome measure in clinical trials involving children with neuromuscular disorders.^{9–11} Generic health-related quality of life instruments^{12,13} have been used most frequently as patient-reported outcome measures; however, these measures may be inadequate in terms of sensitivity for detection of change induced by a treatment. More recently, there have been increasing efforts to develop condition-specific person reported outcomes in neuromuscular diseases^{14–22} for use in clinical trials. Both generic health-related quality of life instruments and disease-specific patient-reported outcome measures have been advocated to determine the *clinical meaningfulness* of a change in more traditional clinical measures of body system impairment, activities, and function.²³

Clinical trials in Duchenne muscular dystrophy have traditionally used quantitative strength, timed functional performance measures, and, more recently, the 6-minute walk test as clinical endpoints to determine therapeutic effectiveness.^{24–33} Two commonly employed health-related quality of life instruments that have been validated in large numbers of children include the PedsQL^{TM}^{12,34–39} and the American Academy of Orthopaedic Surgeons Pediatric Musculoskeletal Function Instrument, also referred to as the Pediatric Outcomes Data Collection Instrument, or PODCI.^{13,40–43} The aims of this study were to (1) determine whether ambulatory boys with Duchenne muscular dystrophy differ significantly by age from typically developing boys (controls) using 2 common patient-reported outcome measures, the Pediatric Outcomes Data Collection Instrument and PedsQL^{TM}; (2) determine whether there is an age-related decline in specific domain scores of the Pediatric Outcomes Data Collection Instrument and PedsQL^{TM} in ambulatory boys with Duchenne muscular dystrophy; (3) determine the relationship between specific domain scores of the Pediatric Outcomes Data Collection Instrument and domain scores of the PedsQL^{TM} in ambulatory Duchenne muscular dystrophy subjects; (4) determine the relationship between common therapist measured clinical endpoints used for clinical trials in Duchenne muscular dystrophy and specific domains of the Pediatric Outcomes Data Collection Instrument and PedsQL^{TM}; and (5) determine whether defined levels of performance on select clinical endpoints (Vignos functional scale, quantitative strength, timed functional performance measures, and walking velocity) are associated with significant differences on patient-reported health-related quality of life domains from the PedsQL^{TM} and PODCI.

Participants and Methods

Study Subjects

Participants included 52 boys with Duchenne muscular dystrophy ages 4 to 15 years (26 recruited from the Northern California Shriners Hospital and 26 recruited from the Portland Shriners Hospital) and 36 typically developing (healthy) control boys in a similar age range recruited by the University of California Davis Medical Center from the Northern California region. English- and Spanish-speaking boys with Duchenne muscular dystrophy were

recruited from our pediatric neuromuscular disease clinics and through a mailing to families of boys with the disease in northern California, the San Francisco Bay area, and the Portland area. Controls were recruited from Northern California through locally posted English- and Spanish-language advertisements. The institutional review boards of the participating institutions approved the study protocol. Informed consent/assent was obtained for each participant prior to conducting any study procedures.

For boys with Duchenne muscular dystrophy, the diagnosis of Duchenne muscular dystrophy was established based on typical clinical presentation and one or more of the following: documentation of disease-causing mutation in the dystrophin gene; complete dystrophin deficiency as shown by immunostaining on muscle biopsy, or elevated serum creatine kinase levels and a family history of an affected relative with either a disease-causing mutation in the dystrophin gene and/or complete dystrophin deficiency by immunostaining on muscle biopsy. Participants with Duchenne muscular dystrophy and typically developing controls were referred for testing if, by report, they could walk for at least 10 minutes. At the time of evaluation they were tested if they could walk independently for at least 10 meters without assistive devices (eg, crutches or leg braces) and/or perform a quantitative knee extension test. In addition, they had to be free of acute illness or other known contraindications to exercise, they had to be free of prescribed or non-prescribed medications that affect heart rate and/or metabolism (eg, amphetamines), and they had to be able to understand and follow simple instructions.

Demographic and Anthropometric Data

Demographic data, including age, height, and weight were obtained and corticosteroid use was recorded.

Test Procedures

All subjects had Vignos functional grading, quantitative lower extremity testing, and timed functional performance measures—time to climb 4 stairs and time to rise from supine to standing and 10 m walk/run—performed in a standardized manner on the first day of evaluation. On the second day of evaluation, the Duchenne muscular dystrophy subjects performed a 10-minute walk test at a self-selected walking velocity for measurement of oxygen cost of walking. Parents completed the appropriate parent-report versions of the PedsQL™ 4.0 Generic Core Scales³⁴ and the Pediatric Outcomes Data Collection Instrument version 2.0 (www.aaos.org/research/outcomes/outcomes_peds.asp) questionnaires. The specific clinical evaluations were as follows:

Vignos Functional Grade—Subjects were classified according to their Vignos functional grade: Vignos 1: walks and climbs stairs without assistance; Vignos 2: walks and climbs stairs with the aid of a railing; Vignos 3: walks and climbs stairs slowly with the aid of a railing (over 12 seconds for 4 standard stairs); Vignos 4: walks unassisted but cannot climb stairs; Vignos 5: walks unassisted but cannot climb stairs or get out of a chair; Vignos 6: walks only with the assistance of braces.^{44,45}

Quantitative lower extremity strength testing—Isometric knee extensor/flexor strength was assessed unilaterally, based on handedness, using the Biodex System 3 Pro isokinetic dynamometer. Strength was assessed with the patient in sitting following Biodex guidelines for set-up and positioning of knee extension/flexion strength. Extensor strength was assessed with the knee in 90° of knee flexion, while flexor strength was assessed at 30° of knee flexion. The isometric testing protocol consisted of three 5-second maximum voluntary contractions performed consecutively, with 10-second rests between contractions. Extensors were tested first, followed by the flexors. The greatest peak torque (N-m)

achieved was used in the analysis and normalized to the subject's weight (in kilograms). Data on knee extensor strength were analyzed for this study because of previous work documenting the relationship between knee extensor strength and ambulatory function in Duchenne muscular dystrophy.⁴⁶

Timed functional performance measures—After sufficient periods of rest, subjects were instructed to climb 4 standard stairs, rise from supine to standing, and walk/run 10 meters as quickly as possible using standardized protocols previously used in clinical trials in boys with Duchenne muscular dystrophy.^{24,31,32,47,48} Time was recorded in seconds.

Gait Velocity—During a 10-minute walk task, energy efficiency was measured in the Duchenne muscular dystrophy subjects with the Cosmed K4b2, which allows for simultaneous collection of VE (expiratory minute ventilation), VO₂ (volume of oxygen), VCO₂, (volume of carbon dioxide) and heart rate. The evaluation consisted of a 10-minute rest period in a semi-recumbent position followed by a 10-minute walk at their self-selected velocity around a 33-meter track or down a 30-meter hallway. Self-selected gait velocity was determined by the distance walked per minute with the mean of the 5 steady state minutes used in the analysis. Only the gait velocity data for Duchenne muscular dystrophy subjects was used for the data analyses included in this manuscript.

Statistical Methods

Because this was an observational study and did not test a predefined hypothesis, sample sizes were not dependent on a formal calculation; we hoped to include 50 boys with DMD and 30 healthy controls. All subjects who performed the 10-meter walk/run and/or the isometric knee extension test were included in the analysis. Data were analyzed using SYSTAT 13 (SYSTAT Software, Inc., Chicago, Illinois).

Significance was set at $P < .05$ for all statistical analyses. Descriptive statistics were calculated for subject's scores in the PODCI domains of upper extremity function, transfers and basic mobility, sports and physical function, comfort/pain, happiness with physical condition, and global function, and in the PedsQL^{TM} domains of physical functioning, school functioning, emotional functioning, social functioning, the psychosocial health summary score (a composite of school, emotional, and social functioning scores), and the total scale. Independent samples *t* tests were used to determine whether there were significant differences in PODCI and PedsQL^{TM} health-related quality of life domain scores between the Duchenne muscular dystrophy patients on corticosteroids ($n = 33$) and the corticosteroid naïve Duchenne muscular dystrophy subjects ($n = 19$). Independent samples *t* tests were also used to compare the scores of Duchenne muscular dystrophy subjects to the scores of healthy controls. As there were no significant effects of corticosteroids on any baseline patient-reported PODCI or PedsQL^{TM} measures, scores of the subjects on corticosteroids and the corticosteroid naïve subjects were pooled together for all further analyses.

For aims 1 and 2, 2-way ANOVA were completed for all PODCI and PedsQL^{TM} domains to assess any significant differences between age group (younger than 7, 7–10, and greater than 10) and disease group means. When significant differences were found, Tukey post hoc tests were used to confirm that these differences were significant. For aims 3 and 4, Pearson and Spearman correlation analyses were performed across all Duchenne muscular dystrophy patients subjects and controls depending on whether the data scale was ordinal or linear. For aim 5, one-way ANOVAs were used to determine if there were significant differences in PODCI and PedsQL^{TM} domain scores among the ambulatory Duchenne muscular dystrophy subjects in the 3 disease severity groups defined by Vignos functional grade, quantitative knee extensor strength scores, timed functional performance measures, and gait velocity.

Group definitions for severity were chosen at either functionally significant performance levels that have been tied to future occurrence of transition to the wheelchair,⁴⁶ or performance levels that distributed subjects into upper, middle, and lower performance levels based on inspection of scatter plots (see Figure 1). The definitions for lower severity (Group I), intermediate severity (Group II) and greater severity (Group III) for ambulatory DMD subjects were included in Table 1. When significant differences were found, Tukey post hoc tests were used to determine where these differences were statistically significant given the multiple comparisons.

Results

Subject Characteristics

Fifty-two boys with Duchenne muscular dystrophy and 36 healthy control boys participated in the study (Table 2). The groups were comparable in age and weight, but boys with Duchenne muscular dystrophy were shorter than control boys across all 3 age ranges ($P < .02$, unpaired t tests). Among boys with Duchenne muscular dystrophy, 33 of 52 (63.5%) were known to be on corticosteroids. These boys were receiving either prednisone or deflazacort, and there were variations in the regimen used.

Effect of Corticosteroids on Outcome Measures

There were no significant effects of corticosteroids on any baseline patient-reported health-related quality of life measures in Duchenne muscular dystrophy subjects.

Comparison of specific domain scores from 2 commonly used Patient-reported Outcome Measures — the PedsQL™ and PODCI — in ambulatory boys with DMD and typically developing boys (controls)

The mean and standard deviation of PODCI and PedsQL™ domain scores are shown for both ambulatory Duchenne muscular dystrophy patients and controls for age ranges <7 , 7–10, and >10 in Tables 3 and 4. For the PODCI, there were significant disease effects (Duchenne muscular dystrophy significantly less than controls) for all comparisons across domains by 2-way ANOVA ($P < .001$). For PODCI, there was a significant age group effect (older age groups had lower scores when comparing age < 7 , age 7–10, and age > 10) for the transfers/basic mobility, sports/physical function, and happiness and global domains by ANOVA ($P < .05$). Other PODCI domains did not show a significant age effect. There was a significant interaction effect between age and disease for the PODCI transfers/basic mobility, and sports/physical function domains by ANOVA ($P < .01$) because the Duchenne muscular dystrophy group showed decreasing scores with increasing age while the controls did not (see Figures 2a – 2b). The happiness domain of the PODCI was significantly lower in the >10 -year-old controls compared with the younger controls.

For the PedsQL™, there were significant disease effects (Duchenne muscular dystrophy scored significantly less than controls) for all comparisons across domains by ANOVA ($P < .001$) as shown in Table 4. For the PedsQL™, there was a significant age group effect (older age groups had lower scores across age < 7 , age 7–10, and age > 10) for the physical domain by ANOVA ($P < .05$). Other PedsQL™ domains did not show a significant age effect. There was a significant interaction effect between age and disease for the physical domain by ANOVA ($P < .01$) because the Duchenne muscular dystrophy group showed decreasing scores with increasing age, while the controls did not (see Figure 2c).

Evaluation of the relationship between domain scores of the PODCI and domain scores of the PedsQL™ in ambulatory Duchenne muscular dystrophy subjects

A correlation matrix showing correlations between PODCI and PedsQL™ domain scores is shown in Table 5. The PODCI domains which correlated best with age included transfers/basic mobility, sports/physical function, happiness and global function as these scores decreased with increasing age ($r = -0.48$ to -0.66). Of these domain scores, the PODCI sports/physical function score had the greatest negative correlation with age ($r = -0.66$). The PedsQL™ domains that correlated best with age were the physical domain ($r = -0.54$), and the total score ($r = -0.43$) which decreased with age. All other PedsQL™ domains had low or modest negative correlations with age ($r = -0.25$ to -0.29). As expected, the PedsQL™ physical functioning domain was highly correlated with the PODCI transfers/basic mobility domain ($r = 0.71$), the PODCI sports/physical function domain ($r = 0.83$), and the PODCI global domain ($r = -0.76$). The PODCI global domain was highly correlated with the PedsQL™ total domain ($r = 0.72$). The PODCI pain/comfort domain score correlated best with the PedsQL™ emotional domain score ($r = 0.42$). The PODCI happiness domain correlated moderately highly with the physical, emotional, and total scores of the PedsQL™ ($r = 0.46$ to 0.51). As expected with this ambulatory Duchenne muscular dystrophy population, the PODCI upper extremity function scale had low correlations with all PedsQL™ domains (Table 5) and low correlations with ambulatory based clinical endpoints.

Determination of the relationship between common clinical endpoints measured by therapists in clinical trials for DMD and specific domains of the PODCI and PedsQL™

We correlated specific domain scores of the PODCI and PedsQL™ that showed a disease-associated negative correlation with age with common clinical endpoints measured by therapists in clinical trials for Duchenne muscular dystrophy. In general, the PODCI transfers/basic mobility scores, and PODCI sports/physical function scores correlated most highly with the clinical endpoints. The PODCI transfers/basic mobility score was the patient-reported domain most highly correlated with the Vignos lower extremity scale, time to stand from supine, time to climb 4 stairs, time to run/walk 10 meters, isometric knee extension per kilogram, and self-selected walking velocity ($r = 0.43$ to -0.53). The PODCI sports/physical function scores was also moderately correlated with time to stand from supine, time to walk/run 10 meters, and isometric knee extension strength ($r = 0.46$ to -0.53) and had slightly lower correlations with time to climb 4 stairs, gait velocity, and Vignos scale ($r = 0.37$ to -0.39). PODCI happiness was moderately correlated with time to stand from supine, and time to walk/run 10 meters ($r = -0.38$ to -0.39). In general, the PODCI transfers/basic mobility and PODCI sports/physical function domain scores had greater correlations with clinical endpoints than the PedsQL™ physical domain score.

Determine if defined levels of performance on selected clinical endpoints used in clinical trials for ambulatory DMD subjects are associated with significant differences on patient-reported domains from the PedsQL™ and PODCI

In Table 7, PODCI mean values (with standard deviations) are shown in groups of ambulatory Duchenne muscular dystrophy subjects with 3 levels of clinical severity defined by Vignos grade, knee extensor strength, time to walk/run 10 meters, time to stand from supine, time to climb 4 stairs, and gait velocity. The PODCI domain scores of transfers/basic mobility and global function were significantly lower in subjects who had reached a Vignos grade of 3 compared with those in groups 1 and 2. Sports/physical function scores were lower in those with Vignos grades 3 as compared to 2. There were no significant differences in PODCI scores among subjects with Vignos grades 1 and 2.

The PODCI domains of transfers/basic mobility and global function were significantly higher in those with stronger isometric knee extension strength (> 0.8 N-m/Kg) as compared

with those with weaker knee extension strength. As shown in Table 7, the sports/physical function scores were significantly higher in those Duchenne muscular dystrophy subjects with stronger isometric knee extension (> 0.8 N-m/Kg) compared with those Duchenne muscular dystrophy subjects with weakest isometric knee extension (< 0.4 N-m/Kg). The PODCI domains of upper extremity function, pain/comfort, and happiness did not differ significantly among those with different values of isometric knee extension strength.

As seen in Table 7, the PODCI domain scores for transfers/basic mobility were significantly higher among those Duchenne muscular dystrophy subjects with best performance on the 10-meter walk/run test (< 6 seconds) compared with those with more impaired performances of both 6 to 12 seconds and >12 seconds. For Sports/physical function, the Duchenne muscular dystrophy group with best performance on the 10-meter walk/run measure (<6 seconds) scored significantly higher than those with worst performance (>12 seconds). The PODCI domains of upper extremity function, pain/comfort, happiness, and global function did not differ significantly among those with different performance values on the time to walk/run 10 meters measure.

For time to stand from supine, it appears that Duchenne muscular dystrophy subjects need to reach a critical value of >10 seconds before they start showing decline on the PODCI domains of transfers/basic mobility and sports/physical function (Table 7). There were no differences in PODCI scores for those with performance on the stand from supine test of both <5 seconds and 5 to 10 seconds. The PODCI domains of upper extremity function, pain/comfort, happiness, and global function did not differ significantly among those with different values of time to stand from supine.

Similarly, for time to climb 4 stairs, it appears that Duchenne muscular dystrophy subjects need to reach a critical value of >10 seconds before they start showing significant decline on the PODCI domains of transfers/basic mobility and sports/physical function (Table 7). As with time to stand from supine, there were no differences in PODCI scores for those with performance on the climb 4 stairs test of both <5 seconds and 5 to 10 seconds. The PODCI domains of upper extremity function, pain/comfort, happiness, and global function also did not differ significantly among those with different values of time to climb 4 stairs.

Those Duchenne muscular dystrophy subjects with faster self-selected gait velocities of >45 meters/minute performed significantly better than those with slower self selected gait velocities on PODCI domains of transfers/basic mobility, sports/physical function, and global function (Table 7). As with the other clinical endpoints—including Vignos grade, quantitative knee extensor strength, and timed function testing—the PODCI domains of pain/comfort and happiness did not differ significantly among those Duchenne muscular dystrophy subjects with different values of self-selected gait velocities.

In Table 8, PedsQL™ mean values (with standard deviations) are shown in groups of ambulatory Duchenne muscular dystrophy subjects with 3 levels of clinical severity defined by Vignos grade, isometric knee extensor strength, time to walk/run 10 meters, time to stand from supine, time to climb 4 stairs, and self-selected gait velocity. The PedsQL™ scores across the domains of emotional, social, psychosocial, and total did not significantly differ among those Duchenne muscular dystrophy subjects with varying levels of clinical severity.

The only PedsQL™ domain scores that were significantly higher were the physical score in those who could stand from supine in <5 seconds versus those with a stand from supine time of >10 seconds, and the school score in those with strongest isometric knee extension (>0.8 N-m/kg) versus those with weakest isometric knee extension (<0.4 N-m/kg).

Discussion

Ambulatory DMD subjects show significant decrements in parent proxy reported health-related quality of life measures versus controls

The study's first aim was to determine if ambulatory boys with Duchenne muscular dystrophy differ significantly by age from typically developing boys (controls) using 2 common patient-reported outcome measures — the PODCI and PedsQL™. The study used parent proxy versions of the instruments because of the age ranges of the participants and the occurrence of cognitive impairment in a significant proportion of subjects with Duchenne muscular dystrophy.^{46,49} A strength of the generic PedsQL™ and PODCI scales is that normative data exists on a large number of healthy children and parent proxies to allow benchmarking. Our control data on parent proxies of boys in similar age ranges to our Duchenne muscular dystrophy subjects compares very favorably to large normative samples published for the PedsQL™³⁷ and PODCI instruments.^{40,41} We documented significant decrements relative to controls in ambulatory Duchenne muscular dystrophy boys across all domains of the PODCI, including upper extremity function, transfers/basic mobility, sports/physical function, pain/comfort, happiness, and global function (Table 3). The greatest decrement was seen in the sports/physical function domain of the PODCI. Similarly, the PedsQL™ documented decrements vis-a-vis healthy controls across all domains including physical, school, emotional, social, psychosocial, and total scores. The greatest decrement on the PedsQL™ was seen in the physical domain (Table 4).

Ambulatory DMD subjects show significant age-related decline in selected domains of physical function, happiness and global function

A second role of a patient-reported outcome measure such as global health-related quality of life is to document clinically meaningful changes experienced by the patient with disease progression or with effective treatment. Age is a concomitant factor to disease progression in Duchenne muscular dystrophy. Other outcome measures commonly used in clinical trials of ambulatory boys with Duchenne muscular dystrophy to document disease severity and/or treatment effect include the Vignos grade, quantitative strength, timed functional performance measures, and walking velocity. The second aim of this study was to determine if there is an age-related decline in specific domain scores of the PODCI and PedsQL™ in ambulatory boys with Duchenne muscular dystrophy. Significant age-related decrements were documented in the transfers/basic mobility, sports/physical function, happiness, and global function domains of the PODCI and the physical domain of the PedsQL™. Thus, in the context of a clinical trial for Duchenne muscular dystrophy, it would be expected that a treatment that favorably impacts age-related diseases progression in ambulatory subjects would be better assessed by patient-reported measures that focus on domains of basic mobility and physical function. Of all patient-reported health-related quality of life domains, the PODCI sports/physical function score had the strongest negative correlation with age in ambulatory Duchenne muscular dystrophy.

Results provide validation for the PODCI and PedsQL™ as health-related quality of life measures in ambulatory boys with Duchenne muscular dystrophy

The correlation matrix shown in Table 5 documents high correlation between the PedsQL™ physical scale score and both the transfers/basic mobility and sports/physical function scores from the PODCI. This supports the construct validity of the physically oriented aspects of health-related quality of life for both these test instruments in DMD. In addition, the PODCI global function score was highly correlated with the PedsQL™ total score in ambulatory Duchenne muscular dystrophy providing validation for the overall constructs of these generic health-related quality of life instruments in this population.

There is a relationship between therapist measured clinical endpoints and specific domains of the PODCI and PedsQL™ documenting the clinical meaningfulness of these clinical endpoints vis-a-vis patient-reported outcome measures

To date there has not been confirmation that traditional clinical endpoints used in clinical trials of ambulatory boys with Duchenne muscular dystrophy—namely timed functional performance measures and quantitative strength measures—are “clinically meaningful” to patients and families. This study documented associations between both timed functional performance measures and isometric knee extension strength normalized to body weight and the physical function scales of 2 established patient-reported health-related quality of life instruments: the PODCI and PedsQL™. This provides evidence that these clinical endpoints are clinically meaningful vis-a-vis 2 different patient-reported outcome measures of health-related quality of life. While time to stand from supine was the clinical measure most strongly associated with age, results of the correlation analyses reported in Table 6 did not provide evidence favoring one clinical endpoint over another with regard to the strength of association with the patient-reported health-related quality of life domains.

Based on comparisons of the patient-reported outcome measures with the therapist-obtained clinical measures of disease severity (Table 6), selected PODCI domains (specifically the transfers/basic mobility and sports/physical function scores) were more strongly associated with clinical measures of disease severity in ambulatory Duchenne muscular dystrophy subjects than the PedsQL™ physical score.

Defined levels of performance on selected outcome measures frequently used in clinical trials of ambulatory Duchenne muscular dystrophy subjects are associated with significant differences on patient-reported health-related quality of life measures from the PedsQL™ and PODCI

Once associations have been established between clinical outcome measures and specific patient-reported health-related quality of life measures, a useful clinical question is to determine whether there are specific threshold levels of performance deficit that may be more strongly associated with further decrements in health-related quality of life. The present study’s baseline and cross-sectional outcome data collected in Duchenne muscular dystrophy subjects over the ambulatory age range provide useful information to begin evaluating levels of performance deficits on therapist-determined clinical outcome measures that are associated with significant decrements on patient-reported outcome instruments. It is anticipated that the meaningfulness of these defined performance levels can be further evaluated with future longitudinal studies with serial measures. For example, with a longitudinal study design of Duchenne muscular dystrophy subjects undergoing serial clinical measures, it can be determined whether a rapid change in ambulatory function and transition to a wheelchair occurs once a strength deficit reaches a critical threshold value. Similarly, there may be a precipitous increase in time required to complete functional tasks once a critical degree of strength decrement, fatigue, or contracture occurs.

As an example of a clinically useful defined level of performance in Duchenne muscular dystrophy, the time to walk/run 10 meters has previously been shown by the author to predict time to transition to full-time reliance on a wheelchair in steroid naïve Duchenne muscular dystrophy subjects.⁴⁶ Those who took >12 seconds to walk this distance generally transitioned to the wheelchair within 12 months. Those who took <6 seconds were greater than 2 years away from transition to a wheelchair.⁴⁶ The present study documents significant and increasing decrements in both the PODCI transfers/basic mobility scores and sports physical function scores in those Duchenne muscular dystrophy subjects that walk/run 10 meters in <6 seconds, 6 to 12 seconds, and >12 seconds. These patient-reported health-related quality of life data further support the clinical meaningfulness of these defined

“performance” or “severity” levels based on the time to walk/run 10 meters outcome measure. Similarly, greater decrements in the transfers/basic mobility and sports/physical function domains of the PODCI were documented in those who took >10 seconds to stand from supine and climb 4 stairs.

Increased decrements in physically oriented health-related quality of life domains were documented by this study in those boys with Duchenne muscular dystrophy who dropped below defined levels of isometric knee extension strength. In a large-scale longitudinal study,⁴⁶ we previously reported that significant changes in ambulatory function (as defined by the Vignos scale) occurred in steroid naïve males with Duchenne muscular dystrophy when knee extension strength approached an antigravity or lower level (grade 3 on manual muscle testing). Once knee extension strength reached this critical threshold value there was a precipitous and rapidly progressive change in function, defined by the Vignos scale, among ambulatory males with Duchenne muscular dystrophy.

The present study documents that health-related quality of life measures show marked changes associated with Duchenne muscular dystrophy subjects progressing from a Vignos scale of 2 (walks and climbs stairs with the aid of a railing) to a Vignos scale score of 3–4 (Vignos 3: walks and climbs stairs slowly with the aid of a railing—over 12 seconds for 4 standard stairs; Vignos 4: walks unassisted but cannot climb stairs).

Gait velocity is determined by stride length and cadence, which both are strongly influenced by disease progression in Duchenne muscular dystrophy.^{50,51} In the present study, gait velocity of <45 m/min was associated with significant decrements in both the PODCI transfers/basic mobility domain and the sports/physical function domain. It should be noted that the walking speed measured in this study was a self-selected comfortable walking speed that is typically slightly slower than the walking speed used during a 6-minute walk test in subjects with Duchenne muscular dystrophy.³³

Comparison of Duchenne muscular dystrophy with other childhood disabling conditions based on health-related quality of life measures

Generic health-related quality of life instruments for children enable comparisons to be made across pediatric populations with diverse conditions. While it may be assumed boys with Duchenne muscular dystrophy may only have mild impacts on health-related quality of life during the ambulatory phase, the Duchenne muscular dystrophy subjects in this study showed rather significant decrements relative to controls across all domains of the PODCI and PedsQL^{TM}. Three other common disabling conditions affecting children that are manifested by significant, but non-progressive motor impairments are cerebral palsy, spina bifida, and traumatic spinal cord injury. In cerebral palsy, the most widely used functional classification tool that has been documented to describe clinically meaningful differences is the Gross Motor Function Classification System.⁵² While the Gross Motor Function Classification System is not applicable directly to Duchenne muscular dystrophy, the PODCI data in our study allows comparison of ambulatory boys with Duchenne muscular dystrophy to ambulatory cerebral palsy patients in similar age ranges vis-a-vis PODCI transfers/basic mobility scores, the PODCI sports/physical function scores, and the PODCI global function scores. In our study, boys with Duchenne muscular dystrophy younger than age 7 had similar magnitude deficits on these PODCI domains to those reported in patients with Gross Motor Function Classification System levels of I; Duchenne muscular dystrophy subjects ages 7–10 had similar magnitude deficits on PODCI domains to cerebral palsy patients with Gross Motor Function Classification System levels of II; and Duchenne muscular dystrophy subjects older than age 10 had deficits on the PODCI that were similar in magnitude to those reported in cerebral palsy patients with Gross Motor Function Classification System levels of III. It is widely accepted that changes from level I

to II and level II to III on the Gross Motor Function Classification System represent *clinically meaningful changes*.

Comparison of ambulatory Duchenne muscular dystrophy subjects with children with thoracic level spina bifida and spinal cord injury gives additional perspective regarding the magnitude of decreases in their health-related quality of life. Ambulatory boys with Duchenne muscular dystrophy ages 7 and older showed more severe decrements on the physical scale of the PedsQL™ than were reported in children with spina bifida and spinal cord injury and thoracic paraplegia.⁵³

Are the generic PODCI and PedsQL™ health-related quality of life measures candidate patient-reported outcomes for clinical trials in Duchenne muscular dystrophy?

Longitudinal natural history data will be necessary to ultimately determine the sensitivity of various patient-reported health-related quality of life measures to change expected in clinical trials. This current study provides initial evidence that selected domains of the PODCI and PedsQL™ may be useful outcome measures for clinical trials in ambulatory DMD subjects. Specifically, the PODCI transfers/basic mobility, PODCI sports/physical function, and PedsQL™ physical functioning domains have the closest associations with age (and hence disease progression), and traditional clinical outcome measures historically employed in clinical trials of ambulatory boys with Duchenne muscular dystrophy. The PODCI global domain score and PedsQL™ total scores are likely correlated with age and clinical outcome measures because they are composite measures which incorporate the physical function domain scores. PODCI happiness did have modest associations with age and selected time functional performance measures. However, it is unlikely that the other domains of the PODCI and PedsQL™ would be useful endpoints at this point in clinical trials of ambulatory Duchenne muscular dystrophy given the lack of association of these domains with age and clinical measures. Parent proxy reports would be needed for the PODCI in children younger than 11 years.

Currently, the innovations of item response theory and computer adapted testing is being increasingly applied to health-related quality of life assessment to increase precision and sensitivity and decrease the response burden on patients and family members. Item response theory, combined with easy accessibility to computers, has led to the rapid growth of computer adapted testing in patient-reported outcomes assessment, where one can administer brief yet precise and individualized tests to every individual, with reliability and scores equivalent to longer, fixed-length assessments.⁵⁴ Further sensitivity of patient-reported outcome measures to changes anticipated with treatment will likely come with the development and refinement of disease specific health-related quality of life instruments.

The use of disease specific health-related quality of life instruments for individuals with neuromuscular diseases: implications for future clinical trials

To address the limitations of the generic health-related quality of life instruments such as the PedsQL™ and PODCI, disease-specific quality of life measures have been developed for individuals with neuromuscular disease including the Individualized Neuromuscular Quality of Life scale (INQoL),¹⁴ PedsQL™ Neuromuscular Module,^{15–17} and the NeuroQOL (www.NeuroQOL.org).^{18–22}

The *Individualized Neuromuscular Quality of Life (INQoL)*¹⁴ is a validated muscle disease specific measure of quality of life developed from the experiences of adult patients with muscle disease that consists of 45 questions within 10 sections. Four of these sections focus on the impact of key muscle disease symptoms (weakness, locking [ie, myotonia], pain, and fatigue), 5 sections look at the impact (degree and importance of impact) muscle disease has

on particular areas of life, and one section asks about the positive and negative effects of treatment. The INQoL has not been validated in children.

The PedsQL™ Disease and Condition Specific Modules have been recently developed to address the limitations in sensitivity of generic health-related quality of life scales in children by measuring dimensions specifically tailored for a variety of pediatric chronic health conditions. The modules comprised parallel child self-report and parent proxy-report formats. *The PedsQL™ Neuromuscular Disease Module (NMM)*^{15–17} has recently been developed and applied to both spinal muscular atrophy and Duchenne muscular dystrophy. The 25-item PedsQL™ 3.0 Neuromuscular Module (NMM) encompasses 3 scales: (1) “About My/My Child’s Neuromuscular Disease (17 items related to the disease process and associated symptomatology), (2) Communication (3 items related to the patient’s ability to communicate with health-care providers and others about his/her illness), and (3) About Our Family Resources (5 items related to family financial and social support systems).

In one study¹⁷ the PedsQL™ NMM was given to 44 males with Duchenne muscular dystrophy (32 full-time wheelchair users, 7 part-time wheelchair users, and 5 ambulators) and their parents. Test-retest reliability and construct validity (between the PedsQL™ 4.0 Generic Core Scales and PedsQL™ 3.0 NMM scales) was established. Poor to fair agreement was found between child and parent report versions of the NMM. Additional construct validity was based on correlations of NMM domains (Total score and the “About My/My Child’s Neuromuscular Disease” score) with a disease-specific measure of percentage-predicted forced vital capacity and wheelchair use. The child self-report and parent proxy-report PedsQL™ NMM scores correlated with percentage-predicted forced vital capacity in the range of 0.15 to 0.46, which was lower or the same as the correlation observed between the PedsQL™ Generic Core Physical Functioning score and percentage-predicted forced vital capacity. Both the PedsQL™ Generic Physical Functioning score and the NMM “About My/My Child’s Neuromuscular Disease” score were significantly different in full-time wheelchair users versus part-time/full-time ambulators. Additional longitudinal studies will be necessary to determine whether The PedsQL™ NMM module will offer advantages in clinical trial applications to the PedsQL™ Generic Core Scales or the PODCI in terms of additional sensitivity to changes experienced due to treatment.

The NeuroQOL measurement system^{18–22} consists of a core set of questions that address dimensions of health-related quality of life that are universal to patients with chronic neurological diseases and supplemental questions or modules that address additional concerns specific to different neurological conditions.⁵⁵ Both adult and child versions (for ages 12 to 18) are currently being developed for use and calibrated short forms are currently undergoing a clinical validation in a multi-site study in the United States and Puerto Rico. Selected conditions include stroke, multiple sclerosis, Parkinson’s disease, adult and pediatric epilepsy, amyotrophic lateral sclerosis, and muscular dystrophy. Researchers conducted patient focus groups and interviews with experts and patients that allowed them to identify important concepts and select sets of items from existing instruments, and to develop new items that could be field tested during the development process. The NeuroQOL for adults and adolescents includes comprehensive item banks with some of its origins from the PROMIS network - Person Reported Outcomes Measurement Information System.⁵⁶ PROMIS is a set of public-domain patient-reported outcomes research tools for clinical trials across all diseases. Measures have been developed and tested for adolescents, with domains including mobility(ambulation, walking aide mobility, wheelchair mobility), upper extremity/activities of daily living, pain, fatigue, emotional health (depression, anxiety, anger), stigma, social health, and perceived cognitive function. Procedures for developing the NeuroQOL item banks/scales are comparable to the standard procedures proposed by the NIH initiative Patient Reported Outcomes Measurement and Information

System. NeuroQOL measures will be available in the public domain once clinical validation efforts are completed and a computer adapted testing interface is also anticipated.

Study Limitations and Future Research Needs

While this study has strengths in terms of the specific health-related quality of life and clinical measures used, the inclusion of a large sample of ambulatory males with Duchenne muscular dystrophy similar to the populations of Duchenne muscular dystrophy subjects that have been included in most clinical trials, and the use of male controls in the same age ranges, there are a number of important limitations. First, these data represent initial analyses of baseline measures. Serial measures collected over a study duration typically employed in a clinical trial (eg, 12 months) will need to be obtained to determine the true associations between changes in disease course over time, change scores in clinical function, and change scores in patient reported health-related quality of life measures. Such prospective longitudinal data collection continues. The fact that this study confirmed associations between clinical measures of disease severity in Duchenne muscular dystrophy and patient-reported health-related quality of life measures at a single point in time does not establish causality.

Second, the age ranges employed in our study necessitated the use of parent proxy measures of health-related quality of life. The PedsQL™ 4.0 Generic Core does include a child self-report format for ages 5 to 7, 8 to 12, and 13 to 18. The PODCI can be administered to both parents and children 11 years and older in a self report format. It should be noted that children 8 years of age and older with neuromuscular disorders such as Duchenne muscular dystrophy and their parents have shown poor to moderate agreement in generic and disease specific health-related quality of life measures.¹⁷ Some of this discrepancy is undoubtedly due to real and important differences in perspectives, but in children younger than age 8 it may be due to cognitive issues as far as reading ability and comprehension. On the PedsQL™ NMM, children with Duchenne muscular dystrophy ages 8 and older showed lower test-retest reliability with the self report form (0.48 to 0.65) as compared with parents with the parent proxy report form (0.75 to 0.80).¹⁷ Such marginal test-retest reliability observed in younger children with Duchenne muscular dystrophy may be inadequate for a clinical trial outcome measure. Indeed, work with children with spinal cord injury indicates that patient-reported outcomes were possible after 8 years of age.⁵⁷ The literature currently suggests that measures of health-related quality of life in neuromuscular disease patients 8 years and older should use both children's and parents' perspectives for clinical research and clinical trials. Parent proxy reports will likely be necessary for subjects younger than 8 years.

Lastly, our study did not use neuromuscular disease-specific health-related quality of life because none had been validated in children at the outset of this study. Future work will need to be done to determine whether the addition of such disease specific measures of health-related quality of life to available generic measures will increase the sensitivity to detect real change experienced with both disease progression and treatment.

Summary

Duchenne muscular dystrophy subjects showed significant decrements in parent proxy-reported PODCI and PedsQL™ measures of health-related quality of life versus controls across all domains. The intercorrelation of PODCI and PedsQL™ domains support the construct validity of the measures. The PODCI transfers/basic mobility, PODCI sports/physical function, and PedsQL™ physical functioning domains had significant associations with age (and hence disease progression), and traditional clinical outcome measures historically employed in clinical trials of ambulatory boys with Duchenne muscular

dystrophy (including timed functional performance and quantitative knee extension). Defined levels of severity based on clinical measures were associated with decrements in health-related quality of life measures. At this time selected domains of the PODCI and generic PedsQL™ are potential patient-reported outcome measures for clinical trials in ambulatory individuals with Duchenne muscular dystrophy. Future work needs to focus on the relationship between changes in both clinical outcome measures and health-related quality of life in longitudinal study designs, new disease specific HRQOL measures, and recent innovations to health-related quality of life assessment, including item response theory and computer adapted testing approaches.

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Figure 1. Definitions of Duchenne muscular dystrophy (DMD) severity level for ambulatory DMD (■) and typically developing control males (□) based on 10 m walk/run test scores plotted by age. Group I: < 6 seconds, Group II: 6–12 seconds, Group III: > 12 seconds.

Figure 2.

Figure 2a: PODCI Transfers/Basic Mobility Domain Scores by age group for DMD and Control subjects. DMD: Duchenne muscular dystrophy; PODCI: Pediatric Outcomes Data Collection Instrument.

Figure 2b: PODCI Sports/Physical Functioning Domain Scores by age group for DMD and Control subjects. DMD: Duchenne muscular dystrophy; PODCI: Pediatric Outcomes Data Collection Instrument.

Figure 2c: PedsQL Physical Domain Scores by age group for DMD and Control subjects. DMD: Duchenne muscular dystrophy; PedsQL: Pediatric Quality of Life Inventory^{TM}.

Table 1

Definitions of Severity Levels for Selected Clinical Endpoints

	Lower Severity (Group I)	Intermediate severity (Group II)	Greater severity (Group III)
Vignos Functional Grade:	Vignos 1	Vignos 2	Vignos 3–6
Isometric Knee Extension Strength:	>.8 torque/kg	.4–.8 torque/kg	<.4 torque/kg
10-Meter Walk:³¹	<6 seconds	6–12 seconds	>12 seconds
Stand from Supine:	<5 seconds	5–10 seconds	>10 seconds
Climb 4 Stairs:	<5 seconds	5–10 seconds	>10 seconds
Gait Velocity:	>45 meters/min	30–45 meters/min	< 30 meters/min

Table 2**Baseline Subject Characteristics**

Group	n	Age	Height	Weight	Percent on Steroids
DMD (Ages <7)	79	5.4 (0.9)	110.8 (8.2)	21.5 (5.0)	57.9% (11/19)
Controls (Ages <7)	13	5.8 (1.0)	116.2(7.7)	23.0 (7.5)	
DMD (Ages 7–10)	19	8.6 (0.8)	124.4 (10.1)	30.0 (8.2)	63.2% (12/19)
Controls (Ages 7–10)	11	9.0 (0.8)	134.6 (6.9)	31.2 (6.5)	
DMD (Ages >10)	14	12.2 (1.3)	141.3 (14.9)	48.1 (17.8)	71.4% (10/14)
Controls (Ages >10)	12	11.6 (0.9)	150.8 (9.6)	53.1 (17.5)	

Abbreviation: DMD, Duchenne muscular dystrophy.

Table 3

Mean (Std Dev) of PODCI Parent Responses by Age, DMD, and Controls

Group	Upper Extremity ^A	Transfers/Basic Mobility A, B, C	Sports/Phys Function A, B, C	Pair ^A	Happiness ^{A,B}	Global ^A
DMD (Ages <7)	72.7 (14.1)	86.6 (11.2)	66.6 (17.6)	87.2 (13.4)	89.4 (14.0)	79.0 (11.7)
Controls (Ages <7)	94.9 (6.8)	100.0 (0.0)	96.5 (4.0)	100.0 (0.0)	100.0 (0.0)	97.8 (2.3)
DMD (Ages 7–10)	76.0 (14.6)	78.1 (13.9)	50.8 (17.7)	80.9 (21.8)	78.8 (18.9)	71.4 (12.1)
Controls (Ages 7–10)	98.1 (3.9)	100.0 (0.0)	96.4 (5.8)	95.8 (12.0)	99.1 (2.0)	97.6 (4.3)
DMD (Ages >10)	83.6 (9.4)	68.9 (19.1)	36.9 (21.0)	84.1 (15.9)	65.8 (13.5)	68.1 (10.9)
Controls (Ages >10)	100.0 (0.0)	100.0 (0.0)	94.9 (7.2)	96.3 (10.7)	92.1 (14.1)	97.8 (2.8)

Abbreviations: DMD, Duchenne muscular dystrophy; PODCI, Pediatric Outcomes Data Collection Instrument; Std Dev, standard deviation.

Steroid and non-steroid scores combined for DMD.

^ASignificant disease effect (DMD vs. Controls) for all comparisons by ANOVA ($P < .001$)

^BSignificant age group effect (Age < 7, Age 7–10, and Age > 10) for the Physical domain by ANOVA ($P < .05$)

^CSignificant interaction effect between age and disease for the physical domain by ANOVA ($P < .01$)

Table 4

Mean (Std Dev) of PedsQL Parent Responses by Age, DMD, and Controls

Group	Physical ^{A, B, C}	School ^A	Emotional ^A	Social ^A	Psychosocial ^A	Total ^A
DMD (Ages <7)	62.2 (23.7)	70.0 (24.7)	70.2 (19.5)	77.2 (18.9)	71.2 (20.0)	66.8 (21.8)
Controls (Ages <7)	90.5 (18.3)	86.9 (16.6)	91.2 (11.0)	97.3 (15.6)	91.8 (9.6)	91.5 (11.2)
DMD (Ages 7–10)	37.0 (21.9)	58.6 (25.4)	61.5 (15.4)	73.8 (18.4)	62.9 (15.4)	54.8 (13.2)
Controls (Ages 7–10)	95.2 (4.7)	82.7 (11.3)	80.9 (14.6)	92.7 (9.2)	85.5 (8.5)	87.9 (7.0)
DMD (Ages >10)	33.8 (26.2)	54.4 (24.3)	63.8 (13.7)	68.4 (18.8)	62.0 (12.6)	52.9 (11.4)
Controls (Ages >10)	93.4 (9.8)	79.6 (15.4)	80.8 (17.2)	86.3 (15.3)	82.2 (14.4)	88.2 (10.8)

Abbreviations: DMD, Duchenne muscular dystrophy; PedsQL, Pediatric Quality of Life Inventory^{TM}; Std Dev, standard deviation.
Steroid and non-steroid scores combined for DMD.

^ASignificant disease effect (DMD vs. Controls) for all comparisons by ANOVA ($P < .001$)
^BSignificant age group effect (Age < 7, Age 7–10, and Age > 10) for the Physical domain by ANOVA ($P < .05$)
^CSignificant interaction effect between age and disease for the physical domain by ANOVA ($P < .01$)

Table 5

Correlation Matrix for PODCI and PedsQL™ Domain Scores Using Pearson Correlations for DMD Subjects

	Age	PedsQL Physical	PedsQL Emotional	PedsQL School	PedsQL Social	PedsQL Psycho-social	PedsQL Total
PODCI - Upper Ext	0.28	0.19	0.08	-0.28	0.05	0.15	0.20
PODCI - Transfers	-0.51	0.71	0.24	0.26	0.21	0.33	0.57
PODCI - Sports/Physical	-0.66	0.83	0.43	0.35	0.38	0.50	0.73
PODCI - Pain/Comfort	-0.06	0.25	0.42	0.09	0.14	0.34	0.33
PODCI - Happiness	-0.53	0.46	0.51	0.04	0.13	0.36	0.46
PODCI - Global	-0.48	0.76	0.45	0.29	0.31	0.53	0.72
Age	1.0	-0.54	-0.25	-0.26	-0.23	-0.29	-0.43

Abbreviations: DMD, Duchenne muscular dystrophy; PODCI, Pediatric Outcomes Data Collection Instrument; PedsQL, Pediatric Quality of Life Inventory™.

Table 6

Correlation Matrix for PODCI and PedsQL™ Domain Scores Correlated with Clinical Endpoint Measures for DMD Subjects

	Age	Vignos lower extremity	Time to Stand from Supine	Time to Climb 4 stairs	Time to Walk/Run 10 meters	Isometric Knee Ext per kg	Walking Velocity
Age	1.0	0.26	0.62	0.28	0.46	-0.37	-0.11
PedsQL Physical	-0.54	-0.20	-0.38	-0.32	-0.34	0.41	0.23
PODCI Sports/Physical	-0.66	-0.38	-0.53	-0.39	-0.46	0.46	0.37
PODCI Transfers	-0.51	-0.52	-0.53	-0.53	-0.53	0.46	0.43
PODCI Happiness	-0.53	-0.05	-0.38	-0.27	-0.39	-0.17	0.06

Abbreviations: DMD, Duchenne muscular dystrophy; PODCI, Pediatric Outcomes Data Collection Instrument; PedsQL, Pediatric Quality of Life Inventory™.

All Correlations are Pearson r values except those that involve the Vignos lower extremity functional scale, which use Spearman rho.

Table 7

Mean (Std Dev) of PODCI Parent Proxy Responses by Clinical Severity Groups for DMD Subjects

	Group	n	U. Extremity	Transfers	Sports	Pain	Happiness	Global
<i>Vignos Grade</i>								
class 1	1	10	78 (14)	88 (6)	59 (14)	76 (21)	73 (27)	75 (9)
class 2	2	31	78 (12)	83 (12)	58 (21)	86 (16)	83 (14)	76 (11)
class 3-4	3	7	69 (20)	59 (21)***	35 (24)^A	82 (20)	74 (20)	61 (18)***
<i>Knee Ext Strength</i>								
>8 N-m/kg	1	10	78 (11)	91 (7)*	70 (21)^A	85 (23)	76 (30)	81 (12)*
.4-.8 N-m/kg	2	23	74 (15)	78 (15)	53 (17)	80 (17)	78 (15)	71 (12)
<.4 N-m/kg	3	13	78 (13)	73 (16)	40 (21)	93 (9)	82 (15)	71 (10)
<i>10 Meter Walk</i>								
<6 seconds	1	23	81 (12)	88 (7)*	63 (17)^A	79 (20)	82 (21)	78 (11)
6-12 seconds	2	17	71 (16)	77 (15)	51 (20)	87 (14)	79 (17)	72 (12)
>12 seconds	3	7	75 (9)	68 (19)	38 (25)	92 (9)	74 (17)	68 (10)
<i>Stand from Supine</i>								
<5 seconds	1	18	76 (13)	86 (10)	64 (19)	81 (22)	83 (21)	77 (12)
5-10 seconds	2	14	80 (14)	86 (8)	61 (15)	84 (15)	83 (15)	78 (8)
>10 seconds	3	6	71 (18)	71 (19)***	35 (16)***	88 (12)	75 (18)	66 (13)
<i>Climb 4 Stairs</i>								
<5 seconds	1	24	79 (12)	86 (10)	64 (19)^A	81 (20)	81 (21)	77 (12)
5-10 seconds	2	15	75 (14)	86 (8)	61 (15)	89 (12)	80 (18)	78 (8)
>10 seconds	3	7	73 (19)	71 (19)***	35 (16)	83 (14)	78 (13)	66 (13)
<i>Gait Velocity</i>								
>45 meters/min	1	29	80 (12)	88 (7)^A	63 (17)^+	82 (19)	80 (19)	78 (11)^+
30-45 meters/min	2	11	65 (15)**	77 (15)	51 (20)	82 (13)	83 (19)	72 (12)
<30 meters/min	3	4	84 (8)	68 (18)	38 (24)	85 (21)	76 (21)	68 (10)

Abbreviations: DMD, Duchenne muscular dystrophy; PODCI, Pediatric Outcomes Data Collection Instrument; Std Dev, standard deviation; U, upper.

* Group 1 is significantly different from all other Groups.

** Group 2 is significantly different from all other Groups.

*** Group 3 is significantly different from all other Groups.
[†] Group 1 is significantly different from only Group 2.
[^] Group 1 is significantly different from only Group 3.
^{^^} Group 2 is significantly different from only Group 3.

Table 8

Mean (Std Dev) of PedsQL™ Parent Proxy Responses by Clinical Severity Groups for DMD Subjects

	Group	n	Physical	School	Emotional	Social	Psychosocial	Total
<i>Vignos Grade</i>								
class 1	1	10	50 (29)	73 (26)	65 (18)	70 (28)	69 (19)	63 (20)
class 2	2	28	45 (25)	58 (28)	64 (18)	74 (18)	66 (17)	59 (18)
class 3-4	3	6	24 (30)	63 (10)	70 (16)	80 (20)	71 (11)	56 (16)
<i>Knee Ext Strength</i>								
>8 N/kg	1	10	58 (34)	80 (25) [^]	71 (25)	76 (35)	75 (25)	70 (27)
4-8 N/kg	2	23	44 (24)	57 (30)	64 (15)	70 (15)	63 (14)	57 (15)
<4 N/kg	3	14	36 (24)	52 (19)	61 (13)	69 (21)	61 (14)	53 (13)
<i>10 Meter Walk</i>								
<6 seconds	1	23	54 (26)	68 (29)	64 (19)	71 (23)	67 (19)	63 (20)
6-12 seconds	2	17	37 (24)	56 (28)	68 (15)	78 (18)	68 (16)	58 (17)
>12 seconds	3	7	29 (27)	57 (10)	65 (19)	72 (19)	65 (13)	53 (15)
<i>Stand from Supine</i>								
<5 seconds	1	18	56 (30) [^]	72 (31)	67 (23)	77 (25)	72 (22)	66 (24)
5-10 seconds	2	14	42 (20)	50 (22)	65 (10)	68 (17)	62 (10)	55 (11)
>10 seconds	3	7	28 (19)	67 (21)	56 (13)	75 (19)	64 (13)	53 (11)
<i>Climb 4 Stairs</i>								
<5 seconds	1	24	52 (27)	69 (27)	69 (19)	73 (23)	70 (18)	64 (19)
5-10 seconds	2	15	39 (26)	58 (28)	62 (15)	77 (17)	65 (15)	56 (17)
>10 seconds	3	7	35 (24)	50 (18)	57 (15)	68 (18)	57 (14)	51 (8)
<i>Gait Velocity</i>								
>45 meters/min	1	29	49 (26)	64 (28)	65 (18)	76 (22)	68 (18)	62 (18)
30-45 meters/min	2	11	38 (26)	59 (29)	65 (14)	67 (17)	63 (17)	56 (19)
<30 meters/min	3	4	36 (40)	67 (18)	66 (24)	85 (17)	72 (19)	60 (24)

Abbreviations: DMD, Duchenne muscular dystrophy; PedsQL, Pediatric Quality of Life Inventory™.

* Group 1 is significantly different from all other Groups.

** Group 2 is significantly different from all other Groups.

*** Group 3 is significantly different from all other Groups.
⁺ Group 1 is significantly different from only Group 2.
[^] Group 1 is significantly different from only Group 3.
^{^^} Group 2 is significantly different from only Group 3.