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PRINCIPAL INVESTIGATOR:

McDonald, Craig M.

RECIPIENT:
University of California Davis
4860 Y Street, Suite 3850
Sacramento, CA 95817

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Craig McDonald, MD
Erik Henricson, PhD, MPH

E-Mail: ehenricson@ucdavis.edu

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University of California Davis
4860 Y Street, Suite 3850
Sacramento, CA 95817

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14. ABSTRACT

Development of novel technologies and therapeutic agents to treat Duchenne muscular dystrophy (DMD) have increased interest by regulatory bodies such as the Food and Drug Administration in the development of "clinically-meaningful" study endpoints for clinical trials. There is a need for the development of person-reported outcome (PRO) instruments that target a broad range of developmental and functional ability while effectively evaluating treatment effects in clinical trials.

Our proposed project will use quality of life questionnaire data from the first 4-7 years of ongoing Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study. Using that data, we will identify questions that show differences between people with different levels of abilities (such as those who can walk or just raise a hand to the mouth), or that show changes over one year that might be seen by researchers during drug clinical trials. Those questions will then be combined and built into a computerized adaptive testing (CAT) system that will produce short, individualized surveys for clinical practice and clinical trial use that are tailored to a patients' level of functional ability.

15. SUBJECT TERMS: NONE LISTED

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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Background: Development of novel technologies and therapeutic agents to treat Duchenne muscular dystrophy (DMD) have increased interest by regulatory bodies such as the Food and Drug Administration in the development of "clinically-meaningful" study endpoints for clinical trials. There is a need for the development of person-reported outcome (PRO) instruments that target a broad range of developmental and functional ability while effectively evaluating treatment effects in clinical trials.
Objective: Our proposed project will use quality of life questionnaire data from the first 4-7 years of ongoing Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study. Using that data, we will identify questions that show differences between people with different levels of abilities (such as those who can walk or just raise a hand to the mouth), or that show changes over one year that might be seen by researchers during drug clinical trials. Those questions will then be combined and built into a computerized adaptive testing (CAT) system that will produce short, individualized surveys for clinical practice and clinical trial use that are tailored to a patients' level of functional ability.
Applicability: Well-designed CAT-PRO questionnaires can be used in both clinical trials and day-to-day clinical practice. For clinical trials, they provide researchers with the ability to put all patients, regardless of their functional abilities, together on the same scale. That means that one tool can be used to evaluate quality of life across many types of studies and many groups of patients, but that the results can still be compared. Those results can then also be compared to other clinical trial measures such as strength tests, timed function tests, or pulmonary function tests to help teach researchers and regulatory authorities about how "in clinic" tests commonly used in clinical trials relate to a persons' quality of life, and whether those tests are "clinically meaningful". In day-to-day clinical practice, it means that doctors can have a single tool that can give feedback on a patient's quality of life, even as their levels of ability change over time. Within 3 years, this project will be able to produce such a useful tool because much of the data has already been collected from the CINRG study and because the rest of the data will be from the large group of over 3000 volunteers who are already part of the Parent Project Muscular Dystrophy DuchenneConnect Registry.
Impact and Contributions: Data from the CINRG DMD natural history study cohort and the DuchenneConnect Registry will provide the basis for development of a "clinical trial-ready" novel CAT-based PRO measure that has been constructed against a background of comprehensive clinical assessments of strength and function across the DMD lifespan. This PRO measure will be rapidly usable as a sensitive measure for use in the growing field of DMD clinical trials, and will help to demonstrate "clinically meaningful" results to regulatory agencies in charge of new drug approval.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Duchenne muscular dystrophy
Person-reported outcomes
Health-related quality of life
Functional health assessment
UC Davis / CINRG Duchenne Natural History Study

3. ACCOMPLISHMENTS: The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?

Aim 1: Development of ICF-based Item Banks from CINRG DNHS PRO Data - We will evaluate item responses across domains to develop domain-specific item banks for a composite PRO measure. We will evaluate responsiveness of PRO subscales and items at differing levels of function that represent functionally-meaningful activities of standing from supine, climbing stairs, rising from a chair, ambulating independently, reaching overhead, raising a hand to the mouth for feeding, and the need for mechanical cough assistance for airway clearance (defined as having a forced vital capacity >50% of predicted values for age). Data will include all available completed PRO form sets for all participants from the baseline visit up to at least the month 48 visit, and will an age range of 5-32+ years, which will represent approximately 1200+ 12-month intervals. Clinical data will include steroid treatment status, anthropometrics, timed motor performance testing (time to stand from supine, time to climb 4 stairs, time to run/walk 10 meters), Brooke and Vignos scales, and forced vital capacity pulmonary function. Some data from the cohort will be available out to 7 years of participation. At each visit time point, participants will be classified into a functional milestone group as previously described. Using that milestone grouping, we will evaluate 12-month change for each year of study participation. Those who increase in milestone scale score will be classified as having lost a functional milestone during that period. Participants will also be classified by steroid-user status as glucocorticoid naïve, previously-treated or currently-treated. Their questionnaire responses will be scored into instrument total and subscale scores per standard guidelines. Responses on all individual items will also be evaluated independently. Each instrument subscale and item will be classified according to ICF domain and subdomain for inclusion in domain-based item banks. Level of significance will be set at $p<0.05$.

Aim 1.1: Selection of Initial Item Bank Content – Using all available PRO data, we will evaluate item responses across domains to develop domain-specific item banks for a composite PRO measure. We will evaluate responsiveness of PRO subscales and items at differing levels of function that represent functionally-meaningful activities of standing from supine, climbing stairs, rising from a chair, ambulating independently, reaching overhead, raising a hand to the mouth for feeding, and the need for mechanical cough assistance for airway clearance (defined as having a forced vital capacity >50% of predicted values for age).

Aim 1.2: To refine the item banks and ensure coverage across the entire spectrum of disease, we will identify ranges of function where overlapping PRO items or gaps in item content exist against a backdrop of the entire range of meaningful functional abilities demonstrated by the DMD population across all age groups.

Aim 1.3: Focus Groups to Develop Supplemental Domain Items – To address areas of overlap and gaps in item content, we will conduct focus group discussions with an expert advisory group of DMD clinical research professionals, health care providers, parent caregivers, and patients with DMD to identify relevant items for inclusion in a composite PRO measure, and to develop new items where suitable ones do not exist.

AIM 2: Pilot Testing of WHO-ICF Domain Item Banks using DuchenneConnect DuchenneConnect is a web-based DMD patient data registry and epidemiology research tool hosted by Parent Project Muscular Dystrophy that is used by more than 3000 families worldwide to track important clinical data related to the health, function and health services utilization of their family member(s) with DMD. We will work with DuchenneConnect administrators to publish an online version of the full PRO banks including all final items across domains. We will ask DuchenneConnect participants to enroll in the study and complete question sets at baseline. One year later participants will be contacted by email and reminded to complete a follow-up set of assessments after 1 year of follow-up. Data will be combined with registry self-report glucocorticoid use and measures of functional "milestone" ability data.

Aim 2.1: Validation of New Domain-Based Item Banks – Prospective 1-year data from the DuchenneConnect registry application of newly-derived item banks will be evaluated using techniques described in Aim 1 to confirm that items are responsive to self-reported changes in milestone ability over a time period consistent with design of contemporary clinical trials. Rasch analysis will be repeated to confirm item fit and performance for retained and newly-developed items.

Aim 2.2: Identification of Item Responsiveness to Group Differences Due to Glucocorticoid Therapy Evaluate the responsiveness of the composite PRO item banks to differences in milestone scores. We will test the hypothesis that functionally-specific mobility and ADL PRO items will be differentially responsive functional "milestone" abilities.

AIM 3: Development of a Computerized Adaptive Testing PRO instrument for use in clinical trials:

Aim 3.1: Perform a CAT simulation from data obtained from the comprehensive PRO item banks. A real data simulation approach will be used to investigate the accuracy of each CAT generated from the full-item banks.

What was accomplished under these goals?

The project accomplished its goal of development of a validated person-reported composite outcome measure of functional health for use across the lifespan in people affected by Duchenne muscular dystrophy. The resulting tool the *Duchenne Muscular Dystrophy Lifetime Mobility Scale (DMD-LMS)* was developed by identifying questionnaire items from the CINRG Duchene Natural History Study cohort that exhibited significant and meaningful changes over one year or demonstrated differences between steroid-treated and non-treated individuals. Questions were grouped into three domains representing the domains *walking and moving, changing and maintaining body position,* and *carrying, moving and handling objects.* Questions were further refined by examining question item response characteristics using Rasch analysis techniques, adapting syntax and question response categories based on Rasch results, and by developing additional questions to address ceiling and floor effects based on review of clinical tools' concepts, input from expert clinicians and input from patients themselves. The resulting questionnaire underwent field evaluation and device performance was evaluated again using both Rasch techniques and classical measures of questionnaire performance to develop a final instrument scoring structure and linearized scoring algorithm. Beginning in the fall of 2019, we are planning to work with the FDA to seek certification of the DMD-LMS through the CDER Clinical Outcome Assessment Qualification Program. The instrument is being employed as a pilot measure by one ongoing industry clinical trial "A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Safety and Efficacy of Intravenous Delivery of Allogeneic Cardiosphere-Derived Cells in Subjects With Duchenne Muscular Dystrophy (NCT03406780)". Efforts to seek publication of the instrument, technical report and scoring guide in a peer-reviewed journal are presently underway.

For additional information, please refer to the attached document entitled *TECHNICAL REPORT: Development and Validation of the Duchenne Muscular Dystrophy Lifetime Mobility Scale (DMD-LMS).*

What opportunities for training and professional development has the project provided?

Nothing to Report

How were the results disseminated to communities of interest?

Results of Aim 1 activities have been presented in multiple conference proceedings and publications. We presented information on responsiveness of Person Reported Outcomes (PROs) in the CINRG Duchenne Natural History Study at the Duchenne Regulatory Sciences Consortium Workshop in April of 2016. Proceedings of the meeting were recently published in PLoS Currents (Larkindale et al, 2017) and are available to the public via PubMed Central (PMC5300692). Work on the relationship between disease-related functional milestones and pulmonary function characteristics over the lifespan was presented at the Parent Project Muscular Dystrophy Pulmonary Care Workshop (April 2106). The workshop was attended by disease experts, representatives of the pharmaceutical research industry and federal government funding and regulatory agencies. A workshop summary publication is currently under review by the *American Journal of Respiratory and Critical Care Medicine*. Two additional publications are in draft from the CINRG group and highlight the disease milestone concepts developed during Aim 1 of this project. The paper, titled *Time to event analysis for the loss of clinically-meaningful milestones in Duchenne muscular dystrophy: The effect of glucocorticoids throughout the lifespan* expands on functional milestone scale items as critical events to assess relative risks of disease progression in steroid-treated and steroid-naïve populations. The paper was accepted for publication by *Lancet* in September 2017.

Beginning in April of 2018 the DMD-LMS was included as a pilot measure in the Capricor, Inc. clinical trial "A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Safety and Efficacy of Intravenous Delivery of Allogeneic Cardiosphere-Derived Cells in Subjects With Duchenne Muscular Dystrophy (NCT03406780)". Data collection is in progress for that study.

In May of 2019 at the request of a group of clinical outcome measure specialists at the FDA's Center for Drug Evaluation and Research Office of New Drugs, Division of Neurology Products we presented the overall project, including Aim 2 and Aim 3 progress and preliminary results. Based on that presentation and resulting conversations, the decision was made to work with the FDA to seek certification of the DMD-LMS through the CDER Clinical Outcome Assessment Qualification Program. This work will proceed starting in the Fall of 2019.

The final technical report and device scoring guide (attached) was completed in September, 2019. The report and scoring guide will be included as a freely-available online appendix to a peer-reviewed journal publication describing the instrument. Submission of the manuscript to a well-known neuromuscular disease journal such as *Neuromuscular Disorders, Muscle and Nerve* or *Developmental Medicine and Child Neurology* is planned during Fall of 2019.

What do you plan to do during the next reporting period to accomplish the goals?

Project complete.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

The project provides a new and well-validated patient-reported outcome measure for use in observational studies, clinical trials and registry/public health settings to evaluate physical mobility of individuals with Duchenne muscular dystrophy across all ages and stages of disease from age 4 and up. The measure demonstrates sensitivity to disease progression as well as sensitivity to treatment effects of the magnitude observed when using clinically-proven glucocorticoid steroid therapies. Unlike other DMD-focused measures, the DMD-LMS incorporates multiple functional domains describing patient's lower extremity, trunk and upper extremity abilities.

What was the impact on other disciplines?

While the study has not yet produced any references of external use, it will add to the body of knowledge regarding use of item-response theory and Rasch analysis methodology in development of person-reported outcome measures across health and disease disciplines.

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

We anticipate that the DMD-LMS will help translational research scientists, regulatory agencies and patient advocacy groups to cross-correlate person-reported DMD-LMS scores with results from quantitative laboratory- and clinically-based measures to better interpret impact of changes in those measures against a backdrop of functionally-meaningful daily living tasks.

5. CHANGES/PROBLEMS: The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to Report

Changes that had a significant impact on expenditures

Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to Report

Significant changes in use or care of vertebrate animals

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to Report

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Publication of the instrument, scoring guides and technical reports is pending – manuscript in preparation:

Henricson EK, Abresch RT, Mayhew AG, Joyce N, Bagley A, Owens CO, McDonald CM. Development and validation of the Duchenne Muscular Dystrophy Lifetime Mobility Scale (DMD-LMS): An instrument measuring whole body mobility across the lifespan. *In preparation, federal support will be acknowledged appropriately.*

Lectures.

2018, Spring **CITRIS Research Exchange Series**
Lecture Title: *Wearables, PROs & Person-Generated Health Data: Community Ambulation and Perceived / Measured Mobility in Duchenne Muscular Dystrophy*
UC Berkeley School of Engineering, Berkeley CA

2017, Summer **UC Davis Precision Medicine Symposium**
PRECISION MEDICINE AND MUSCULAR DYSTROPHY: Similarities and synergies between human and canine models
Lecture Title: *Wearables, PROs and person- generated health data*.
Davis, CA

2017, Summer **Parent Project Muscular Dystrophy Drug Development Roundtable**
Lecture Title: *Finding clinical meaning in patient-reported functional health: Development of the Duchenne Muscular Dystrophy Lifetime Mobility Scale.*
Parent Project Muscular Dystrophy Annual Meeting
Chicago, IL

2017, Spring **Duchenne Regulatory Sciences Consortium Annual Meeting**
Lecture Title: *Finding clinical meaning in patient-reported functional health: Development of the Duchenne Muscular Dystrophy Lifetime Mobility Scale.*
Critical Path Institute, D-RSC
Washington, DC

Poster Presentations

Henricson EK, McDonald CM, Mayhew A, Bagley A, Joyce N, Oskarsson B, Sodeberg-Miller L, Liu S, Abresch R and the CINRG Investigators. *Finding clinical meaning in patient-reported functional health: Development of the Duchenne Muscular Dystrophy Lifetime Mobility Scale*. World Muscle Society, October 2017. St. Malo, France.

- **Website(s) or other Internet site(s)**

  Nothing to Report

- **Technologies or techniques**

  Nothing to Report

- **Inventions, patent applications, and/or licenses**

  Nothing to Report

- **Other Products**

  Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Craig McDonald, MD (PI) - No Change
Name: Erik Henricson, MPH (Co-Investigator) - No Change
Name: Nanette Joyce, DO (Co-Investigator) - No Change
Name: Anita Bagley, PhD, MPH (Co-Investigator) - No Change
Name: Corey Owens, MS (Data Manager) – Concluded participation October 2018
Name: Erica Goude, MS (Outreach Coordinator) - No Change
Name: Mary Jane Mulcahey, PhD (Co-Investigator) – No Change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

Appendix 1: TECHNICAL REPORT: Development and Validation of the Duchenne Muscular Dystrophy Lifetime Mobility Scale (DMD-LMS)

TECHNICAL REPORT:

Development and Validation of the Duchenne Muscular Dystrophy Lifetime Mobility Scale (DMD-LMS)

Erik Henricson, PhD, MPH[1]
Craig McDonald, MD[1]
Nanette Joyce, DO[1]
The CINRG DNHS Investigators[2]

[1]University of California, Davis Department of Physical Medicine & Rehabilitation, Sacramento CA
[2]The Cooperative International Neuromuscular Research Group Duchenne Natural History Study

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PART 1: Initial domain and item set development.

Initial Development and Characteristics of the DMD Lifetime Mobility Scale (DMD-LMS)

The Duchenne Muscular Dystrophy Lifetime Mobility Scale (DMD-LMS) is an instrument comprised of three subdomains representing 1) walking and moving, 2) transfers and trunk stability, and 3) carrying, moving and handling objects measuring from early ambulatory to late non-ambulatory stages of disease, and each subdomain is scored out of 100 points. The DMD-LMS, developed using Rasch analysis methods from data collected during the CINRG Duchenne Natural History Study (DNHS)[1], has demonstrated internal validity and is capable of differentiating between steroid-treated and non-treated groups, between functional "milestone" groups, and has demonstrated significant change over one year across all stages of disease.

Using data from the CINRG DNHS, we employed our previously described clinically-meaningful "milestone scale"[2] combined with "clinically-meaningful" PRO item changes over time to evaluate PRO items that show clinically-important differences in response to either disease progress over one year or loss of a milestone. Using the resulting set of PRO items, we constructed item banks based on the WHO-ICF domains representing the basic health condition, body structure and function, activities and participation, personal and environmental factors (Figure 1).

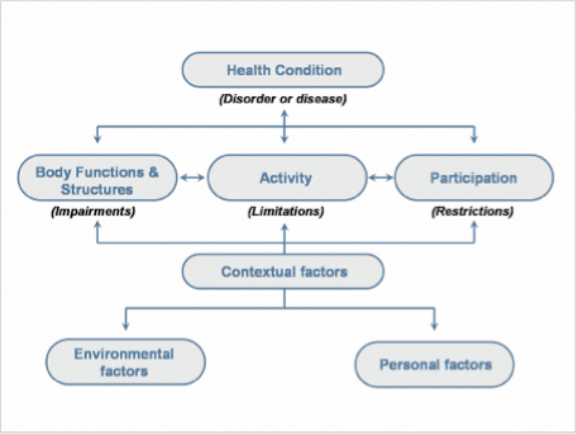


Figure 1: Duchenne Natural History Study Structure - The WHO ICF Model Encourages Study of Multi-Level Interactions

The past several years have seen a markedly increased interest by pharmaceutical companies in conducting ground-breaking research and development into effective treatment agents for DMD. Therapeutic approaches under development for clinical trials in DMD include antisense oligonucleotide (AON) exon skipping therapies, gene therapy strategies, stem cell therapies, as well as a host of small-molecule therapies (e.g. compounds that induce read-through of premature stop-codon mutations, promotion of muscle growth via myostatin inhibition, utrophin upregulation, and steroid analogs with improved side effect profiles). While these therapeutic approaches will not be curative, there is significant hope that new therapies on the horizon will significantly alter disease progression, improve function, and improve quality of life. Ideal clinical endpoints used for future clinical trials need to be clinically meaningful both with regard to a) patient-reported outcome measures focused on well-being and health-related quality of life and b) clinically meaningful milestones such as loss of ambulation, self-feeding, and reliance on non-invasive ventilation.

Here we used 4-7 years of existing PRO data from our WHO-ICF-based Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study to develop "item banks" of questions that can detect both differences due to variation in functional abilities and that are capable of detecting changes over a one-year period of time. An *item bank* comprises items that define and quantify common themes and thus provide an operational definition of a latent trait[3]. These item banks can provide the foundation for testing using either dynamic computerized adaptive testing (CAT) or static testing using multiple created short-forms. CAT is a process of test administration in which items are selected on the basis of the patients' responses to previously administered items[4]. This process uses an algorithm to estimate *person level* to choose the next best item and administer the test under specifications such as content coverage and scale length. This capacity to measure all patients on the same continuum, even if they have not been presented any items in common, offers a scale that is individually tailored to each patient.

Specific Aims

Using the CINRG DNHS data, we employed Rasch analysis techniques to analyze PRO measure item responses to develop a novel DMD-specific composite PRO measure that measures multiple domains and spans the entire spectrum of DMD severity and progression.

We conducted a retrospective analysis of 4-7 years of longitudinal multicenter WHO ICF-based data (PODCI, PedsQL, SF-36, Life Satisfaction Index, DMD Sleep Quality Index, WHO-QoL, NeuroQoL) on health conditions, body structure and function, activity, participation, personal and environmental factors, and person-reported quality of life (Figure 2) from patients and parents of the 420 families enrolled in the CINRG DNHS.

Figure 2: WHO ICF Elements in the UCD/CINRG Duchenne Natural History Study

CINRG Duchenne Natural History Study
WHO ICF Model Elements

Health Condition	Body Structure and Function	Activity	Participation	Personal Factors	Environmental Factors
• Molecular Diagnostics • DNA for SNP / GWAS analysis • Dystrophin Immuno-histochemistry • Medical Status Review • Steroid therapy	• Strength • Pulmonary Function • Anthropometrics • Vital signs • Body composition • Range of motion • Spine deformity • Cardiac evaluation	• Functional testing • Timed motor performance • 6-minute walk • 9-hole peg • North Star • EK Scale	• PedsQL • PedsQL Neuromuscular Module • POSNA • NeuroQoL • WHO QoL Brief • SF-36 • Pittsburgh Sleep Quality Index	• PedsQL • Life Satisfaction Index • Sociodemographic Data (NIFD Questionnaire) • Educational attainment	• Health Service Utilization • WHO-QoL • Sociodemographic Data (NIFD Questionnaire) • Community Accessability • Educational environment

With over 1600 person-years of follow up available from this cohort, we addressed the following specific aims:

Aim 1: Development of draft WHO-ICF domain-based lists using PRO items from the UC Davis/CINRG Duchene Natural History Study (DNHS). Using individuals items from the POSNA PODCI, PedsQL, WHO-QoL, SF-36, NeuroQoL, Life Satisfaction Index and Pittsburgh Sleep Quality Index we will assign each to domain-based lists representing latent constructs representing the WHO-ICF domains for Mobility, General Tasks and Demands, Interpersonal Relationships, Community Social and Civic Life, Major Life Areas, Mental (Psychological) Functions, Pain, Neuromuscular and Movement Functions, Support and Relationships, and Services Systems and Policies. Following assignment, the domain-based lists will be circulated to a panel of expert reviewers. Mis-fit items will be discussed by the review panel members, who will determine final domain list assignments.

Aim 2: Evaluation of item responsiveness to differences in disease stage and steroid treatment. Using all available PRO data, we will evaluate item responses across domains to refine domain-specific item banks for future use in composite PRO measures. We will evaluate responsiveness of PRO items at differing levels of clinically-meaningful "milestone" function represented by ability to stand from supine, climb stairs, rise from a chair, ambulate independently, raise a hand to the mouth for feeding, and the requirements for mechanical cough assistance for airway clearance (defined as having a forced vital capacity >50% of predicted values for age). We will evaluate item change over a one-year period of time consistent with current clinical trial designs.

Aim 3: Rasch Analysis to evaluate latent construct validity and item content. We will use Rasch Unidimensional Measurement Model (RUMM2030) software to evaluate domain list item responses to examine whether items are clinically meaningful, if they are targeted across the observable range of phenotype and are independent, whether individual and item responses fit within an overall model and whether the resulting scale reliably identifies differences between individuals. This will occur in a two-step process, with initial evaluation, followed by item list refinement and re-evaluation.

Aim 4: Validation of final domain-based item banks. Using Rasch analysis-based validity testing methods described in Aim 3, we will evaluate the final domain-based item lists to determine their ability to quantitatively measure their proposed latent constructs. From the output, we will construct a 0-100 point linear logit-transformed scoring scale for each domain-based bank.

Methods

Timing and Content of Assessments

Because the DNHS was a long-term study, procedures were essentially the same every time the participant visits the clinic for their annual checkup. This study was designed so that assessments were completed according to **Table 1**. All ambulant study subjects, during Year 1 were to complete study visits every 3 months at Month 1, Month 3, Month 6, Month 9 and Month 12. For all non-ambulant study subjects, the optimal Year 1 visit schedule was every 3 months. However, the first-year visit schedule was adjusted to reflected local standard of care practice at some centers. For those participating sites where standard of care occurred every 6 months, study visits were only required at Month 1, Month 6, and Month 12.

TABLE 1: Schedule of Study Visits by Year

Calendar Year by Month	Baseline	Month 3	Month 6	Month 9	Month 12
Year 1: Ambulant	x	X	x	x	x
Year 1: Non-ambulant	x		x		x
Year 2			x		x
Year 3					x
Year 4					x
Year 5					x
Subsequent Years					x

Some assessments were age- or disease stage-specific, and so were only completed at some visits. Likewise, if a test subject was unable to cooperative with an examiner for behavioral or developmental reasons, or because of an injury, the test was skipped and re-introduced at the next visit. Details on assessments are provided below and include age- and disease stage-specific guidelines. Specific DNHS assessment methods are described in by McDonald and colleagues[1].

Anthropometrics (All ages): Anthropometric measures included standing height, weight, and ulnar length. Standing height was only measured for individuals who were able to stand unassisted.

Timed Function Testing (Age 2 as able and up): Timed motor performance (e.g. time to walk 10 m., time to climb 4 stairs and time to stand from supine from floor) tests followed the protocol reported by our group[5],[6].

Brooke upper extremity scale and Vignos lower extremity scale (Age 4 and older, as able): The functional classification used by CINRG utilizes a scale modified from the upper extremity scale reported by Brooke et al.[7] and the lower extremity scales used by Vignos et al.[8] The functional grades consist of six levels of function for the upper extremities. For participants able to perform the first level they were also asked to complete this level with small weights. The lower extremity includes eleven levels.

Pulmonary Function Testing (PFT) (Age 6 as able and up): Pulmonary Function Tests (PFT) were performed in sitting and supine positions. PFTs included maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), forced vital capacity (FVC), forced expiratory volume 1 (FEV1), peak expiratory flow (PEF), and peak cough expiratory flow (PCEF).

Review of Systems – Physician Visit: Physicians conducted a detailed review of systems that included a physical and neurological examination and medical history. This was aided by review of the completed intake or annual review of systems form packet. Following the physicians review of systems, participants or guardians reviewed past month medication use with either the physician or study coordinator using the medication form included in the intake or annual review of systems form packet. Physicians or study coordinators attempted to gather trade/generic name, dose, route, frequency and indication for each medication that was reported on the form. Participants or guardians brought all medications to the visit with them to facilitate this review.

POSNA (Every visit, Ages 5 and older): The Pediatric Orthopaedic Functional Health Questionnaire of the Pediatric Orthopaedic Society of North America (POSNA) was developed by the POSNA in 1994[9,10]. The POSNA assessment is designed to measure actual functional levels of pediatric orthopedic patients. The primary scales of the instrument include assessment of upper extremity function, transfers/mobility, physical function and sports, comfort/pain, happiness and satisfaction and expectations for treatment. Both parent proxy and adolescent self-report forms have been validated. This is a self-administered questionnaire. Parents/guardians completed a proxy assessment for all children under 18. Teens (11-17) completed a self-report assessment.

PedsQL (5-17) (Every visit. All Participants): Pediatric Quality of Life Inventory, Version 4 (Peds QL 4.0)[11–13]. The Pediatric Quality of Life (PedsQL) Inventory is a self-report measure designed to measure core health dimensions in children from 5 to 17 years old. The measure consists of 23 items in four scales: physical functioning, emotional functioning, social functioning, and school functioning. Parents/guardians completed a proxy assessment for all children under 18. Teens (11-17) completed a self-report assessment.

WHO QOL Brief (Every visit. Adult Subject 18 years and older): The World Health Organization Quality of Life Assessment – Brief (The WHO QOL Group, Geneva) has been widely used to assess individuals perceptions on their quality of life with respect to culture, values, goals, standards and concerns. The 26-item assessment covers contains major domains that assess physical health, psychological health, social relationships and environment [14,15]. This is a self-administered questionnaire.

Life Satisfaction Index (Every visit. Teens (11-17) and Adults with DMD): Life Satisfaction Index for Adolescents[16]. The Life Satisfaction Index for Adolescents consists of five domains: general well-being, interpersonal relationships, personal development, personal fulfillment, and leisure and recreation. Each item is ranked on a five-point rating scale. Domain scores and a total score are derived.

DMD Sleep Quality Index (Every visit. Teens (11-17) and Adults with DMD and Parent/Guardian (proxy)): The DMD Sleep Quality Index is an adaptation of the Pittsburgh Sleep Quality Index (PSQI)[17]. The PSQI is self-rated and assesses sleep quality over the preceding 1 month. Major domains include subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of medication and daytime dysfunction. The DMD-related modification incorporates items associated with common DMD-related orthopedic and respiratory complications that are thought to impact sleep in affected individuals.

Pediatric and Adult NeuroQOL: Adult and child/adolescent versions of the NeuroQOL were administered at baseline and each annual visit[18–20]. Participants were asked a series of Likert-scale questions covering domains including Mobility/Ambulation, Activities of Daily Living/Upper Extremity, Social Health, Emotional Health, Stigma, Perceived Cognitive Function, Fatigue and Pain domains. The item responses are compared to population response frequencies using Item response theory thus yielding a z-score for each response and a standard score with mean of 50 and standard deviation of 10. Both parallel child self-report (for ages > 10) and parent proxy-report formats (for all subjects) were used in pediatric populations. The same domains from the adult version of the survey were used in participants at least 18 years of age.

Analysis of Data

Classification of Question Items to WHO-ICF Categories: Individual question items from each instrument were classified by a group of expert reviewers according to WHO-ICF categories and subcategories for Part B: Function, Part D: Activities and Participation, and Part E: Environmental Factors. Where applicable, questions were classified into multiple categories. When there were disagreements regarding category assignment, items were discussed until consensus was reached.

Principle Component Factor Analysis and Scale Reliability: Using the raw item response scores for items assigned by expert review to each WHO-ICF subcategory, we conducted confirmatory principle components factor analysis to evaluate whether items were likely to represent a "pure" construct. To evaluate reliability of these item lists, we calculated Cronbach's alpha statistic.

Analysis of Item Sensitivity to Disease Progression and One Year Change: We used the previously described 6-level composite of individual functional "milestone" tasks[2], combining the results from the ability to perform the timed function tests as well as the Brooke and Vignos functional scales. To further differentiate among non-ambulatory individuals with limited upper limb ability, we added a seventh level representing limited respiratory function with a forced vital capacity of <30% indicating a need for full-time mechanical ventilation. The levels of this composite scale are: (0) able to complete all 3 timed tests; (1) unable to stand from supine but performed the 4 step climb and the walk; (2) unable to climb 4 standard stairs, can walk 10 meters, Vignos grade <5; (3) cannot rise from chair, but can walk 10 meters, Vignos scale <7; (4) cannot walk 10 m, but can raise hand to mouth, Brooke <5; (5) unable to raise a hand to the mouth, Brooke scale 5 or 6; (6) unable to raise a hand to the mouth, Brooke scale 5 or 6 and FVCP<30%. We then grouped participants according to whether or not they had changed milestone grades over the one-year period between evaluations. We defined a "successful" instrument or instrument subscale as one that: a) differentiated between milestone groups; b) showed significant change over a one-year period of time, and c) was deemed "clinically significant" by meeting or exceeding change of 1/3 the standard deviation of the measure for either the group as a whole or among individuals who showed a change in milestone scale score indicating loss of a key functional ability.

Psychometric Evaluation using Rasch Analysis: Rasch analysis is form of item response theory that is used as an alternative to classical test theory methods of determining reliability and validity of scale-based measurement tools, which have been criticized as "weak" measurements because of lack of continuous measures, scale-dependent scores, lack of sensitivity to change and floor and ceiling effects that hamper interpretation of scores[21]. Rasch analysis provides a "strong" construct-based approach to assessing responses to question items by individuals in a given patient population whereby item response probabilities are modelled for each individual response item and individuals are placed according to their response characteristics on a continuous scale representing fixed intervals across a phenotypic range. Analysis using the Rasch Unidimensional Measurement Model (RUMM2030) software aids in evaluation of instrument responses to examine whether items are clinically meaningful, if they are targeted across the observable range of phenotype and are independent, that individual and item responses fit within an overall model and whether the resulting scale reliably identifies differences between individuals.

Clinical Meaning: Clinical meaningfulness is assessed through ordering of locations of items and response thresholds in terms of ascending or descending difficulty across the population studied, and is displayed on the threshold ordering map. We expected that

items would locate in a way that is consistent with previous clinical natural history observations of ordinal loss of function in DMD patients[2].

Targeting: Targeting is assessed by evaluating item locations relative to the locations of individuals along the continuum representing good to poor function, and is displayed on the person-item threshold distribution. Appropriately targeted measures demonstrate an equally distributed range of item thresholds that extends beyond the location of all individuals in the studied population. This indicates freedom from floor and ceiling effects of the measurement tool.

Dependency: Dependency is assessed by evaluating the correlation coefficients of residual fit values generated by comparing aggregate actual responses to modelled responses. Items with a high degree of correlation (defined here as >0.4), and thus a high degree of dependency often show that response on one item directly dictates response on another.

Fit: Fit can be assessed for both items and individuals by calculating residual values comparing actual responses to modeled responses for an individual across items or for an item across individuals. The lower the residual value and the higher the p-value for inclusion in the model, the better the fit. For individual items and individuals, a residual value of $<|3.0|$ is considered acceptable, with acceptance for inclusion in a model set here at $p>0.01$, where items with high residuals exhibit less fit and statistically significant p-values indicate that observed variance is non-random.

Person Separation Index: The Person Separation Index (PSI) indicates the power of overall ability of a model construct to individuate between respondents. A PSI value of >0.8 is generally accepted as "good" overall model fit.

Iterative Approach to Model Construction: Datasets were constructed for each domain construct list using all clinically-responsive items as determined according to the item sensitivity analysis section listed above. The approach to data analysis was to conduct an initial analysis based on all items in the data set. The initial analysis generated information on overall model fit, individual item fit, item response threshold order and item dependency. Results from the first-pass analyses were used to determine which overall domain and subdomain set demonstrated the highest initial model fit based on the available responses across different age groups. For the selected domain / subset group, a secondary analysis including item rescoring and item selection was conducted. For the secondary analysis, items that demonstrated disordered item response thresholds were evaluated to determine whether any response items could be condensed in a clinically meaningful way, and were recoded if that was possible, or otherwise were not retained. Items that demonstrated a high degree of correlation and dependency were examined to determine whether they represented a similar construct (i.e. they measure similar or different levels of the same thing). Where such items were considered duplicative and items were administered consistently across the sample group, only the most clinically representative item was retained for further analysis. For similar items that were administered only to specific sub-populations (ie. only children for one question, only teens for its similar counterpart), items were retained but were noted as requiring possible future consolidation. Then data was re-analyzed using only retained items to determine whether model characteristics improved.

Results

Study Population

Four hundred and ten patient-parent/guardian pairs completed survey instruments and clinical evaluation testing. Full details on the content and timing of visits and the overall subject population have been previously published[1,2]. Participants represented a wide range of ages representative of the disease (age at initial visit 11.3[5.7] years, range 4 – 28 years). The number of completed visits per participant ranged from 1 to 13 (mean 5[3]) with follow-up in some participants to month 96, for a total of 3066 completed visits. At baseline 125 (30%) of participants were glucocorticoid steroid-naïve, 49 (12%) were previous steroid users, and 236 (58%) were steroid users. At baseline 253 (62%) were ambulatory, and 47 (11%) had a forced vital capacity <30% of predicted for age.

Grouping Question Items by WHO-ICF Domains

Using a group of expert reviewers, we classified 367 question items according to the WHO-ICF domains for Function (Part B), Activities and Participation (Part D) and Environmental Factors (Part E), with each question being considered for inclusion under each construct. A summary of the number of items included in each construct and subdomain, by original instrument is included as Table 2. When classified under the Function construct, 142 items were assigned to the Mental Function subdomain, 10 to the Sensory Functions and Pain subdomain, 8 to the Functions of the Hematological, Immunological and Respiratory Systems subdomain, 148 to Neuromusculoskeletal and Movement-Related Functions subdomain, and one to the Functions of the Skin and Related Structures subdomain. Items were further subclassified under each subdomain as noted in Table V.2. When classified under the Activities and Participation construct, 12 items were assigned to the Learning and Applying Knowledge subdomain, 20 to General Tasks and Demands, 12 to Communications, 110 to Mobility, 60 to Self-Care, two to domestic life, 28 to Interpersonal Interactions and Relationships, 10 to Major Life Areas, and 26 to Community, Social and Civic Life. Under the Neuromusculoskeletal and Movement-Related Functions

subdomain, we created further sub-classifications that represents domains from the Performance of the Upper Limb (PUL)[22] and North Star Ambulatory Assessment (NSAA)[23] clinical evaluations with the goal of subdividing self-report tasks according to existing models of upper limb function and ambulatory mobility. When classified under the Environmental Factors construct, 30 items were assigned to the Products and Technology subdomain, 10 to Natural Environment and Human-Made Changes to the Environment, 14 to Support and Relationships, two to attitudes, and 27 to Services, Systems and Policies.

Item Sensitivity to One-Year Change and Disease Progression

We evaluated each question item to evaluate whether it was able to detect differences between individuals of different functional milestone groups, and its ability to demonstrate significant change in a one-year period of time consistent with the duration of most contemporary clinical trials. Taken together, item responsiveness screening yielded a list of 138 of the original 367 question items (37.6%). A summary of the numbers and percent of sensitive question items by WHO-ICF domain/subdomain and instrument is presented in Table 2. In the Function construct, only a very small number of questions in the Mental Functions subdomain (0.4%) and none of the items in the Functions of the Skin and Related Structures subdomain met criteria for being responsive. Approximately half of the items in the Sensory Functions and Pain (40%) and Functions of the Cardiovascular, Hematological, Immunological and Respiratory Systems subdomains (50%) demonstrated responsiveness. Three quarters (75%) of items assigned to the Neuromuscular and Movement-Related Functions subdomain demonstrated responsiveness. In the Activities and Participation construct, relatively small percentages of items demonstrated responsiveness in the Learning and Applying Knowledge subdomain (25%), General Tasks and Demands (5%), Interpersonal Interactions and Relationships (11%), Major Life Areas (0%), and Community, Social and Civic Life (27%). Approximately half of items in the Communication subdomain (50%), Self Care (53%) and Domestic Life (50%) demonstrated responsiveness, although the latter was comprised of a single item. Of 110 items initially assigned to the Mobility subdomain, 74 (67%) demonstrated responsiveness to disease stage and progression over time. The percentage of responsive items in the Environmental Factors construct subdomains varied, representing none (0%) in Attitudes, 11% in Services, Systems and Policies, 21% in Support and Relationships, 30% in Natural Environment and Human-Made Changes to the Environment, and 50% in Products and Technology.

Table 2

Responsive Items / All Items by WHO-ICF Domain and Instrument (#/%)									
Domain/Subdomain	**LSI-A**	**NeuroQoL**	**PedsQL**	**PedsQL NMM**	**POSNA PODCI**	**PSQI**	**SF-36**	**WHO-QoL**	**All Instruments**
ICF Part B: Function									
Subdomain: Mental Function									***6/142 (0.4%)***
Intellectual Function	0/3 (0%)		0/1 (0%)						0/4 (0%)
Temperament and Personality Functions	0/9 (0%)		0/1 (0%)		0/1 (0%)				0/11 (0%)
Energy and Drive Functions	0/4 (0%)	0/17 (0%)	**1/1 (100%)**	0/2 (0%)	0/2 (0%)	0/1 (0%)	0/4 (0%)	0/1 (0%)	**1/32 (3%)**
Sleep Functions		0/1 (0%)	0/1 (0%)	**1/1 (100%)**		**3/10 (30%)**			**4/13 (31%)**
Attention Functions			0/1 (0%)					0/1 (0%)	0/2 (0%)
Memory Functions			0/1 (0%)						0/1 (0%)
Emotional Functions: Anxiety		0/13 (0%)	0/1 (0%)				0/2 (0%)		0/16 (0%)
Emotional Functions: Depression	0/2 (0%)	0/13 (0%)	0/1 (0%)				0/3 (0%)	0/2 (0%)	0/21 (0%)
Emotional Functions: Fear	0/1 (0%)	0/3 (0%)	0/1 (0%)						0/5 (0%)
Emotional Functions: Frustration	0/2 (0%)		0/1 (0%)						0 (0%)
Emotional Functions: Satisfaction	0/14 (0%)	0/1 (0%)			**1/5 (20%)**			0/14 (0%)	**1/34 (3%)**
Subdomain: Sensory Functions and Pain									***4/10 (40%)***
Sensory Functions and Pain			**1/1 (100%)**	**1/2 (50%)**	0/3 (0%)	**2/3 (66%)**		0/1 (0%)	**4/10 (40%)**
Subdomain: Functions of the Cardiovascular, Hematological, Immunological and Respiratory Systems									***4/8 (50%)***
Functions of the Hematological and Immunological Systems				**1/2 (50%)**		0/2 (0%)			**1/8 (25%)**
Functions of the Respiratory System				**1/2 (50%)**					**1/2 (50%)**
Functons Related to the Digestive System				**1/1 (100%)**					**1/1 (100%)**
Functions Related to Metabolism and the Endocrine System				**1/1 (100%)**					**1/1 (100%)**
Subdomain: Neuromusculoskeletal and Movement-Related Functions									***112/148 (75%)***
PUL High Level: Shoulder Dimension		**7/11 (64%)**	**1/1 (100%)**		**6/8 (75%)**				**14/20 (70%)**
PUL Mid-Level: Elbow Dimension		**14/18 (77%)**		0/1 (0%)	**3/3 (100%)**				**17/22 (22%)**
PUL Distal-Level: Wrist and Finger Dimension		**8/11 (73%)**		**2/2 (100%)**	**1/1 (100%)**				**11/14 (79%)**
Complex: Standing from Supine		**2/3 (66%)**							**2/3 (67%)**
Complex: Standing from Seated		**6/7 (86%)**			**1/1 (100%)**				**7/8 (88%)**
Complex: Transfers		**7/10 (70%)**		**1/1 (100%)**	**1/1 (100%)**				**9/12 (75%)**
Head/Neck		**1/1 (100%)**							**1/1 (100%)**
Trunk: Standing		**6/7 (86%)**	**1/1 (100%)**	**1/1 (100%)**	**1/1 (100%)**				**9/10 (90%)**
Trunk: Sitting		**6/8 (75%)**			**4/4 (100%)**				**12/12 (100%)**
LL: Running		0/6 (0%)	**2/2 (100%)**		**4/5 (80%)**				**6/13 (46%)**
LL: Climbing		**2/7 (29%)**			**3/3 (100%)**				**5/10 (50%)**
LL: Walking		**12/15 (80%)**	**2/3 (66%)**		**5/5 (100%)**				**19/23 (83%)**
Subdomain: Functions of the Skin and Related Structures									***0/1 (0%)***
Functions of the Skin and Related Structures				0/1 (0%)					0/1 (0%)
ICF Part D: Activities and Participation									
Subdomain: Learning and Applying Knowledge									***3/12 (25%)***
Learning and Applying Knowledge	0/3 (0%)	0/2 (0%)	**2/5 (40%)**		**1/1 (100%)**			0/1 (0%)	**3/12 (25%)**
Subdomain: General Tasks and Demands									***1/20 (5%)***
Undertaking Multiple Tasks	0/1 (0%)	0/3 (0%)							0/4 (0%)
Carrying Out a Daily Routine	0/3 (0%)	0/1 (0%)		**1/1 (100%)**	0/2 (0%)	0/2 (0%)		0/6 (0%)	**1/15 (7%)**
Handling Stress and Other Psychological Demands		0/1 (0%)							0/1 (0%)
Subdomain: Communication									***6/12 (50%)***
Communication	0/1 (0%)	**5/7 (72%)**		0/3 (0%)	**1/1 (100%)**				**6/12 (50%)**
Subdomain: Mobility									***74/110 (67%)***
Changing and Maintaining Body Position		**19/21 (90%)**		**1/1 (100%)**	**8/8 (100%)**				**28/30 (93%)**
Carrying, Moving and Handling Objects		**13/24 (54%)**	**1/1 (100%)**	**2/2 (100%)**	**4/4 (100%)**				**20/31 (65%)**
Walking and Moving		**13/29 (45%)**	**2/2 (100%)**		**10/12 (83%)**			0/1 (0%)	**25/44 (57%)**
Moving Around Using Transportation		0/3 (0%)			**1/1 (100%)**			0/1 (0%)	**1/5 (20%)**
Subdomain: Self-Care									***32/60 (53%)***
Washing Onesself		**6/8 (75%)**	**1/1 (100%)**	**1/1 (100%)**					**8/10 (80%)**
Caring for Body Parts	0/1 (0%)	**3/4 (75%)**			**1/1 (100%)**			0/1 (0%)	**4/7 (57%)**
Toileting		**4/5 (80%)**		**1/1 (100%)**					**5/6 (83%)**
Dressing		**7/8 (88%)**			**2/2 (100%)**				**9/10 (90%)**
Eating		**1/2 (50%)**		0/1 (0%)	**1/1 (100%)**				**2/4 (50%)**
Drinking		**1/1 (100%)**							**1/1 (100%)**
Looking After One's Health	0/1 (0%)			0/1 (0%)	0/6 (0%)	**3/9 (33%)**		0/5 (0%)	**3/22 (14%)**
Subdomain: Domestic Life									***1/2 (50%)***
Domestic Life		0/1 (0%)	**1/1 (100%)**						**1/2 (50%)**
Subdomain: Interpersonal Interactions and Relationships									***3/28 (11%)***
Informal Social Relationships	0/3 (0%)	**1/6 (17%)**	0/5 (0%)		0/3 (0%)			0/2 (0%)	**1/19 (5%)**
Family Relationships	0/4 (0%)			**2/3 (66%)**					**2/7 (29%)**
Intimate Relationships	0/1 (0%)							0/1 (0%)	0/2 (0%)
Subdomain: Major Life Areas									***0/10 (0%)***
Major Life Areas	0/9 (0%)							0/1 (0%)	0/10 (0%)
Subdomain: Community, Social and Civic Life									***7/26 (27%)***
Community Life	0/2 (0%)	0/2 (0%)		**1/1 (100%)**					**1/5 (20%)**
Recreation and Leisure	0/8 (0%)	0/4 (0%)	**1/1 (100%)**	**1/1 (100%)**	**4/6 (66%)**			0/1 (0%)	**6/21 (29%)**
ICF Part E: Environmental Factors									
Subdomain: Products and Technology									***15/30 (50%)***
Products and Technology	0/1 (0%)	**8/17 (47%)**		**2/3 (66%)**	**5/7 (71%)**	0/1 (0%)		0/1 (0%)	**15/30 (50%)**
Subdomain: Natural Environment and Human-Made Changes to the Environment									***3/10 (30%)***
Natural Environment and Human-Made Changes to Environment		**3/10 (30%)**							**3/10 (30%)**
Subdomain: Support and Relationships									***3/14 (21%)***
Support and Relationships	0/8 (0%)			**3/3 (100%)**				0/3 (0%)	**3/14 (21%)**
Subdomain: Attitudes									***0/2 (0%)***
Attitudes	0/1 (0%)			0/1 (0%)					0/2 (0%)
Subdomain: Services, Systems and Policies									***3/27 (11%)***
Services, Systems and Policies	0/12 (0%)		**2/3 (66%)**	0/3 (0%)	**1/1 (100%)**			0/8 (0%)	**3/27 (11%)**

** Note: A total of n=366 question items were reviewed. Each question was assigned to subdomains in Part B, Part D and Part E as applicable.*

Table 3: Principle component factor list by WHO-ICF domain and subdomain

Factor List by Domain / Subdomain		
ICF Part B: Function		
Subdomain: Mental Function	Sleep Functions	F1 - Nightime Awakening
Subdomain: Sensory Functions and Pain	Sensory Functions and Pain	F1 - Pain
Subdomain: Neuromusculoskeletal and Movement-Related Functions	PUL High Level: Shoulder Dimension	F1 - Unweighted or Range of Motion F2 - Weighted or Strength
	PUL Mid-Level: Elbow Dimension	F1 - Fine Motor and Reaching the Face F2 - Dressing F3 - Bimanual Strength Tasks
	PUL Distal-Level: Wrist and Finger Dimension	F1 - Hand Weakness F2 - Pointing F3 - Writing F4 - Holding Objects F5 - Email/Texting (Key Use)
	Complex: Standing from Seated	F1 - Standing from a Chair F2 - Standing from a Chair without Aid of Arms F3 - Standing from a Bathtub
	Complex: Transfers	F1 - Changing Positions in Bed F2 - Getting off the Toilet F3 - Wheelchair Transfers
	Trunk: Standing	F1 - Low to High Bending Reach F2 - Toilet and Sink Standing F3 - Bathing (Bath or Shower) F4 - Bathing (Shower Only)
	Trunk: Sitting	F1 - Bending at the Waist / Torso Control F2 - Torso Control - Toilet or Wheel Chair F3 - Unsupported Sitting with Time Element F4 - Unsupported Sitting F5 - Bathing Ability (Bathtub)
	LL: Running	F1-F3 - Sports Participation and Running (Not distinct factors)
	LL: Climbing	F1 - Long Duration or High Climbs F2 - Short Duration or Low Climbs
	LL: Walking	F1 - Long Duration Walks F2 - Short Walks and Uneven Surfaces F3 - Long Distance Walks (Ability to Do) F4 - Balance and Falls F5 - Long Distance Walks (Perception of Problem)
ICF Part D: Activities and Participation		
Subdomain: Learning and Applying Knowledge	Learning and Applying Knowledge	F1 - Missing School
Subdomain: Communication	Communication	F1 - Pointing and Manipulating Keyboards F2 - Writing F3 - Texting and Email (Behavioral Component)
Subdomain: Mobility	Changing and Maintaining Body Position	F1 - Transfers and Positional Changes F2 - Standing from Seated or Supine F3 - Sitting
	Carrying, Moving and Handling Objects	F1 - Tasks that Require Strength F2 - Tasks that Require Manual Dexterity F3 - Wheelchair-Related Manual Tasks
Subdomain: Self-Care	Washing Onesself	F1 - Washing, Drying in Bath or Shower F2 - Bathing, Bathtub Only F3 - Transfer to Bathtub
	Caring for Body Parts	F1 - Combing Hair, Brushing Teeth
	Toileting	F1 - Transfering to and From Toilet F2 - Self-Care on Toilet
	Dressing	F1 - Getting Dressed and Undressed F2 - Working Buttons and Zippers
Subdomain: Community, Social and Civic Life	Recreation and Leisure	F1-F3 Participation in Sports and Recreation (Not distinct factors)
ICF Part E: Environmental Factors		
Subdomain: Natural Environment and Human-Made Changes to the Environment	Natural Environment and Human-Made Changes to Environment	F1 - Ambulating Short Distances
Subdomain: Support and Relationships	Support and Relationships	F1 - Family Stress and Coping

Principle Components Analysis: Following construction of the expert review-generated WHO-ICH-based responsive item lists, we examined each set of items using confirmatory principal components factor analysis in order to determine whether there were any potential underlying sub-constructs. A summary of factor analysis results is shown in Table 3. Lists for sleep, pain, school function, caring for body parts, recreation and leisure, and family relationships all demonstrated an appreciable level of unidimensionality. However, most of the lists demonstrated multidimensionality even within groups of items that are frequently grouped together in clinical outcome measure tools. This suggests that even when question items are subdivided into categories according to the WHO-ICF model, there may be multiple underlying "pure" or latent constructs that could further elaborate on those subdivisions.

First Pass Rasch Analysis

We conducted a first-pass Rasch analysis of disease progression-responsive questions in each domain construct question list. Results are summarized in Table 4. Twenty-nine disease progression-responsive question lists were evaluated under the ICF Part B Structure and Function Domain. Twelve of 29 lists contained enough responsive items to conduct an initial Rasch analysis, with 10 of the lists representing various neuromusculoskeletal and movement-related physical functions, 1 representing sensory functions and pain, and 1 representing sleep functions. Only three of those 12 lists demonstrated a somewhat acceptable person separation index of >0.7. and none of the lists covered an acceptable spectrum of disease severity from early ambulatory to late non-ambulatory patients. Twenty-three disease progression-responsive question lists were evaluated under the ICF Part D Activities and Participation Domain. Thirteen of 23 lists contained enough responsive items to conduct an initial Rasch Analysis. Of those 13 lists, 1 represented learning and applying knowledge, 1 represented communication, 3 represented mobility, 6 represented self-care, 1 represented interpersonal interactions and relationships, and 1 represented recreation and leisure activities. Only the mobility domains demonstrated acceptable person-separation indices of 0.7-0.887, and question lists covered the spectrum of disease severity from early ambulatory to late non-ambulatory patients. Five disease progression-responsive question lists were evaluated under the ICF Part E Environmental Factors Domain. Three of 5 lists contained enough responsive items to conduct an initial Rasch analysis. Of

those 3 lists, 1 represented use of products and technology, 1 represented the natural environment and man-made changes to the environment, and 1 represented support and relationships. None of the domains demonstrated acceptable person-separation indices.

Table 4: Psychometric / Rasch analysis summary statistics for responsive item lists by domain/subdomain

Psychometric / Rasch Analysis Summary Statistics for Responsive Item Lists by Domain/Subdomain							
Domain/Subdomain	**CFA # of Factors**	**Cronbach's Alpha**	**Item Fit Residual (mean[SD])**	**Person Fit Residual (mean[SD])**	**PSI (w/Extremes)**	**PSI (w/o Extremes)**	**Person/Item Separation Index**
ICF Part B: Function							
Subdomain: Mental Function							
Intellectual Function	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Temperament and Personality Functions	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Energy and Drive Functions	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Sleep Functions	1	0.531	-4.6(2.7)	-0.32(0.76)	0.197	-0.332	0.278
Attention Functions	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Memory Functions	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Emotional Functions: Anxiety	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Emotional Functions: Depression	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Emotional Functions: Fear	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Emotional Functions: Frustration	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Emotional Functions: Satisfaction	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Subdomain: Sensory Functions and Pain							
Sensory Functions and Pain	1	0.51 - 0.776	-3.6(2.7)	-0.71(0.82)	0.329	0.064	0.074
Subdomain: Functions of the Cardiovascular, Hematological, Immunological and Respiratory Systems							
Functions of the Hematological and Immunological Systems	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Functions of the Respiratory System	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Functons Related to the Digestive System	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Functions Related to Metabolism and the Endocrine System	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Subdomain: Neuromusculoskeletal and Movement-Related Functions							
PUL High Level: Shoulder Dimension	2	0.891	0.51(8.19)	-0.28(1.08)	0.793	0.761	0.767
PUL Mid-Level: Elbow Dimension	3	0.952	0.18(1.59)	-0.33(0.68)	0.713	0.583	0.586
PUL Distal-Level: Wrist and Finger Dimension	5	0.763	0.26(3.70)	-0.94(0.64)	-0.646	-0.472	-0.44
Complex: Standing from Supine	*ND*	0.949	0.73(0.61)	0.21(0.25)	0.760	0.790	0.859
Complex: Standing from Seated	3	0.755	-0.2(2.14)	-0.42(0.51)	-0.111	-3.972	-3.293
Complex: Transfers	3	0.970	0.48(2.8)	-0.71(0.91)	0.035	-2.230	-1.997
Head/Neck	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Trunk: Standing	4	0.935	1.04(1.35)	-0.30(1.28)	0.034	-0.685	-0.587
Trunk: Sitting	5	0.957	-0.97(2.56)	-0.37(0.71)	0.717	0.616	0.619
LL: Running	3	0.596	0.36(5.04)	-0.34(1.34)	0.490	0.578	0.581
LL: Climbing	2	0.953	-0.02(4.31)	-0.39(0.79)	0.772	0.689	0.691
LL: Walking	5	0.966	-0.93(5.46)	-0.30(1.21)	0.756	0.782	0.786
Subdomain: Functions of the Skin and Related Structures							
Functions of the Skin and Related Structures	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
ICF Part D: Activities and Participation							
Subdomain: Learning and Applying Knowledge							
Learning and Applying Knowledge	1	0.691	-0.04(2.39)	-0.44(0.78)	0.561	0.415	0.421
Subdomain: General Tasks and Demands							
Undertaking Multiple Tasks	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Carrying Out a Daily Routine	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Handling Stress and Other Psychological Demands	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Subdomain: Communication							
Communication	3	0.125	0.02(3.58)	-0.40(0.26)	-1.068	-3.034	-2.93
Subdomain: Mobility							
Changing and Maintaining Body Position	3	0.986	-1.00(4.06)	-0.38(1.02)	0.848	0.848	0.850
Carrying, Moving and Handling Objects	3	0.956	0.42(5.22)	-0.29(1.11)	0.735	0.701	0.704
Walking and Moving	*ND (highly collinear)*	0.929	-1.65(6.70)	-0.58(1.28)	-0.312	0.885	0.887
Moving Around Using Transportation	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Subdomain: Self-Care							
Washing Onesself	3	0.553	0.45(2.41)	-1.13(1.31)	-1.192	-2.535	-2.117
Caring for Body Parts	1	0.921	0.13(2.26)	-0.22(0.18)	-0.163	-3.068	-2.960
Toileting	2	0.915	-0.42(1.40)	-1.28(1.06)	0.558	0.234	0.277
Dressing	2	0.961	0.82(1.14)	-0.44(0.93)	0.535	-0.026	-0.009
Eating	*ND*	0.838	0.73(0.28)	-0.13(0.13)	-0.272	-1.99	-1.760
Drinking	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Looking After One's Health	*ND*	0.531	-0.38(2.35)	-0.28(0.73)	0.198	-0.333	-0.289
Subdomain: Domestic Life							
Domestic Life	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Subdomain: Interpersonal Interactions and Relationships							
Informal Social Relationships	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Family Relationships	*ND*	0.723	0.67(0.49)	-0.45(0.93)	0.359	0.305	0.345
Intimate Relationships	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Subdomain: Major Life Areas							
Major Life Areas	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Subdomain: Community, Social and Civic Life							
Community Life	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Recreation and Leisure	3	0.804	0.81(4.60)	-0.30(1.17)	0.501	0.448	0.454
ICF Part E: Environmental Factors							
Subdomain: Products and Technology							
Products and Technology	*ND (highly collinear)*	0.268	-0.06(3.55)	-0.60(1.13)	0.276	0.390	0.445
Subdomain: Natural Environment and Human-Made Changes to the Environment							
Natural Environment and Human-Made Changes to Environment	1	0.866	-0.05(0.64)	-0.22(0.37)	0.697	0.576	0.600
Subdomain: Support and Relationships							
Support and Relationships	1	0.799	0.36(1.31)	-0.45(1.19)	0.554	0.544	0.57
Subdomain: Attitudes							
Attitudes	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Subdomain: Services, Systems and Policies							
Services, Systems and Policies	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*

** Note: A total of n=366 question items were reviewed. Each question was assigned to subdomains in Part B, Part D and Part E as applicable.*

*** ND = Not done due to having too few or no items unless otherwise noted.*

Construct and Item Selection

Based on the first-pass Rasch analysis results, we selected the ICF Part D Activities and Participation Mobility domain question lists for further study and refinement using a second pass Rasch analysis. Selection of these subdomains, representing Walking and Moving, Changing and Maintaining Body Position, and Carrying, Moving and Handling Objects was not entirely unexpected because the initial responsive item evaluation was based on the concept of item change over time and with progressive loss of strength and mobility. In addition, the overall Activities and Participation Mobility construct represents multiple mobility functions across functional groups, where the Structure and Function neuromusculoskeletal and movement-related function-based lists focused tasks on specific affected parts of the body, thus limiting question set applicability to subpopulations for whom that function is still possible. The resulting questions comprise three domain-based item lists (Tables 5 – 7) reflecting a general latent construct of mobility, including functions of

the upper extremities, trunk stability and lower extremities using person-reported question items representing crucial functions across the lifespan from early childhood to adulthood. The item lists included questions from the POSNA PODCI, PedsQL, PedsQL Neuromuscular Module and Neuro-QoL instruments. These items are questions with polytomous 1-4 or 1-5 Likert-type response ratings representing level of difficulty of performing a specific task (eg. climbing stairs).

Principle component analysis of the 3 item lists demonstrated multidimensionality in two. In the Changing and Maintaining Body Position question list, 3 factors suggested underlying functions associated with transfers and positional changes (Factor 1), standing from seated or supine (Factor 2), and unsupported sitting (Factor 3). In the Carrying, Moving and Handling Objects list, 3 factors suggested underlying functions associated with tasks that require strength (Factor 1), tasks that require manual dexterity (Factor 2), and a factor that may suggest manual tasks done in a wheelchair (Factor 3). Taken together the questions represent a range of function from near full function to significant impairment lacking the ability to walk and with minimal use of hands and reduced respiratory capacity.

Table 5: Disease Progression-Responsive Item List for Walking and Moving

Instrument	Item Number / Question
NeuroQOL	1. I could keep my balance while walking for 30 minutes
NeuroQOL	4. I could walk for 15 minutes
NeuroQOL	5. I could walk between rooms
NeuroQOL	12. I could walk for 30 minutes
NeuroQOL	20. I fall down easily
NeuroQOL	21. I could walk on slightly uneven surfaces (such as cracked pavement)
NeuroQOL	22. I lose my balance easily
NeuroQOL	24. I could walk on rough, uneven surfaces (such as lawns, gravel driveway)
NeuroQOL	25. I could walk up and down ramps or hills
NeuroQOL	26. I could walk up and down curbs
NeuroQOL	31. I could walk across the room.
NeuroQOL	39. I could walk up 2-3 stairs
PedsQL	1. Walking more than one block
PedsQL	2. Running
POSNA PODCI	38. Run short distances?
POSNA PODCI	39. Bicycle or tricycle?
POSNA PODCI	40. Climb three flights of stairs?
POSNA PODCI	42. Walk more than a mile?
POSNA PODCI	43. Walk three blocks?
POSNA PODCI	44. Walk one block?
POSNA PODCI	34. How often does your child need help from another person for walking and cliimbing?
POSNA PODCI	52. How often did your child need help from another person for propelling a wheelchair outside on uneven surfaces such as grass, sidewalk or gravel?
POSNA PODCI	54. During the past one month, has it been easy or hard for your child to drive his power wheelchair or scooter by himself?

Table 6: Disease Progression-Responsive Item List for Changing and Maintaining Body Position

Instrument	Item Number / Question
Factor 1: Transfers and Positional Changes	
NeuroQOL	4. I could move between my wheelchair and another seat such as a chair or bed
NeuroQOL	6. I could manage getting on and off the tub bench from a wheelchair
NeuroQOL	7. I could manage getting on and off the toilet from a wheelchair
NeuroQOL	10. I could get in and out of an adultsized chair
PedsQL NMM	16. It is hard to turn myself during the night.
NeuroQOL	16. I could keep my balance while walking for 15 minutes

NeuroQOL	19. I could turn my head all the way to the side to look at someone or something
NeuroQOL	21. I was able to cover my nose when sneezing
NeuroQOL	26. I was able to change positions in my bed.
POSNA PODCI	33. How often did your child use assistive devices (such as braces, crutches or a wheelchair) for walking or climbing?
POSNA PODCI	25. Stand while washing his hands and face at a sink?
POSNA PODCI	26. Sit in a regular chair without holding on?
POSNA PODCI	27. Get on and off a toilet or chair?
NeuroQOL	30. I was able to get out of bed by myself.
POSNA PODCI	28. Get in and out of bed?
NeuroQOL	31. I was able to get into bed by myself.
POSNA PODCI	31. How often did your child need help from another person for sitting and standing?
POSNA PODCI	32. How often did your child use assistive devices (such as braces, crutches or a wheelchair) for sitting and standing?
Factor 2: Standing from Seated or Supine	
NeuroQOL	2. I could get down on my knees without holding on to something.
NeuroQOL	8. I could stand up from an armless straight chair using my wheelchair
NeuroQOL	9. I could get on and off a low chair
NeuroQOL	11. I could get on and off a chair without using my arms.
NeuroQOL	13. I could get up from the floor by myself
NeuroQOL	17. I could stand on my tiptoes to reach for something
POSNA PODCI	30. Bend over from a standing position and pick up something off the floor?
NeuroQOL	33. I could bend over to pick something up.
Factor 3: Unsupported Sitting	
NeuroQOL	14. I could sit on a bench without support for 15 minutes
NeuroQOL	15. I could sit on a bench without back support for 30 minutes

Table 7: Disease Progression-Responsive Item List for Carrying, Moving and Handling Objects

Instrument	**Item Number / Question**
Factor 1: Tasks that require strength	
POSNA PODCI	7. Lift heavy books?
POSNA PODCI	8. Pour a half gallon of milk?
POSNA PODCI	9. Open a jar that's been opened before?
PedsQL	4. Lifting something heavy
NeuroQOL	17. I was able to pick up a gallon of milk with one hand and set it on the table
NeuroQOL	33. I was able to open a jar by myself.
NeuroQOL	36. I was able to pull open heavy doors.
NeuroQOL	37. I was able to open the rings in school binders.
Factor 2: Tasks that require manual dexterity	
NeuroQOL	1. I was able to open small containers like snack bags or vitamins (regular screw top)
NeuroQOL	8. I was able to hold a full cup of water in my hand.
PedsQL NMM	8. My hands are weak.
PedsQL NMM	11. It is hard to use my hands.
NeuroQOL	12. I was able to use a knife to spread butter or jelly on bread
NeuroQOL	15. I was able to hold a plate full of food
NeuroQOL	19. I was able to cut a piece of paper in half with scissors

NeuroQOL	23. I was able to open a can of soda
POSNA PODCI	29. Turn doorknobs?
Factor 3: Manual tasks from a wheelchair.	
NeuroQOL	16. I could open a door that faced away from my wheelchair
NeuroQOL	17. I could open a door that was facing my wheelchair
NeuroQOL	19. I could manage the armrests on my wheelchair
NeuroQOL	20. I could manage the footrests on my wheelchair.

Rasch Analysis of the Activities and Participation Mobility Domain and Subdomains.

Walking and Moving

First Pass Analysis

In the first pass Rasch analysis, a person separation index of 0.88 demonstrated an excellent power of the overall model to individuate between respondents. Summary statistics showed that using all response items to model a "latent" construct of walking and moving ability across ambulatory and non-ambulatory stages of disease moderately over-discriminated, with a fit residual mean(SD) of -1.65(6.7), and a person fit residual mean(SD) of -0.58(1.28). The negative mean fit residual suggested that there was some degree of response dependency between items that required exploration. Review of individual item fit characteristics suggested that of the 23 items included in the model, 14 either contributed appreciably to model misfit (with an item residual >|3.0|), or showed non-random patterns in their variance (chi square p-values <0.01). Seven of the 23 items demonstrated ordered response thresholds.

Item Rescoring: The first pass analysis revealed multiple items with disordered item response thresholds, indicating a lack of uniformity in the way individuals select question response choices, such as choices "with a little trouble" and "with some trouble", or "never" and "almost never", or "almost never" and "sometimes". For items such as these with overlapping response curves, we rescored the items to combine overlapping responses into a single score. Eighteen items were rescored. Following rescoring, items displayed ordered response thresholds, but also demonstrated high residuals indicating poor overall model fit. As a result, nine items were dropped, resulting in a final list of 15 items representing ambulatory functions.

Second-Pass Analysis

Model and Item Fit: Because the remaining questions all addressed ambulatory ability, analysis was restricted to individuals with ambulatory milestone scores only, and included 1,498 scorable responses and 139 extreme scores. In the second pass analysis, the person separation index at 0.88 continued to demonstrate very good power of the overall model to individuate between respondents. Summary statistics showed that using the selected subset of response items to model a construct of ambulatory ability still moderately over-discriminated, with a fit residual mean(SD) of -0.55(2.39), and a person fit residual mean(SD) of -0.36(0.98). The negative fit residual suggests that there is still a degree of response dependency that requires exploration. Fit statistics for the final model are displayed in Table 8. Review of individual item fit (Table 9) suggested that of the 15 items included in the model, 3 continued to contribute somewhat to model misfit (with an item residual >|3.0|).

Table 8. Summary Test of Fit Statistics

Item Fit	**Fit Residual Mean**	**SD**
	-0.55	2.39
Person Fit	-0.36	0.98
Chi Squared Probability	1.0000	
Degrees of freedom	132	
Person Separation Index (PSI)	0.88	

Table 9. Individual Item Fit for the 15 Items by item location (i.e. order of difficulty, most difficult to easiest). Items contributing to model Mis-fit items are shown in BOLD.

Seq	Item	Type	Location	SE	Residual	DF	ChiSq	DF	Prob
5	Q5	Poly	-3.654	0.513	-0.158	38.43	1.758	8	0.987543
13	Q13	Poly	-1.342	0.256	-0.512	38.43	0.790	8	0.999258
18	Q18	Poly	-1.100	0.252	-0.423	38.43	0.429	8	0.999926
17	**Q17**	**Poly**	**-1.065**	**0.047**	**-4.010**	**1236.51**	**7.130**	**9**	**0.623609**
1	Q1	Poly	-0.675	0.296	0.070	37.60	1.377	9	0.997960
20	Q20	Poly	-0.114	0.306	0.465	37.60	1.364	9	0.998034
12	Q12	Poly	0.096	0.045	-2.884	1238.18	5.103	9	0.825255
23	Q23	Poly	0.164	0.303	-1.136	36.76	1.450	9	0.997499
4	Q4	Poly	0.208	0.301	-0.233	37.60	0.945	9	0.999554
19	Q19	Poly	0.507	0.328	0.319	37.60	1.997	9	0.991515
7	**Q7**	**Poly**	**0.755**	**0.052**	**5.978**	**1247.37**	**6.757**	**9**	**0.662455**
16	**Q16**	**Poly**	**0.765**	**0.043**	**-4.618**	**1236.51**	**7.083**	**9**	**0.628463**
6	Q6	Poly	1.522	0.338	-0.791	37.60	1.435	9	0.997598
9	Q9	Poly	1.837	0.046	-0.715	1243.19	2.725	9	0.974214
14	Q14	Poly	2.096	0.045	0.390	1243.19	3.516	9	0.940286

Individual Person Fit: Residuals values for person fit represent the difference between modeled responses and the individual's actual responses. Residual fit values < |3.0| can be considered acceptable. Residuals for individual person fit ranged from -4.18 to 2.56 (mean -0.36, SD 0.98) indicating that overall, individuals in the sample fit the model well, with only 1 response (0.07%) falling outside the acceptable range.

Correlation of Residuals: Items in this domain-based list represented a latent construct of mobility in the context of a progressively debilitating disease measured using different representations (ie. standing, climbing, walking, breathing) of that mobility or lack thereof. Thus, we expected a moderate degree of covariation or dependency between variables, where a response on two items (ex. Ability to walk 1 block vs. Ability to walk 3 blocks) are both dependent on the underlying ability to walk long distances. For purposes of this analysis, we were willing to accept a moderate degree of correlation (ie. <0.4) between items. Items exceeding our acceptable limit of moderate residual correlation are shown in **Table 10**. Of the items with moderately correlated residuals, only Question 13 and Question 18 seemed to represent a similar function of walking on uneven surfaces. The remainder of the correlated items seemed to represent items that are expected go together at different levels of function, most specifically items oriented toward walking distances versus climbing grades. Thus, we elected to include these items in the model with the expectation that it might be possible at some later point to condense these items into one or more questions with responses that capture a continuum of function, thus reducing or eliminating local dependency.

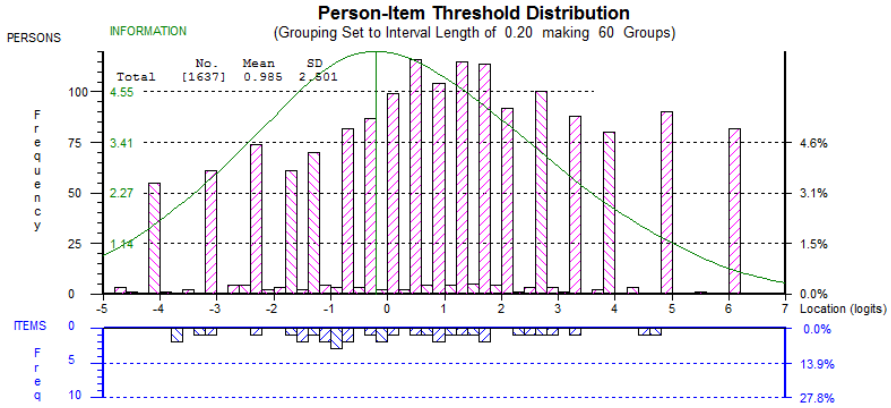
Table 10. Local Dependency for Walking and Moving Scale Items

	Q1	Q4	Q9	Q12	Q13	Q16	Q17	Q18
Q12	-0.474	-0.499						
Q16	-0.417		-0.413	-0.458				
Q17					-0.781			
Q18					0.434	-0.400	-0.647	
Q19				-0.583				
Q20						-0.469	-0.495	
Q23					0.418	-0.524	-0.707	0.481

Person-Item Threshold Location: The person-item threshold distribution shown in **Figure 3** reflects the overall distribution of the population examined (persons in pink), in this case children and adolescents with Duchenne muscular dystrophy, over a continuous logit scale. The individuals' position on the scale represents their overall level of function in a latent construct representation of ambulatory mobility as assessed using the selected set of person-reported response items from our Duchenne natural history study. The blue items then indicate the position of item thresholds, or points of change, between response categories for items included in the mobility domain list, and represent boundaries of the domain list's ability to readily differentiate between individuals at a given level of function. Points to the right indicate better function, points to the left indicate worse function. The distribution indicated that approximately 10% of respondents scored to the right of the measurable scale (ie. ceiling effect), and slightly over 3% scored to the left (ie. floor effect). This suggested that the current list did an acceptable job of assessing differences across a range of ambulatory individuals who were mildly affected to those who were on the verge of losing ambulation, but that it may lack the ability to evaluate individuals who are more severely affected. When evaluated by age group, mean(SD) scores for <4, 4-6, 7-9, 10-12, 13-15, 16-18 year old participants were statistically significantly different (p=0.0000001) at 2.1(1.26), 1.96(2.12), 1.43(2.35), 0.19(2.54), 0.21(2.63) and -0.65(1.75)

respectively, in a pattern that overlapped but that is consistent with our understanding of disease progression with age in DMD. However, when evaluated according to clinically-measured functional milestones, those differences became more pronounced between individuals who were fully functional (Group 0), those who had lost the ability to stand from supine (Group 1), those who had in addition lost the ability to climb stairs (Group 2), and those who had subsequently lost the ability to rise from a chair but who remained ambulatory (Group 3). Group mean(SD) scores for those grades were statistically significantly different (p=0.0000001) at 1.65(2.27), -0.36(2.04), -1.84(1.67) and -2.35(1.56), respectively.

Figure 3. Person-Item Threshold Distribution for the Walking and Moving Question Set

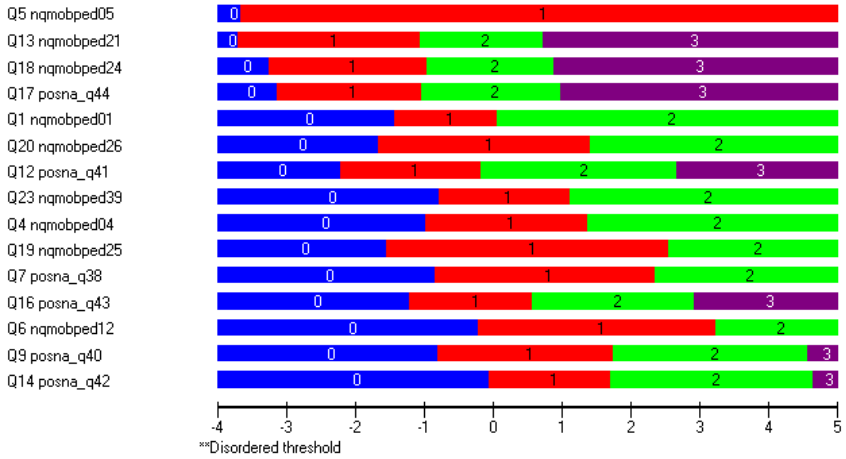


Threshold Ordering, Item Locations and Clinical "Face" Validity: Placing the questions in location order from easiest to most difficult yielded the draft question set noted in **Table 11**. The item location threshold map is presented as **Figure 4**. Overall, these items represented a range of ambulatory mobility tasks that are progressively lost, starting with long distance and long duration walks and climbs, and running, followed by moderate distance and duration walks and climbs, followed by short walks, walks on uneven surfaces, and walking household distances. This is consistent with the clinical presentation and natural history of the disease and spans nearly the entire range of ambulatory function, suggesting that our construct has face validity as a representation of mobility.

Table 11: Final Draft Walking and Moving Question Set

Q5	nqmobped05	I could walk between rooms
Q13	nqmobped21	I could walk on slightly uneven surfaces (such as cracked pavement)
Q18	nqmobped24	I could walk on rough, uneven surfaces (such as lawns, gravel driveway)
Q17	posna_q44	Walk one block?
Q1	nqmobped01	I could keep my balance while walking for 30 minutes
Q20	nqmobped26	I could walk up and down curbs
Q12	posna_q41	Climb one flight of stairs?
Q23	nqmobped39	I could walk up 2-3 stairs
Q4	nqmobped04	I could walk for 15 minutes
Q19	nqmobped25	I could walk up and down ramps or hills
Q7	posna_q38	Run short distances?
Q16	posna_q43	Walk three blocks?
Q6	nqmobped12	I could walk for 30 minutes
Q9	posna_q40	Climb three flights of stairs?
Q14	posna_q42	Walk more than a mile?

Figure 4: Draft Walking and Moving Question Set Item Location Threshold Map.



Changing and Maintaining Body Position

First Pass Analysis

In the first pass analysis, a person separation index of 0.84 demonstrated an excellent power of the overall model to individuate between respondents. Summary statistics showed that using all response items to model a "latent" construct of trunk stability across ambulatory and non-ambulatory stages of disease moderately over-discriminated, with a fit residual mean(SD) of -1.00(4.06) and a person fit residual mean(SD) of -0.38(1.02). The negative mean fit residual suggested that there was some degree of response dependency between items that required exploration. Review of individual item fit characteristics suggested that of the 28 items included in the model, 9 either contributed appreciably to model fit or showed non-random patterns in their variance. Twelve of the 28 items demonstrated ordered response thresholds.

Item Rescoring: The first pass analysis revealed multiple items with disordered item response thresholds, indicating a lack of uniformity in the way individuals select question response choices, such as choices "with a little trouble" and "with some trouble", or "never" and "almost never", or "almost never" and "sometimes". For items such as these with overlapping response curves, we rescored the items to combine overlapping responses into a single score. Sixteen items were rescored. Following rescoring, items displayed ordered response thresholds. All items were retained in the model, resulting in a final list of 28 items representing functions related to changing and maintaining body position.

Second Pass Analysis

Model and Item Fit: The questions presented in the list represent a range of functions that do not directly require the ability to ambulate, and thus the analysis included responses from all participants. Available data included 2,324 scorable responses and 927 extreme scores. In the second pass analysis, the person separation index at 0.86 continued to demonstrate very good power of the overall model to individuate between respondents. Summary statistics showed that using the selected subset of response items to model a construct representing mobility during positional transfers still moderately over-discriminated, with a fit residual mean(SD) of -1.02(4.05), and a person fit residual mean(SD) of -0.45(1.29). The negative fit residual suggested that there was still a degree of response dependency that required exploration. Fit statistics for the final model are displayed in Table 12. Review of individual item fit (Table 13) suggested that of the 28 items included in the model, 6 continued to contribute somewhat to model misfit (with an item residual >|3.0|).

Table 12. Summary Test of Fit Statistics

Item Fit	**Fit Residual Mean**	**SD**
	-1.42	4.05
Person Fit	-0.45	1.29
Chi Squared Probability	0.999992	
Degrees of freedom	251	
Person Separation Index (PSI)	0.86	

Table 13. Individual Item Fit for the 28 items. Items contributing to model mis-fit items are shown in BOLD.

Seq	Item	Type	Location	SE	FitResid	DF	ChiSq	DF	Prob
1	Q1	Poly	2.512	0.234	-1.069	82.03	0.644	9	0.999911
2	Q2	Poly	-0.601	0.175	2.309	72.32	3.437	9	0.944436
3	Q3	Poly	0.054	0.187	1.349	67.03	1.551	8	0.991836
4	Q4	Poly	-0.333	0.236	-1.836	68.80	1.473	9	0.997344
5	Q5	Poly	-0.113	0.231	0.672	68.80	0.950	9	0.999544
6	Q6	Poly	1.332	0.247	-1.411	82.91	0.803	9	0.999773
7	Q7	Poly	0.180	0.228	-1.174	82.03	1.379	9	0.997949
8	Q8	Poly	2.517	0.280	-0.980	82.91	0.781	9	0.999798
9	Q9	Poly	2.228	0.279	-0.518	82.03	1.117	9	0.999117
10	Q10	Poly	-0.903	0.171	1.668	85.55	2.434	9	0.982607
11	Q11	Poly	0.304	0.172	2.158	85.55	10.129	9	0.340126
12	Q12	Poly	-1.354	0.142	-1.130	239.02	1.090	9	0.999201
13	Q13	Poly	0.653	0.227	-1.795	82.03	0.940	9	0.999563
14	Q14	Poly	1.436	0.199	-1.238	82.03	1.096	9	0.999182
15	Q15	Poly	-3.518	0.169	0.022	88.20	1.543	9	0.996812
16	Q16	Poly	-3.047	0.207	-0.207	94.37	0.359	9	0.999993
17	Q17	Poly	-1.044	0.169	1.134	88.20	1.495	9	0.997186
18	**Q18**	**Poly**	**-0.194**	**0.040**	**8.776**	**1991.56**	**13.183**	**9**	**0.154485**
19	**Q19**	**Poly**	**-0.379**	**0.040**	**-8.788**	**2003.03**	**17.583**	**9**	**0.040329**
20	**Q20**	**Poly**	**-1.840**	**0.043**	**4.278**	**2028.60**	**37.566**	**9**	**0.000021**
21	**Q21**	**Poly**	**0.266**	**0.041**	**-10.759**	**2021.55**	**21.876**	**9**	**0.009280**
22	Q22	Poly	-0.304	0.171	-2.460	87.32	0.858	9	0.999702
23	**Q23**	**Poly**	**-0.175**	**0.041**	**-10.698**	**2022.43**	**22.708**	**9**	**0.006887**
24	Q24	Poly	-0.290	0.170	-2.313	85.55	0.906	9	0.999626
25	**Q25**	**Poly**	**1.380**	**0.035**	**-5.266**	**2011.85**	**6.512**	**9**	**0.687816**
26	Q26	Poly	1.522	0.206	-0.002	82.03	1.131	9	0.999071
27	Q27	Poly	0.168	0.041	0.297	2000.38	7.519	9	0.583239
28	Q28	Poly	-0.458	0.040	0.301	2003.91	4.464	9	0.878324

Individual Person Fit: Residuals values for person fit represent the difference between modelled responses and the individual's actual responses. Residual fit values < |3.0| can be considered acceptable. Residuals for individual person fit ranged from -22.6 to 3.08 (mean -0.45, SD 1.29) indicating that overall, individuals in the sample fit the model moderately well, with 43 responses (1.8%) falling outside the acceptable range.

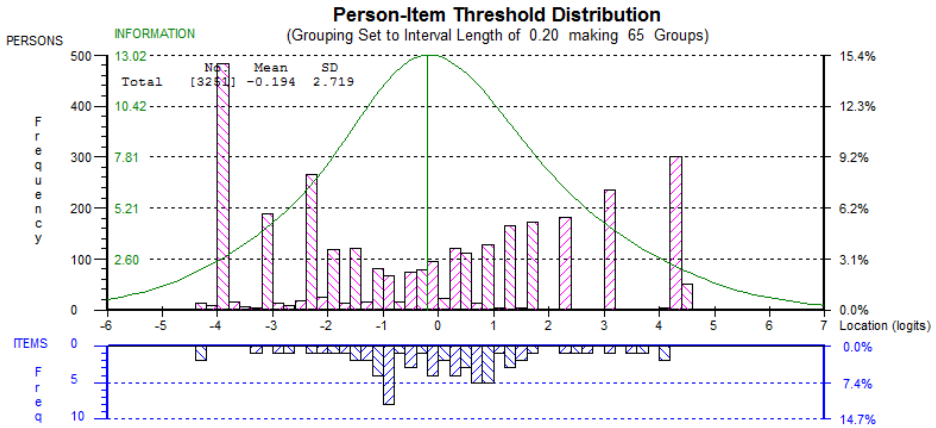
Correlation of Residuals: As noted previously, for purposes of this analysis we were willing to accept a moderate degree of correlation (ie. <0.4) between items. Items exceeding our acceptable limit of moderate residual correlation are shown in **Table 14**. Q1 is getting down on knees without holding on to something. This correlated moderately with getting out of chairs, getting up from the floor, and use of assistive devices. Q4 is getting on/off a toilet from a wheelchair, which correlated with Q11 sitting on a bench without back support for >30 minutes. Q10 is sitting on a bench for >15 minutes, which correlated with sitting on a bench for >30 minutes, and getting out of bed. Q19 is standing at a sink, which correlates with getting into bed. Q22 is getting out if bed, which correlates with Q24 getting into bed, and Q23 getting into and out of bed. In similar fashion, Q23 and Q24 were correlated. Q24 getting into bed also correlated moderately with bending over to pick something up. It was clear that many of these items constitute questions regarding similar functions. However, the similar function items are often from different instruments (ie. PODCI versus NeuroQoL) which were not uniformly administered across the participant age groups, because NeuroQoL items were added to a more recent version of the protocol. Thus, dropping one item in favor of the other resulted in significant reduction in the overall sample available for analysis. Thus, we elected to include these items in the model with the expectation that it might be necessary during further instrument validation to condense the items into one or more questions that could be uniformly administered to future study populations.

Table 14. Local Dependency for Changing and Maintaining Body Position Scale Items

	Q1	Q4	Q10	Q19	Q22	Q23	Q24
Q6	0.560						
Q8	0.412						
Q9	0.443						
Q11		0.416	0.492				
Q18	-0.471						
Q22			-0.431				
Q23					0.460		
Q24				0.519	0.780	0.451	
Q26							-0.42
Q28	-0.457						

Person-Item Threshold Location: The person-item threshold distribution shown in **Figure 5** reflects the overall distribution of the population examined (persons in pink), in this case individuals with Duchenne muscular dystrophy, over a continuous logit scale. The distribution indicates that approximately 12% of respondents score to the right of the measurable scale (ie. ceiling effect), and slightly over 18% score to the left (ie. floor effect). This suggested that the list did an acceptable job of assessing differences across a range of ambulatory and non-ambulatory individuals from those who were ambulatory and moderately affected to those who had lost ambulation but still retained some ability to sit unsupported. When evaluated by age group, mean(SD) scores for <4, 4-6, 7-9, 10-12, 13-15, and 16-18 year old participants were statistically significantly different (p=0.0000001) at 3.6(1.32), 2.76(1.43), 1.98(1.91), -0.54(2.47), -1.56(2.27) and -2.17(1.83) respectively, in a pattern that overlapped but that was consistent with our understanding of disease progression with age in DMD. When evaluated according to clinically-measured functional milestones across the entire disease severity spectrum, those differences remained pronounced between individuals who were fully functional (Group 0), those who had lost the ability to stand from supine (Group 1), those who had in addition lost the ability to climb stairs (Group 2), those who had subsequently lost the ability to rise from a chair but who remained ambulatory (Group 3), those who had lost the ability to walk but who could bring their hand to their mouth (Group 4), those who had lost the ability to bring their hand to their mouth (Group 5), and those who could not bring their hand to their mouth and who had a forced vital capacity <30% predicted (Group 6). Group mean(SD) scores for those groups were statistically significantly different (p=0.0000001) at 2.52(1.49), 1.01(1.21), 0.25(0.84), -0.49(0.85), -2.28(1.30), -2.92(1.17) and -3.01(1.16), respectively.

Figure 5. Person-Item Threshold Distribution for the Changing and Maintaining Body Position Question Set



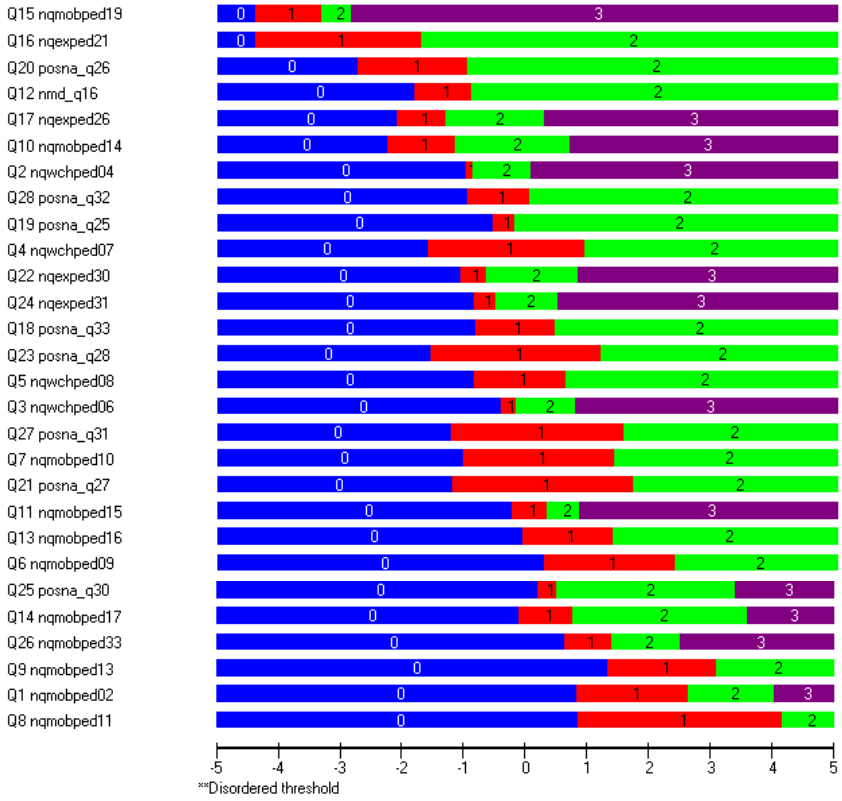
Threshold Ordering, Item Locations and Clinical "Face" Validity: Placing the questions in location order from easiest to most difficult yielded the draft question set noted in **Table 15**. The item location threshold map is presented as **Figure 6**. Overall, these items represent a range of positional change and transfer abilities that are progressively lost, starting with standing from a chair without use of the arms, followed by bending to pick items off of the floor, followed by self-transfer to a chair, toilet or bed using the arms, followed by changing positions in bed, followed by ability to turn the head. This is consistent with the clinical presentation and natural history of the disease and spans a large range of function, suggesting that our construct has face validity as a representation of transfer and positional change

mobility. Referring to the apparent latent factors identified in the principle component analysis, items aligning with the second factor (standing from seated or supine) predominated in the stronger end of the spectrum, while items aligning with the first factor (transfers and positional changes) predominated in the weaker 2/3 of the scale. Tasks associated with the third factor (unsupported sitting) ended up in the middle and probably represent a short period of time where individuals are wheelchair users but still have some ability to maintain seated balance and trunk posture. As discussed previously, several of these questions from different instruments used in different sub-populations duplicated similar activities and align in similar fashion with respect to order of difficulty and could potentially be condensed into single items.

Table 15: Final Draft Changing and Maintaining Body Position Question Set

Q15	nqmobped19	I could turn my head all the way to the side to look at someone or something
Q16	nqexped21	I was able to cover my nose when sneezing
Q20	posna_q26	Sit in a regular chair without holding on?
Q12	nmd_q16	It is hard to turn myself during the night.
Q17	nqexped26	I was able to change positions in my bed
Q10	nqmobped14	I could sit on a bench without support for 15 minutes
Q2	nqwchped04	I could move between my wheelchair and another seat such as a chair or bed
Q28	posna_q32	How often did your child use assistive devices (such as braces, crutches or a wheelchair) for sitting and standing?
Q19	posna_q25	Stand while washing his hands and face at a sink?
Q4	nqwchped07	I could manage getting on and off the toilet from a wheelchair
Q22	nqexped30	I was able to get out of bed by myself.
Q24	nqexped31	I was able to get into bed by myself.
Q18	posna_q33	How often did your child use assistive devices (such as braces, crutches or a wheelchair) for walking or climbing?
Q23	posna_q28	Get in and out of bed?
Q5	nqwchped08	I could stand up from an armless straight chair using my wheelchair
Q3	nqwchped06	I could manage getting on and off the tub bench from a wheelchair
Q27	posna_q31	How often did your child need help from another person for sitting and standing?
Q7	nqmobped10	I could get in and out of an adultsized chair
Q21	posna_q27	Get on and off a toilet or chair?
Q11	nqmobped15	I could sit on a bench without back support for 30 minutes
Q13	nqmobped16	I could keep my balance while walking for 15 minutes
Q6	nqmobped09	I could get on and off a low chair
Q25	posna_q30	Bend over from a standing position and pick up something off the floor?
Q14	nqmobped17	I could stand on my tiptoes to reach for something
Q26	nqmobped33	I could bend over to pick something up.
Q9	nqmobped13	I could get up from the floor by myself
Q1	nqmobped02	I could get down on my knees without holding on to something.
Q8	nqmobped11	I could get on and off a chair without using my arms.

Figure 6: Draft Changing and Maintaining Body Position Question Set Item Location Threshold Map.



Carrying, Moving and Handling Objects

First Pass Analysis

In the first pass analysis, a person separation index of 0.73 demonstrated acceptable power of the overall model to individuate between respondents. Summary statistics showed that using all response items to model a "latent" construct of upper extremity ability across ambulatory and non-ambulatory stages of disease discriminated moderately well, with a fit residual mean(SD) of 0.42(5.21) and a person fit residual mean(SD) of -0.29(1.10). Review of individual item fit characteristics suggested that of the 21 items included in the model, 5 either contributed appreciably to model fit or showed non-random patterns in their variance. Nine of the 21 items demonstrated ordered response thresholds.

Item Rescoring: The first pass analysis revealed multiple items with disordered item response thresholds, indicating a lack of uniformity in the way individuals select question response choices, such as choices "with a little trouble" and "with some trouble", or "never" and "almost never", or "almost never" and "sometimes". For items such as these with overlapping response curves, we rescored the items to combine overlapping responses into a single score. Twelve items were rescored. Following rescoring, items displayed ordered response thresholds. All items were retained in the model, resulting in a final list of 21 items representing functions related to carrying, moving and handling objects.

Second Pass Analysis

Model and Item Fit: The questions presented in the list represent a range of functions that do not directly require the ability to ambulate, and thus the analysis included responses from all participants. Available data included 2,908 scorable responses and 672 extreme scores. In the second pass analysis, the person separation index at 0.75 continued to demonstrate acceptable power of the overall model to individuate between respondents. Summary statistics showed that using the selected subset of response items to model a construct of representing manual mobility still discriminated moderately well, with a fit residual mean(SD) of 0.14(4.96), and a person fit residual mean(SD) of -0.32(1.06). Fit statistics for the final model are displayed in Table 16. Review of individual item fit (Table 17) suggested that of the 21 items included in the model, 3 continued to contribute somewhat to model misfit (with an item residual >|3.0|).

Table 16. Summary Test of Fit Statistics

Item Fit	**Fit Residual Mean**	**SD**
	0.14	4.96
Person Fit	-0.32	1.06
Chi Squared Probability	1.00	
Degrees of freedom	189	
Person Separation Index (PSI)	0.75	

Table 17. Individual Item Fit for the 21 items. Items contributing to model mis-fit are shown in BOLD.

Seq	Item	Type	Location	SE	FitResid	DF	ChiSq	DF	Prob
1	**Q1**	**Poly**	**0.875**	**0.027**	**-7.290**	**2364.62**	**11.953**	**9**	**0.215950**
2	Q2	Poly	-0.578	0.130	0.797	86.55	0.847	9	0.999716
3	**Q3**	**Poly**	**0.717**	**0.025**	**-9.572**	**2360.54**	**15.537**	**9**	**0.077204**
4	Q4	Poly	-0.130	0.026	-0.188	2356.46	4.659	9	0.862926
5	**Q5**	**Poly**	**0.774**	**0.033**	**18.034**	**2163.76**	**47.962**	**9**	**0.000000**
6	Q6	Poly	-1.225	0.178	0.414	84.92	2.055	9	0.990567
7	Q7	Poly	-0.368	0.101	1.197	255.57	0.614	9	0.999927
8	Q8	Poly	-1.341	0.114	0.397	253.12	0.705	9	0.999868
9	Q9	Poly	-0.893	0.181	-0.244	86.55	0.894	9	0.999645
10	Q10	Poly	0.215	0.136	0.443	82.47	1.073	9	0.999250
11	Q11	Poly	0.084	0.187	1.258	68.59	1.777	9	0.994518
12	Q12	Poly	0.093	0.145	0.378	69.40	0.469	9	0.999977
13	Q13	Poly	1.975	0.220	-1.292	80.02	0.911	9	0.999617
14	Q14	Poly	-0.784	0.169	-0.211	71.04	0.822	9	0.999749
15	Q15	Poly	-1.093	0.135	2.561	86.55	1.661	9	0.995764
16	Q16	Poly	-0.231	0.185	1.798	69.40	0.668	9	0.999895
17	Q17	Poly	0.030	0.178	-0.187	82.47	0.925	9	0.999592
18	Q18	Poly	-0.887	0.035	-1.436	2298.48	10.752	9	0.293093
19	Q19	Poly	0.868	0.150	-0.974	81.65	0.573	9	0.999945
20	Q20	Poly	1.791	0.213	-1.309	80.83	1.009	9	0.999416

Individual Person Fit: Residuals values for person fit represent the difference between modelled responses and the individual's actual responses. Residual fit values < |3.0| can be considered acceptable. Residuals for individual person fit ranged from -10.6 to 2.86 (mean -0.32, SD 1.06) indicating that overall, individuals in the sample fit the model moderately well, with only 8 responses (0.27%) falling outside the acceptable range.

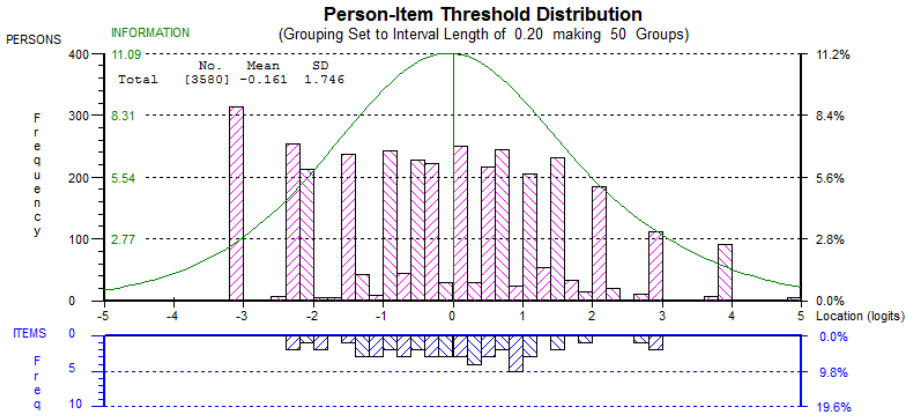
Correlation of Residuals: As noted previously, for purposes of this analysis we were willing to accept a moderate degree of correlation (ie. <0.4) between items. Items exceeding our acceptable limit of moderate residual correlation are shown in **Table 18**. Q3 is opening a gallon of milk, which correlates with opening heavy doors. Q5 is lifting something heavy, which correlates with Q14 using scissors, Q17 opening a can of soda and Q21 opening rings on school binders. Q14 using scissors also correlates with Q16, managing footrests on a wheelchair. Taken together, the items represent different activities, although the use of scissors, opening a soda can and opening school binders are activities that require maintenance of manual dexterity but also a moderate degree of finger strength. Because the correlation between these activities and lifting heavy objects is negative, it is likely that these items represent a continuum of strength-related activities. However, as they represent different levels of strength, we have elected to include them all in the model. It may be necessary at some point to condense these items into a smaller number of questions or a single question representing strength.

Table 18. Local Dependency for the Carrying, Moving and Handling Objects Scale Items

	Q3	Q5	Q14
Q14		-0.428	
Q16			0.406
Q17		-0.405	
Q20	0.432		
Q21		0.518	

Person-Item Threshold Location: The person-item threshold distribution shown in **Figure 7** reflects the overall distribution of the population examined (persons in pink), in this case individuals with Duchenne muscular dystrophy, over a continuous logit scale. The distribution indicated that approximately 5% of respondents scored to the right of the measurable scale (ie. ceiling effect), and slightly over 13% scored to the left (ie. floor effect). This suggests that the list did an acceptable job of assessing differences across a range of ambulatory and non-ambulatory individuals from those who were ambulatory and mildly to moderately affected to those who had lost ambulation but still retained some moderate degree of hand function to perform small manual tasks that do not require strength. When evaluated by age group, mean(SD) scores for <4, 4-6, 7-9, 10-12, 13-15, 16-18 and >18 year old participants were statistically significantly different (p=0.0000001) at 0.39(0.72), 1.03(1.46), 0.90(1.38), -0.07(1.63), -0.49(1.69), -0.94(1.66) and -1.45(1.27), respectively, in a pattern that overlapped but that is consistent with our understanding of disease progression with age in DMD. It is important to point out the slightly lower score for children under 4 years of age relative to children from 4-9 years old, and for whom it would be developmentally normal to require assistance in many of the represented tasks. When evaluated according to clinically-measured functional milestones across the entire disease severity spectrum, those differences remained pronounced between individuals who were fully functional (Group 0), those who had lost the ability to stand from supine (Group 1), those who had in addition lost the ability to climb stairs (Group 2), those who had subsequently lost the ability to rise from a chair but who remain ambulatory (Group 3), those who had lost the ability to walk but who could bring their hand to their mouth (Group 4), those who had lost the ability to bring their hand to their mouth (Group 5), and those who could not bring their hand to their mouth and who had a forced vital capacity <30% predicted (Group 6). Group mean(SD) scores for those groups were statistically significantly different (p=0.0000001) at 1.15(1.35), 0.84(1.27), 0.24(1.09), 0.02(1.20), -0.63(1.34), -1.69(1.19) and -2.10(0.76), respectively. It should be noted that while this domain did not perform well in young children whose developmental abilities are still growing, it is the only one to demonstrate an appreciable point difference between late stage individuals who were only subdivided according to respiratory function differences.

Figure 7. Person-Item Threshold Distribution for the Carrying, Moving and Handling Objects Question Set



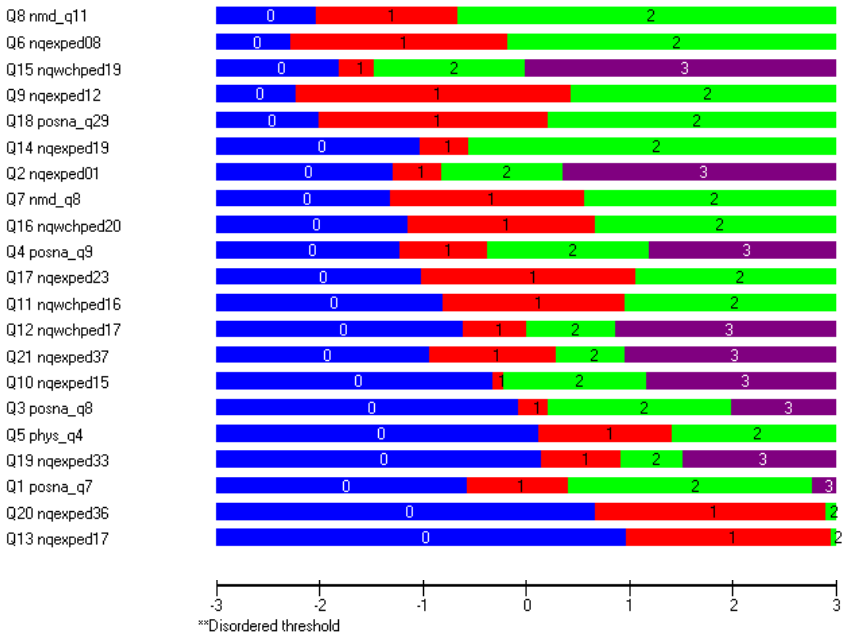
Threshold Ordering, Item Locations and Clinical "Face" Validity: Placing the questions in location order from easiest to most difficult yielded the draft question set noted in Table 19. The item location threshold map is presented as Figure 8. Overall, these items represent a range of manual abilities that are progressively lost, starting with lifting and moving heavy objects such as heavy books, a half-gallon of milk and heavy doors, followed by manual tasks such as opening school binders or soda cans or opening doors from a wheelchair, followed by opening small containers or using scissors, followed by using utensils or holding a cup. This is consistent with the clinical presentation and natural history of the disease and spans a large range of function, suggesting that our construct has face validity as a representation of manual abilities. Referring again to the apparent latent factors identified in the principle component analysis, items aligning with the first factor (tasks that require strength) predominated in the stronger end of the spectrum, while items from the second factor (tasks that require manual dexterity) predominated in the weaker end of the spectrum. Tasks associated with the third factor (tasks from a wheelchair) ended up in the middle and probably represent a short period of time where individuals are wheelchair users but still have some functional degree of shoulder and elbow use. Given that the question set still demonstrated a floor effect for a portion of the population, there was a clear need for adoption of additional questions to address fine motor and hand functions such as writing ability or keyboard use.

Table 19: Final Draft Carrying, Moving and Handling Objects Question Set

Q8 nmd_q11	It is hard to use my hands.
Q6 nquexped08	I was able to hold a full cup of water in my hand.
Q15 nqwchped19	I could manage the armrests on my wheelchair
Q9 nquexped12	I was able to use a knife to spread butter or jelly on bread

Q18 posna_q29	Turn doorknobs?
Q14 nquexped19	I was able to cut a piece of paper in half with scissors
Q2 nquexped01	I was able to open small containers like snack bags or vitamins (regular screw top)
Q7 nmd_q8	My hands are weak.
Q16 nqwchped20	I could manage the footrests on my wheelchair.
Q4 posna_q9	Open a jar that's been opened before?
Q17 nquexped23	I was able to open a can of soda
Q11 nqwchped16	I could open a door that faced away from my wheelchair
Q12 nqwchped17	I could open a door that was facing my wheelchair
Q21 nquexped37	I was able to open the rings in school binders.
Q10 nquexped15	I was able to hold a plate full of food
Q3 posna_q8	Pour a half gallon of milk?
Q5 phys_q4	Lifting something heavy
Q19 nquexped33	I was able to open a jar by myself.
Q1 posna_q7	Lift heavy books?
Q20 nquexped36	I was able to pull open heavy doors.
Q13 nquexped17	I was able to pick up a gallon of milk with one hand and set it on the table

Figure 8: Draft Carrying, Moving and Handling Objects Question Set Item Location Threshold Map.



Discussion

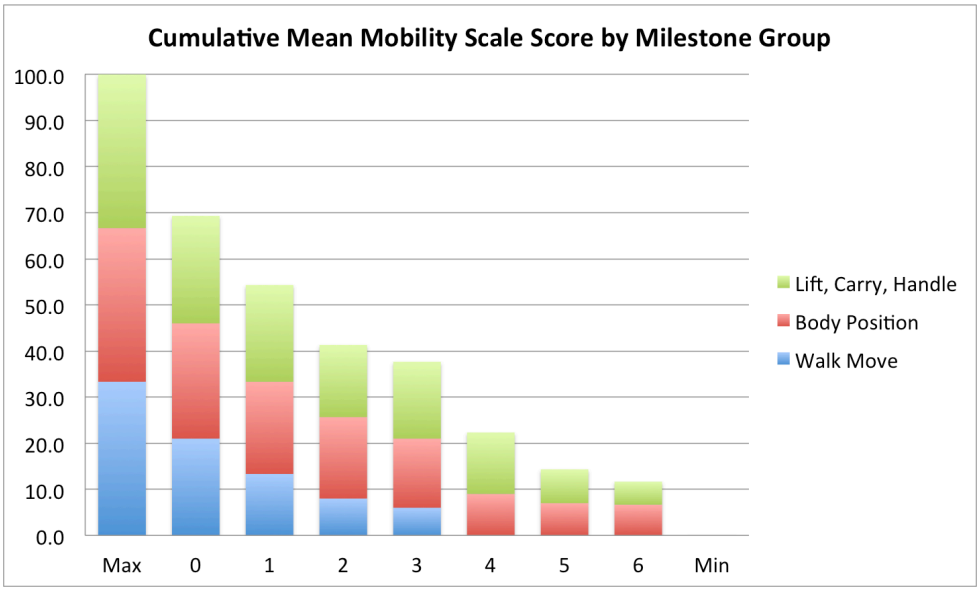
The initial results of our evaluation of sensitivity to disease milestones and one-year change yielded a list of items that spans multiple domains within the WHO-ICF framework. Few items existed, however, that represented functions that are unrelated to neuromusculoskeletal function and movement. Certainly, the devices we selected in the Duchenne Natural History Study (DNHS) have previously demonstrated deficits among DMD patients relative to typically developing controls and other groups in non-mobility-related domains such as life satisfaction, but our results suggest that, at least between contiguous milestone classification groups or over relatively short one-year periods of time, many of those deficits remain somewhat fixed. That those more psychosocial-oriented items failed to show differences or changes is not entirely unexpected, and there are likely to be classification schemes other than disease milestones where those items might demonstrate change over time.

Subsequently, we focused here on a set of items that demonstrated sensitivity to disease and one-year change that corresponded to the mobility subdomain domain of the WHO-ICH Activities and Participation domain and described arm, leg and trunk functions that are progressively lost during the course of Duchenne muscular dystrophy. We demonstrated that despite the continuing existence of ceiling and floor effects in each of the three person-reported mobility-oriented domain scores discussed above, they describe a continuum of individuals with Duchenne muscular dystrophy across most of the currently observed range of ages and stages of disease whom we have profiled in the DNHS #19,21. Furthermore, taken together, the scales provide a patient (or patient proxy)-assessed range of functional ability of the arms, legs and trunk that ranges from newly diagnosed and nearly typical-appearing young children to severely impaired young adults at the end of their expected life span. Through the Rasch analysis approach and comparison with previously described

functional milestones that are progressively and predictably lost as the disease progresses, we have demonstrated the initial psychometric characteristics and clinical validity of each scale, and provided initial estimates of mean linearized mobility domain scores for each functional milestone group.

While each of the mobility domain scores may be useful in its own right, the power of this approach is in the development of a combined and linear mobility score that can be used across the entire range of functional abilities associated with the disease. Figure 9 below demonstrates one potential method of achieving this such a combined score. By converting each of the three mobility domain logit location ranges to a simple 0-100 point scale (with 100 representing best function and 0 representing worst), we are able to then combine all three scores to create an average mobility score for each milestone group. As depicted below then, individuals at near full function in Milestone Group 0 have average score of 70 points, with each mobility domain contributing approximately 1/3 of the total score. As milestones are progressively lost, we see that on average the functions described in the Walking and Moving domain are lost first, followed by a gradual and somewhat proportional loss of the Maintaining Body Position and Carrying, Moving and Handling Objects domain functions.

Figure 9



Revisions to Question Syntax and the Response Structure

While the combined scale initially appeared to possess the desirable qualities of being a continuous assessment scale that can be used across the entire span of ages and stages of the disease, the three domains still had mis-fitting items and ceiling and floor effects that could be optimized through revisions to the question set. First, it appeared that overall, the items derived from the PODCI device continued to yield high fit residuals, suggesting that there may be a moderate degree of subjectivity in the way that patients select their responses. In comparison, items from the NeuroQOL devices more frequently demonstrated acceptable fit residuals, suggesting that they are answered in a much more predictable pattern as the disease progresses. We previously noted that the lack of responsiveness of the PedsQL relative to 6-minute walk velocity may be due in part to the wording of the questions such that they ask "In the past 7 days, *how much of a problem* has it been for you to..." (responses Never, Almost Never, Sometimes, Often, Almost Always), while the more responsive PODCI instrument asks questions in the manner of "During the last week, has it been easy or hard for you to…" (responses Easy, A Little Hard, Very Hard, Can't Do)[24]. While this is a subtle difference, the former adds a *subjective* aspect of whether an activity is *desirable* in addition to its level of difficulty, while the PODCI items simply ask about overall difficulty. Here with respect to the PODCI versus the NeuroQOL, we may have observed a similar effect. Items from the NeuroQOL scales underwent extensive testing, response revision and cognitive debriefing prior to publication using the syntax "In the past 7 days, I could _____ (responses: With no trouble, With a little trouble, With some trouble, With a lot of trouble"). It was apparent from our rescoring efforts to correct disordered response thresholds on many of our items that there was still some inconsistency in differentiating between "With a little trouble" and "With some trouble", and this question style lacked a "can't do at all" response, but we felt it may be appropriate to revise the questions to reflect a combination of PODCI and NeuroQOL styles, with a syntax that read: "In the past 7 days, I could _____ (responses: With no trouble, With some trouble, With a lot of trouble, Can't do)."

In addition to revision of individual question presentation, our mixed use of instruments across different ages resulted in the retention of multiple items that were from different instruments but that related to the same overall concept. For instance, use of the PODCI and

NeuroQOL in different groups gave us one question about getting in and out of bed, one question about getting into bed, and one question about getting out of bed. These items, naturally, were highly co-dependent, and ideally only one would be left in the final model.

Comparable instruments from clinical practice: The North Star Ambulatory Assessment, Egen Klassifikation Scale, and Performance of the Upper Limb (PUL) Assessment.

Another issue with the initial domain item lists was the continued existence of ceiling and floor effects in all three mobility domains. In the Walking and Moving item list, questions represented a wide range from difficult (walking more than a mile) to easy (walking between rooms). In the Changing and Maintaining Body Position list, tasks ranged from difficult (getting out of a chair without using one's arms) to easy (moving one's head to look to the side). In the Carrying, Moving and Handling Objects list, tasks ranged from difficult (picking up a gallon of milk) to easy (holding a cup of water). However, we could identify candidate tasks on the more difficult and easier ends of these scales by referring to some of the analogous validated functional clinical examinations that are currently in use. The North Star Ambulatory Assessment (NSAA) contents are similar to those from the Walking and Moving item list; the Egen Klassifikation (EK) Scale is similar in content to the Changing and Maintaining Body Position list; and the Performance of the Upper Limb (PUL) Assessment is similar to the Carrying, Moving and Handling Objects list.

Both the NSAA and the PUL were developed using Rasch techniques for construction and validation tools[22,23]. Mayhew and colleagues collected cross-sectional NSAA assessment data from the North Star database for 191 ambulatory boys with DMD between 3-15 years of age and examined properties of the instrument that included clinical meaningfulness, appropriateness of item targeting, order of item response categories, Rasch model fit, and instrument reliability and stability. They determined that Rasch analysis upheld reliability and validity of the instrument as a measure of mobility and ambulatory function in DMD that logically follows functional loss resulting from disease progression. Furthermore, they described an S-shaped curve relationship for a transformation scale between raw scores and logit-based location on the continuous Rasch-based scale. That function illustrated that raw scale scores yield different continuous interval score changes over the possible range of instrument, with continuous score changes that are magnified at both tails of the distribution relative to the middle. In a longitudinal follow up paper, Mayhew used a similar cohort of 198 DMD patients between 4 and 18 years of age from the North Star database to examine NSAA responsiveness to disease progression over time and minimal clinically-important difference (MCID) of mean scores for GC-treated and GC-naïve patients[25]. They also reported a 0-100 point logit transformed scale relative to the 0-32-point NSAA raw score scale. In both GC-treated and GC-naïve patients, they showed the instrument is responsive to previously described improvements in ambulatory ability scores for children under 7 due to milestone attainment during the early childhood growth spurt[26,27], as well as functional loss due to disease progression over the range of individuals in the sample. Importantly, they also demonstrated that by linearizing items on the Rasch model scale, distribution-based minimal clinically important differences in score across the range of function can be directly linked to loss of specific functional abilities. The authors illustrated this by demonstrating that a change from a score of 50 to 40 on the transformed scale directly corresponds to loss of ability to rise from the floor without assistance.

The EK scale was developed by the Danish muscular dystrophy association as a clinical tool to assess overall functional ability in the non-ambulatory DMD population[28,29]. This tool includes assessments comprised of functional assessments measuring interaction of physical components such as muscle strength, range of motion, respiratory status, wheelchair dependence and age. The Scale assesses ten functional categories (EK 1-10), each contributing to an overall picture of function.

Mayhew et al also developed the upper limb assessment tool called the Performance of the Upper Limb module for Duchenne muscular dystrophy[22]. The device was developed using upper limb functional performance items from the Brooke upper extremity functional scale[7], the Jebsen-Taylor Hand Function Test (JTHFT)[30] and the Motor Function Measure (MFM)[31] selected on the basis of a conceptual framework that items should provide assessment of upper limb and hand mobility including impact of weakness, growth and development of joint contractures across both ambulatory and non-ambulatory phases of disease. Item selection by a key informant workgroup of clinicians occurred following assessment using the full instrument measures performed on 61 volunteers with DMD 11-30 years of age. The resulting item list was then assessed in 86 volunteers with DMD between 5-27 years of age. Rasch analysis of the pilot instrument data demonstrated excellent item fit and good reliability, with some collapsing of disordered item responses into broader but clinically appropriate categories. Development of the PUL instrument is ongoing. Application of Rasch analysis using the two clinician-reported outcome scales, both of which represent different aspects of mobility, strongly suggests the utility of evaluating similarly constructed items from commonly used patient-reported instruments alone or in combination with clinically-obtained assessments.

Item list-specific recommendations for instrument development.

Using the Rasch analysis-derived feedback on item syntax and response category characteristics, and using the three clinical measurement instruments as guides to examine other possible elements of mobility function specific to DMD, as well as possible

mobility functions that may exist outside of our currently appreciated ceiling and floor effects, we formulated specific recommendations regarding future modifications of each mobility domain item list.

Walking and Moving: In the walking and moving list, we noted that there were several high-residual items from the PODCI instrument. In addition, there were multiple items from the NeuroQoL that were missing a "Can't Do" response category. As discussed above, we considered revising the question set so that items follow a format so that items are phrased as "In the past 7 days, I could _____" (responses With no trouble, With some trouble, With a lot of trouble, Can't do). This rephrasing would help to improve disordered responses by reducing ambiguity in the light to moderate difficulty responses, and could help somewhat in extending the "floor" of the scale by accounting for individuals who cannot perform the tasks. The title of the scale itself dictated the items that it addresses, and "Walking and moving" as a construct related to strength applied only to those who are ambulatory to some degree. Wheelchair mobility items, on the whole, were not sensitive to changes in disease status / milestone, at least as defined here. Some of the questions we evaluated were aimed at manual wheelchair use, and some at power wheelchair use, and it is likely that there is a differential response between users of one technology vs. another, though we did not have the data to examine this directly. There is likely also a relationship between distal/hand ability and wheelchair driving, but technologies related to power wheelchair mobility are continuously evolving, and even individuals with very severe strength limitation are generally able to move about in their power chairs fairly easily. Wheelchair mobility should be a topic of discussion in future instrument development, to see whether any important topic areas emerge, and to develop pilot questions. It remains unclear whether wheelchair mobility, as an activity that is dictated by access to technology rather than disease progression specifically, represents a true physical mobility domain or more accurately reflects activity and participation – for example, it is hard to imagine that wheelchair mobility would be tested as an endpoint in a clinical trial of a drug to improve overall function. However, within the ambulatory group of patients, we can look to the North Star Ambulatory Assessment tool for suggestions on items that are easier (ie. to the right of the item thresholds) to address floor effects, and more difficult items (ie. to the left of the item thresholds) to address ceiling effects. When compared to the NSAA (Table 20), our questions address NSAA functions of running, walking, climbing a box step, and descending a box step. On the easier end of the spectrum, the NSAA grades the lowest level of walking function as Walking Grade 0: "Loss of independent ambulation – may use KAFOs or walk short distances with assistance." Our most difficult question "I could walk between rooms" is from the NeuroQOL and thus the most difficult response was "With a lot of trouble". As suggested by the NSAA scoring paradigm, addition of a "Can't do" response as noted above may then be expected to lower the "floor" of the instrument somewhat. On the most difficult end of the spectrum, our hardest question is "Walk more than a mile". Here it was instructive to look at the NSAA items (Table 21) that were not represented in our current list, including jumping, hopping, standing on the heels, standing on one leg, and lifting the head while supine – all functions that have been noted as early deficits in children with DMD, and which may show to be more difficult than a one-mile walk. With the exception of the last item (lifting the head), all of these functions appear at face value to relate directly in some way to ambulatory ability – a model that has been validated by Mayhew and colleages through their Rasch analysis of the NSAA instrument. Some children with DMD never attain the ability to hop on one foot, and thus addition of questions targeted to these four functions thus may extend the range of the question set to cover the entire young and more functional end of the DMD spectrum. From a standpoint of simplification and consolidation of multiple questions into a single item with responses directed at multiple levels of ability, it appeared it would be helpful for us to look at how the questions in our subscale are related to the items in the clinical scale (Table 20). For instance, our question items that fall under the NSAA Item 6 and 7: Climbing and Descending steps domain might prove appropriate to consolidate into a single item that reflects to perform climbs of increasing height and/or duration.

Table 20. Items linking the North Star Ambulatory Assessment and the Walking and Moving Scale.

NSAA Item 2: Walking.
2 - Walks with heel-toe or flat-footed gait pattern
1 - Persistent or habitual toe walker, unable to heel-toe consistently
0 - Loss of independent ambulation – may use KAFOs or walk short distances with assistance

Linking Items (In order of difficulty)

Q5	nqmobped05	I could walk between rooms
Q13	nqmobped21	I could walk on slightly uneven surfaces (such as cracked pavement)
Q18	nqmobped24	I could walk on rough, uneven surfaces (such as lawns, gravel driveway)
Q17	posna_q44	Walk one block?
Q1	nqmobped01	I could keep my balance while walking for 30 minutes
Q4	nqmobped04	I could walk for 15 minutes
Q19	nqmobped25	I could walk up and down ramps or hills
Q16	posna_q43	Walk three blocks?
Q6	nqmobped12	I could walk for 30 minutes
Q14	posna_q42	Walk more than a mile?

NSAA Item 6, 7: Climb Box Step
2 - Faces step – no support needed
1 - Goes up sideways or needs support
0 - Unable

NSAA Items 8, 9: Descend Box Step
2 - Faces forward, climbs down controlling weight bearing leg. No support needed
1 - Sideways, skips down or needs support
0 - Unable

Linking Items

Q20	nqmobped26	I could walk up and down curbs
Q12	posna_q41	Climb one flight of stairs?
Q23	nqmobped39	I could walk up 2-3 stairs
Q9	posna_q40	Climb three flights of stairs?

NSAA Item 17: Run (10m)
2 - Both feet off the ground (no double stance phase during running)
1 - 'Duchenne jog'
0 – Walk

Linking Item

Q7	posna_q38	Run short distances?

Table 21. Functions from NSAA that are missing in the Walking and Moving item list.

NSAA Item 5: Stand on one leg.
2 - Able to stand in a relaxed manner (no fixation) for count of 3 seconds
1 - Stands but either momentarily or needs a lot of fixation e.g. by knees tightly adducted or other trick
0 – Unable

NSAA Item 12: Lifts head
2 – In supine, head must be lifted in mid-line. Chin moves toward chest
1 – Head is lifted but through side flexion or with no neck flexion
0 – Unable

NSAA Item 13: Stands on heels
2 – Both feet at the same time, clearly standing on heels only (acceptable to move a few steps to keep balance) for count of 3
1 – Flexes hip and only raises forefoot
0 – Unable

NSAA Item 14: Jump
2 – Both feet at the same time, clear of the ground simultaneously
1 – One foot after the other (skip)
0 – Unable

NSAA Item 15, 16: Hop
2 – Clears forefoot and heel off floor
1 - Able to bend knee and raise heel, no floor clearance
0 - Unable

Changing and Maintaining Body Position: In the changing and maintaining body position list, we observef that there were several high-residual instruments from the PODCI instrument. In addition, multiple items from the NeuroQoL were missing a "Can't Do" response category. As discussed above, considered revising the question set so that items follow a format so that items are phrased as "In the past 7 days, I could _____" (responses With no trouble, With some trouble, With a lot of trouble, Can't do). This rephrasing would help to improve disordered responses by reducing ambiguity in the light to moderate difficulty responses, and would also extend the "floor" of the scale by accounting for individuals who cannot do the tasks. Extension of the "floor" of the scale could also be informed through comparison of the current question items to items contained in the EK scale (Table 22). When compared to the EK scale, our questions address functions of standing, transferring to and from a wheelchair, balancing in a wheelchair (or chair), moving the arms, turning in bed, and head control. On the easier end of the spectrum, the EK scale grades the lowest level of head control as Head Control Grade 3 – "When sitting still in a wheelchair needs head support". Our most difficult question "I could turn my head all the way to the side to look at someone or something" is from the NeuroQOL and thus the most difficult response was "With a lot of trouble". As we previously noted, addition of a "Can't do" response could be expected to lower the "floor" of the instrument. In addition, it was instructive to examine the other high-difficulty responses from the EK scale questions. Other difficult items that would lower the instrument floor included items from the wheelchair transfer question (Grade 2 - Needs assistance to transfer with or without additional aids; Grade 3 - Needs to be lifted with support of the head when transferring from wheelchair), Ability to balance in the wheelchair (Grade 3 – Unable to change position of the upper part of the body, cannot sit without total support of the trunk or head), Ability to turn in bed (Grade 2 – Unable to turn himself in bed. Has to be turned 0-3 times per night; Grade 3 – Unable to turn himself in bed, Has to be turned >4 times per night), and head control (Grade 3 – When sitting still in a wheelchair needs head support). Other items in the EK scale that were not represented in this question set (Table 23) were primarily concerned with other functions not directly related to body position control but that could be instructive when considering hand and arm function (refer to the next section). On the most

difficult end of the spectrum, our hardest question was "I could get on and off a chair without using my arms". The EK scale was developed as a tool for non-ambulatory individuals, and thus in this instance is not very informative. However, when we examined disease-related milestones we observed that loss of the ability to stand from supine precedes loss of ability to rise from a chair, and thus the NSAA item 11: Rise from floor became relevant, as rising from supine could be considered a positional transfer. Addition of an item on the "difficult" end of the scale that addresses not only overall ability to rise from the floor, but the quality of such a motion would extend the "ceiling" of the instrument in the direction of more functional individuals. A question such as "In the past 7 days, I could stand from the floor without putting my hands on my knees" (responses With no trouble, With some trouble, With a lot of trouble, Can't do) might prove to be effective at identifying children who can still stand without evidence of the classic "Gower's manoeuvre" that is an early telltale sign of early disease progress. From a standpoint of simplification and consolidation of multiple questions into a single item with responses directed at multiple levels of ability, it was helpful for us to look at how the questions in our subscale are related to the items in the clinical scale (Table 22). For instance, our bed, chair or toilet question items that fall under the EK Item 2: Ability to transfer from wheelchair domain could be appropriate to consolidate into a single item that reflect similar transfers of varying degrees of difficulty.

TABLE 22. Items linking the NSAA and EK Scale and the Changing and Maintaining Body Position item list.

NSAA Item 11: Rise from floor
- 2 – From supine, no evidence of Gower's manoeuvre
- 1 – Gower's evident
- 0 – Needs external support object (eg. Chair) or unable

Linking Items

Q9	nqmobped13	I could get up from the floor by myself

EK Item 2: Ability to transfer from wheelchair
- 0 – Able to transfer from wheelchair without help
- 1 – Able to transfer independently from wheelchair, with use of aid
- 2 – Needs assistance to transfer with or without additional aids (hoist, easy-glide)
- 3 – Needs to be lifted with support of the head when transferring from wheelchair

Linking Items

Q24	nqexped31	I was able to get into bed by myself.
Q23	posna_q28	Get in and out of bed?
Q22	nqexped30	I was able to get out of bed by myself.
Q2	nqwchped04	I could move between my wheelchair and another seat such as a chair or bed
Q3	nqwchped06	I could manage getting on and off the tub bench from a wheelchair
Q4	nqwchped07	I could manage getting on and off the toilet from a wheelchair
Q5	nqwchped08	I could stand up from an armless straight chair using my wheelchair
Q7	nqmobped10	I could get in and out of an adultsized chair
Q21	posna_q27	Get on and off a toilet or chair?
Q6	nqmobped09	I could get on and off a low chair
Q8	nqmobped11	I could get on and off a chair without using my arms.

EK Item 3: Ability to Stand
- 0 – Able to stand with knees supported, as when using braces
- 1 – Able to stand with knees and hips supported, as when using standing aids
- 2 – Able to stand with full body support
- 3 – Unable to stand or be stood

Linking Items

Q19	posna_q25	Stand while washing his hands and face at a sink?
Q27	posna_q31	How often did your child need help from another person for sitting and standing?

EK Item 4: Ability to balance in the wheelchair
- 0 – Able to push himself upright from complete forward flexion by pushing up with hands
- 1 – Able to move the upper part of the body >30 degrees in all directions from the upright position, but cannot push himself upright as above
- 2 – Able to move the upper part of the body <30 degrees from one side to the other
- 3 – Unable to change position of the upper part of the body, cannot sit without total support of the trunk or head.

Linking Items

Q11	nqmobped15	I could sit on a bench without back support for 30 minutes

EK Item 5: Ability to move the arms
- 0 – Able to raise the arms above the head with or without compensatory movements
- 1 – Unable to lift the arms above the head, but able to raise the forearms against gravity (ie. hand to mouth with/without elbow support)
- 2 – Unable to lift the forearms against gravity, but able to use the hands against gravity when the forearm is supported
- 3 – Unable to use the hands against gravity, but able to use the fingers

Linking Items

Q16	nqexped21	I was able to cover my nose when sneezing

EK Item 7: Ability to turn in bed
- 0 – Able to turn himself in bed when under bed sheets or cover
- 1 – Needs some help to turn in bed or can turn in some directions
- 2 – Unable to turn himself in bed. Has to be turned 0-3 times per night.
- 3 – Unable to turn himself in bed. Has to be turned >4 times per night.

Linking Items
Q12 nmd_q16 It is hard to turn myself during the night.
Q17 nqexped26I was able to change positions in my bed

EK Item 12: Head control
0 – Does not need head support
1 – Needs head support when going up and down slope (15 degree standard ramp)
2 – Needs head support when driving wheelchair
3 – When sitting still in a wheelchair needs head support
Linking Items
Q15 nqmobped19 I could turn my head all the way to the side to look at someone or something

Table 23. Functions from the EK Scale that are missing in the Changing and Maintaining Body Position item list.
EK Item 1: Ability to Use a Wheelchair
0 – Able to use a manual wheelchair on flat ground (10m < 1 minute)
1 - Able to use a manual wheelchair on flat ground (10m > 1 minute)
2 – Unable to use manual wheelchair, requires power wheelchair
3 – Uses power wheelchair, but occasionally has difficulty steering
EK Item 6: Ability to use hands and arms for eating
0 – Able to eat and drink without elbow support
1 – Eats or drinks with support at elbow
2 – Eats and drinks with elbow support; with reinforcement of the opposite hand + or – aides
3 – Has to be fed
EK Item 8: Ability to cough
0 – Able to cough effectively
1 – Has difficulty to cough and sometimes needs manual reinforcement. Able to clear throat.
2 – Always needs help in coughing. Only possible to cough in certain positions.
3 – Impossible to cough, needs suction and/or hyperventilation techniques or IPPB in order to keep airways clear
EK Item 9: Ability to speak
0 – Powerful speech, able to sing and speak loudly
1 – Speaks normally, but cannot raise his voice
2 – Speaks with a quiet voice, and needs a breath after 3-5 words
3 – Speech is difficult to understand, except to close relatives
EK Item 10: Physical well-being
0 – No complaints, feels good
1 – Easily tires, has difficulty resting in a chair or bed
2 – Has loss of weight, loss of appetite, scared of falling asleep at night, sleeps badly
3 – Experiences additional symptoms: change of mood, stomach ache, palpitations, perspiring
EK Item 11: Daytime fatigue
0 – Doesn't get tired during the day
1 – Need to limit activity to avoid getting too tired
2 – Need to limit activity *and* have a rest period to avoid getting too tired
3 – Get tired during the day even if I rest and limit activity
EK Item 13: Ability to control joystick
0 – Uses a standard joystick without adaptation
1 – Uses an adapted joystick or has adjusted wheelchair in order to use joystick
2 – Uses other techniques for steering than joystick such as blowing sucking systems or scanned driving
3 – Unable to operate wheelchair, needs another person to operate it
EK Item 14: Food Textures
0 – Eats all textures of food
1 – Eats cut up/chunky food or avoids hard/chewy foods
2 – Eats minced/pureed food with supplementation as required
3 – Main intake consists of being tube fed
EK Item 15: Eating a meal
0 – Able to consume a whole meal in the same time as others sharing the meal
1 – Able to consume a whole meal in the same time as others only with encouragement or needs some additional time (approximately 10 minutes)
2 – Able to consume a whole meal but requires substantially more time compared to others eating the same meal (15 minutes or more extra)
3 – Unable to consume a whole meal
EK Item 16: Swallowing
0 – Never has problems when swallowing, and never chokes on food/drink
1 – May experience occasional (less than once a month) problems swallowing certain types of food or occasionally chokes
2 – Has regular trouble swallowing food/drink or chokes on food/drink (more than once a month)
3 – Has trouble swallowing saliva or secretions
EK Item 17: Hand function
0 – Can unscrew the lid of a water or fizzy drink bottle and can break the seal
1 – Can write two lines *or* use the computer keyboard
2 – Can write signature *or* send text *or* use remote control
3 – Cannot use hands

Carrying, Moving and Handling Objects: In the carrying, moving and handling objects list, we observed that there were high-residual instruments from the PODCI instrument. In addition, we observed multiple items from the NeuroQoL that were missing a "Can't Do" response category. As discussed above, we considered revising the question set so that items follow a format so that items are phrased as "In the past 7 days, I could _____" (responses With no trouble, With some trouble, With a lot of trouble, Can't do). This rephrasing would help to improve disordered responses by reducing ambiguity in the light to moderate difficulty responses, and could help to extend the "floor" of the scale by accounting for individuals who cannot perform the tasks. Extension of the "floor" of the scale was

also informed by comparing the existing question items to those contained in the PUL Assessment (Table 24). When compared to the PUL Assessment, our questions addressed functions of lifting heavy weights, opening containers, holding items while supinating the hand, and fine motor ability. On the more difficult end of the spectrum, the PUL assessment contains multiple hand functions relating to fine motor control that could fall below our weakest items of "It's hard to use my hands" (Table 25). These items include tearing paper, tracing a path with a pencil, pushing on a light switch, placing a finger on a number diagram, and pinch, 3-point and thumb grips. All of these functions are maintained until very late in disease progression, and developing questions to address similar daily tasks would extend the "floor" of our instrument to a much larger number of very weak individuals. Recent Rasch analysis results of the development of the Person Reported Measure Upper Limb (PROM UL) by Katrijn Klingel and colleagues[32] revealed a list of upper extremity functional tasks that extended past our current set of items on the weaker end of the spectrum. Question items, which range from "Screw the cap off a bottle that has not been opened before" (strong end) to "Use a TV remote control" are presented in Table 26. Klingel noted an outlier group on the stronger end of the scale. This makes sense when we view the combination of our item list and the PROM-UL items in order from easiest to most difficult (Table 27). We observe that the order of tasks is somewhat in agreement, with considerable overlap in the middle of the spectrum. As noted, PROM-UL items cover the weaker end of the spectrum, and our items cover the stronger end. We continue to observe a ceiling effect that produces outlier individuals on the stronger end of the spectrum. However, in considering additional questions on the stronger end, we could refer look to PUL Assessment items that evaluate shoulder function, namely shoulder abduction and flexion to or above shoulder height, and we could identify daily activities that might require that type of motion. These activities might involve high level tasks such as brushing hair, scratching the top of the head, or reaching for highly placed objects. Some of the shoulder-height tasks could have already been represented by our questions regarding ability to open doors (doorknobs are often at shoulder height for children and individuals in wheelchairs). From a standpoint of simplification and consolidation of multiple questions into a single item with responses directed at multiple levels of ability, it was again be helpful for us to look at how the questions in our subscale were related to the items in the clinical scale (Table 25). For instance, our container opening question items that fall under the PUL Item M: Remove lid from container heading could be appropriate to consolidate into a single item that reflect similar tasks of varying degrees of difficulty.

Table 24. Items linking the PUL and the Changing and Carrying, Moving and Handling Objects item list.

PUL Item H: Move weight on table
- 5 – Can lift 1kg weight from outer to centre circle without compensation
- 4 - Can lift 500g weight from outer to centre circle without compensation
- 3 - Can lift 200g weight from outer to centre circle without compensation
- 2 - Can lift 100g weight from outer to centre circle without compensation
- 1 - Can slide 100g weight from outer to centre circle without compensation
- 0 - Unable

Linking Items

Q5 phys_q4	Lifting something heavy
Q1 posna_q7	Lift heavy books?

PUL Item J: Lifting Heavy Cans
- 5 – Lift 5 (furthest away from preferred) [Note this is across body midline]
- 4 – Lift 4
- 3 – Lift 3 (Centre)
- 2 – Lift 2
- 1 – Lift 1 (Outer)
- 0 - Unable

Linking Items

Q6 nquexped08	I was able to hold a full cup of water in my hand.
Q3 posna_q8	Pour a half gallon of milk?
Q13 nquexped17	I was able to pick up a gallon of milk with one hand and set it on the table

PUL M: Remove Lid from Container
- 1 – Opens completely
- 0 – Unable to open

Linking Items

Q2 nquexped01	I was able to open small containers like snack bags or vitamins (regular screw top)
Q17 nquexped23	I was able to open a can of soda
Q4 posna_q9	Open a jar that's been opened before?
Q19 nquexped33	I was able to open a jar by myself.

PUL Item Q: Supination
- 4 – Picks up the light, and turns the hand over completely without any compensatory movements
- 3 – Picks up the light and turns it over completely with compensatory movements
- 2 – Picks up the light and turns the hand over incompletely
- 1 – Picks up the light but cannot turn the hand over

0 – Cannot pick up the light

Linking Items
Q10 nquexped15 I was able to hold a plate full of food

PUL Item R: Picking up coins
3 – Can pick up and hold six coins in one hand
2 – Can pick up and hold three coins in one hand
1 – Can pick up one coin
0 – Cannot pick up one coin

Linking Items
Q8 nmd_q11 It is hard to use my hands.
Q7 nmd_q8 My hands are weak.

Table 25. Functions from the PUL Assessment that are missing in the Carrying, Moving and Handling Objects item list.

PUL Item B: Shoulder abduction to shoulder height
4 – 1000g
3 – 500g
2 – 200g
1 – Able, no weights
0 – Unable

PUL Item C: Shoulder abduction above shoulder height
4 – 1000g
3 – 500g
2 – 200g
1 – Able, no weights
0 – Unable

PUL Item D: Shoulder flexion to shoulder height
4 – 1000g
3 – 500g
2 – 200g
1 – Able, no weights
0 – Unable

PUL Item D: Shoulder flexion above shoulder height
4 – 1000g
3 – 500g
2 – 200g
1 – Able, no weights
0 – Unable

PUL Item F: Hand to mouth
3 – Able to bring 200g in cup to mouth with one hand and no elbow support
2 – Able to bring 200g in cup to mouth either with 2 hands or one hand with elbow support
1 – Able to bring 50g in cup to mouth using 2 hands
0 – Unable

PUL Item G: Hand(s) to table from lap
3 – Two hands completely and simultaneously to table
2 – Two hands completely on table but not at same time
1 – Gets both hands on table but incompletely
0 – Unable

PUL Item I: Lifting light cans
5 – Lift 5 (furthest away from preferred) [Note this is across body midline]
4 – Lift 4
3 – Lift 3 (Centre)
2 – Lift 2
1 – Lift 1 (Outer)
0 – Unable

PUL Item K: Stacking Light Cans
5 – Stack 5th can
4 – Stack 4th can
3 – Stack 3rd can
2 – Stack 2nd can
1 – Unable to stack 2nd can

PUL Item L: Stacking Heavy Cans
5 – Stack 5th can
4 – Stack 4th can
3 – Stack 3rd can
2 – Stack 2nd can
1 – Unable to stack 2nd can

PUL Item N: Tearing paper
- 4 – Tears the sheet of paper folded in 4, beginning from the fold edge
- 3 - Tears the sheet of paper folded in 2, beginning from the fold edge
- 2 – Tears the unfolded sheet of paper
- 1 – Can hold unfolded sheet of paper but cannot tear it
- 0 – Cannot hold paper or tear it

PUL Item O: Tracing path
- 4 – Able to pick up pencil and able to complete the path without stops or raising hand from paper
- 3 – Able to complete the path but needs to stop or raises hand from paper
- 2 – Able to follow the path for at least 5cm but unable to complete the path
- 1 – Able to hold pencil and can make a mark on the paper
- 0 – With pencil in hand unable to hold it or to make a mark

PUL Item P: Push on the light
- 3 – Able to turn the light on permanently with one hand
- 2 – Able to turn the light on momentarily with one hand
- 1 – Able to turn the light on momentarily with two hands
- 0 – Unable to turn the light on momentarily with two hands

PUL Item S: Place finger on number diagram
- 3 – Raises finger and places it successively on the numbers of the diagram without touching the lines
- 2 – Raises finger and places it imprecisely on the numbers
- 1 – Cannot raise finger to place it on a drawing but can slide it between at least two squares
- 0 – Cannot raise finger or slide it on the diagram

PUL Item T: Finger pinch grip
- 2 – Able to finger pinch and lift weight
- 1 – Able to achieve finger pinch grip but can't move weight
- 0 – Unable to achieve finger pinch grip

PUL Item U: 3 point grip
- 2 – Able to 3 point grip and lift weight
- 1 – Able to achieve 3 point grip but can't move weight
- 0 – Unable to achieve 3 point grip

PUL Item V: Thumb (key) grip
- 3 – Able to grip and lift weight
- 2 – Able to achieve thumb grip but can't lift weight
- 1 – Unable to achieve thumb grip but can move end of thumb
- 0 – Unable to achieve thumb grip or bend end of thumb

Table 26: PROM Items by Order of Difficulty, easiest to hardest (Katrijn Klingels' slide presentation, Rome UL meeting, June 10, 2015)

Use a TV remote control
Use a mouse
Type on a computer with a keyboard
Sign name
Turn the pages of a book
Pick up small objects from the table
Dial/Text on a cell phone (this may be adapted to "use a touchscreen")
Eat a meal
Press buttons on an elevator
Open a drawer
Turn a light switch on/off on the wall at a standard height
Drink from a half-full glass without a straw
Reach out to shake hands
Bring a phone to your ear
Wash hands
Write several lines
Wipe nose
Brush teeth
Take money from a wallet from your pocket to pay for something
Scratch head
Take a book out of a bag on your lap
Open a fridge door
Open a pack of crisps (chips)
Pour a drink from a half-liter bottle
Fasten a zipper
Cut up different textures of food
Pick up a pen from the floor
Put a jacket on
Button up (a shirt for example)
Pull up trousers after using the toilet
Open a can of soft drink
Screw the cap off a bottle that has not been opened before

Table 27: Combined items from the Carrying, Moving and Handling Objects scale and the experimental PROM-UL device (bold), in apparent order from easiest to most difficult

Use a TV remote control	
Use a mouse	
Type on a computer with a keyboard	
Sign name	
Turn the pages of a book	
Pick up small objects from the table	
Dial/Text on a cell phone (this may be adapted to "use a touchscreen")	
Q8 nmd_q11	It is hard to use my hands.
Q6 nquexped08	I was able to hold a full cup of water in my hand.
Q15 nqwchped19	I could manage the armrests on my wheelchair
Q9 nquexped12	I was able to use a knife to spread butter or jelly on bread
Eat a meal	
Q18 posna_q29	Turn doorknobs?
Q14 nquexped19	I was able to cut a piece of paper in half with scissors
Press buttons on an elevator	
Open a drawer	
Turn a light switch on/off on the wall at a standard height	
Drink from a half-full glass without a straw	
Reach out to shake hands	
Bring a phone to your ear	
Wash hands	
Write several lines	
Wipe nose	
Brush teeth	
Take money from a wallet from your pocket to pay for something	
Scratch head	
Take a book out of a bag on your lap	
Open a fridge door	
Q2 nquexped01	I was able to open small containers like snack bags or vitamins (regular screw top)
Open a pack of crisps (chips)	
Pour a drink from a half-liter bottle	
Fasten a zipper	
Cut up different textures of food	
Pick up a pen from the floor	
Put a jacket on	
Button up (a shirt for example)	
Pull up trousers after using the toilet	
Q7 nmd_q8	My hands are weak.
Q16 nqwchped20	I could manage the footrests on my wheelchair.
Q4 posna_q9	Open a jar that's been opened before?
Open a can of soft drink	
Q17 nquexped23	I was able to open a can of soda
Q11 nqwchped16	I could open a door that faced away from my wheelchair
Q12 nqwchped17	I could open a door that was facing my wheelchair
Q21 nquexped37	I was able to open the rings in school binders.
Q10 nquexped15	I was able to hold a plate full of food
Screw the cap off a bottle that has not been opened before	
Q19 nquexped33	I was able to open a jar by myself.
Q3 posna_q8	Pour a half gallon of milk?
Q1 posna_q7	Lift heavy books?
Q20 nquexped36	I was able to pull open heavy doors.
Q13 nquexped17	I was able to pick up a gallon of milk with one hand and set it on the table

Part 1 Conclusion

As an initial step to developing and refining a formal tool, the construction of item lists representing multiple aspects of mobility using assessments from the UC Davis / CINRG Duchenne Natural History Study gives us insight into the utility of question items from multiple person-reported instruments. Based on an overall construct of mobility using the WHO-ICF model, our list of items creates a continuous scale that spans ambulatory and non-ambulatory stages of the disease, which is critically needed for conduct of clinical trials. Overall model fit is good, and items sort in an order that is consistent with clinical progression of disease, with loss of endurance, followed by loss of mobility and ambulation, followed by loss of upper limb and finally hand function. Individual items show variation in overall model fit, and the final result still indicates a moderate degree of over-discrimination that suggests that there is still local dependency among items. This is not surprising given that the combined items were not formally developed as a unified scale, and given there is significant variability in both phenotype and rate of progression across the range of clinical function represented in this cohort. We see ceiling effects that suggest that inclusion of items representing higher levels of function might be necessary to assess less affected individuals. There is also a potential reduced sensitivity toward more severe end of the scale suggesting a need for inclusion of additional items at that end. However, the items adequately cover a population of children with early disease, adolescents who are transitioning between ambulatory and non-ambulatory phases of the disease (who are all currently being targeted for inclusion in clinical

trials), and advanced-stage non-ambulatory individuals. Individual person fit indices for most of the cohort indicate a moderately good degree of model fit, and the Person Separation Index statistics indicate a moderately good ability to discriminate between individuals. While there is some local dependency of items, it is due in part to similarity of questions measuring the same types of tasks under the mobility construct. We reduced overall dependency somewhat by removing duplicative items where possible, and it is possible that this might be further reduced through construction of polytomous responses where multiple dichotomous questions currently exist. Overall, our data supports the concept that lists of commonly-themed items can be constructed from multiple concurrently administered instruments according to the latent domains they represent. In the mobility domain, we demonstrate that question items from existing PRO measures can be combined with clinically-derived functional "milestone" assessments on the same linearized scale, thus enabling measurements across multiple ages and stages of disease. Such lists should be refined into item banks with responses that can be used in development of targeted clinical trial assessments, PRO CAT tools, and potentially even self-reported measures of clinical function.

Part 2: Instrument refinement and field testing of the final measure

Introduction

There were two main recommendations resulting from the initial technical development phase of the DMD Lifetime Mobility Scale. The first recommendation was to standardize the presentation syntax and response options for questions throughout the study. We did this in order to mimic original questions whose response characteristics across multiple ages/stages of disease were stable and followed a logical order in correlation with progressive loss of function. We standardized the syntax of all questions to indicate a 7-day recall, to indicate actual ability rather than preference for that ability, to indicate ability *without assistance*, and to limit choices on level of difficulty. The resulting question format was "In the past 7 days, I could (task) without help: With no difficulty; With some difficulty; With a lot of difficulty; Could not do it." The second recommendation was to create additional questions at the higher and lower ends of functional ability (ex. hopping and jumping vs. pushing buttons on a smart phone) to address ceiling and floor effects on each scale. We did this by reviewing commonly-used clinical functional evaluations and constructing analogous questions based on those functional tasks. Additional questions, mirroring items from the NSAA[23] and PUL[22] evaluations and the UL-PROM[32] addressed ability to hop with both feet off the ground, hop on one foot, lift one's head when supine, and a variety of upper, mid-level and distal upper extremity and manual tasks.

Instrument refinement through patient interviews

We then conducted semi-structured patient and parent interviews with 20 parent/child pairs and 5 adults with DMD to review and give feedback on the draft question set. These interviews were used to evaluate face validity and to confirm understanding of underlying concepts represented by each question, to evaluate questions as to their patient acceptance, and to identify alternative ceiling and floor items as identified by the participants themselves. Based on the data from the interviews, we drafted an updated version of the instrument that we are testing through this online field study. Overall, there were no items that patients or parents noted as unacceptable. Comprehension of the revised syntax and concepts of items themselves was excellent, except for those items addressing adjustment of wheelchair components. As previous analyses had also shown that the wheelchair items did not align well with others in factor analyses, these were dropped from the question set. The patients and parents recommended several additional question topics, including ability to crawl across a room, crawl up and down stairs, get on and off a toilet, get in and out of a low vehicle (car), get in and out of a high clearance vehicle (SUV or truck), open a jar that has not been opened before, push / pull open heavy doors, feed oneself a meal, cover one's nose when sneezing, use a computer track pad, and play videogames with a handheld controller.

Field Testing of the Final Measure

To field test the final instrument with the additional questions and updated syntax, we conducted a national, internet-based administration of the instrument using REDCap survey tools provided by the UC Davis Clinical and Translational Research Center, with recruiting and advertising assistance from Parent Project Muscular Dystrophy and the Muscular Dystrophy Association. We constructed the online survey using formatting that would facilitate ease of use on mobile devices by individuals with limited hand mobility. We presented questions individually and sequentially for each of the 3 domains, and we formatted the four response choice buttons so that they filled the screen laterally to facilitate thumb swipe/tap motions. Participants included parents of children under 10, parents/child pairs for children 10-17, and adults with DMD. Once enrolled in the online study, participants were prompted by timed automated email messages (at enrollment and one month following enrollment) with web links to questionnaire forms. One hundred thirty-seven participants provided complete initial responses, and 87 provided one-month follow-up responses for a total of 224 completed surveys. The following Rasch analysis includes first-time administrations of the device, and the internal and repeated measures validity analyses include all available baseline and 1-month responses.

Rasch Analysis of the Activities and Participation Mobility Domain and Subdomains

Walking and Moving Subscale

Model and Item Fit: The analysis included 65 scorable responses, excluding zero scores for non-ambulatory patients. The person separation index of 0.95 demonstrates very good power of the overall model to individuate between respondents. Summary statistics show that using a revised subset of the updated response items to model a construct of ambulatory ability demonstrates a good item fit residual mean(SD) of -0.09(0.79), and a person fit residual mean(SD) of -0.04(0.22). Fit statistics for the final model are displayed in Table 28. Review of individual item fit (not shown) demonstrates that no items that would be expected to contribute to model misfit

(with an item residual >|3.0|). Using more traditional methods, the 21 items show a Cronbach's Alpha internal consistency statistic that is excellent at 0.9899, with a Kaiser-Meyer-Olkin Sampling Adequacy measure of 0.957 and a Bartlett's Test of Sphericity Chi Square that is significant at <0.0001. Confirmatory principle components factor analysis demonstrates loading of the question set on a single factor explaining 83% of the variance.

Table 28. Summary Test of Rasch Fit Statistics

Item Fit	Fit Residual Mean	SD
	-0.09	0.79
Person Fit	-0.04	0.22
Chi Squared Probability	0.583	
Degrees of freedom	42	
Person Separation Index (PSI)	0.95	

Individual Person Fit: Residuals values for person fit represent the difference between modelled responses and the individual's actual responses. Residual fit values < |3.0| can be considered acceptable. Residuals for individual person fit ranged from -0.82 to 0.68 (mean -0.41, SD 0.22) indicating that overall, individuals in the sample fit the model very well, with no responses falling outside the acceptable range.

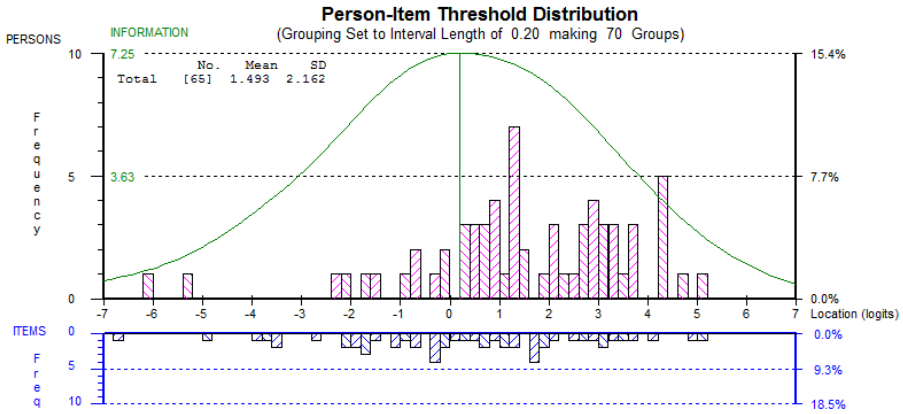
Correlation of Residuals: Items in this domain-based list represent a latent construct of mobility in the context of a progressively debilitating disease measured using different representations (ie. standing, climbing, walking) of that mobility or lack thereof. Thus, we expect a moderate degree of covariation or dependency between variables, where a response on two items (ex. Ability to walk 1 block vs. Ability to walk 3 blocks) are both dependent on the underlying ability to walk long distances. For purposes of this analysis, we were willing to accept a moderate degree of correlation (r<0.4) between items. Items exceeding our acceptable limit of moderate residual correlation are shown in **Table 29**. Of the items with moderately correlated residuals, questions related to walking or crawling different distances or durations showed some moderate correlation but represented different levels of effort or capacity that are meaningful in day to day life. Ability to balance showed a similar pattern. Thus, we have selected to include these items in the model.

Table 29. Local Dependency for Walking and Moving Scale Items

Item	Walk 30 Minutes	Walk a Mile	Walk 3 Blocks	Walk Between Rooms	Balance for 30 Minutes
Walk 15 Minutes	0.52				
Walk a Mile	0.541				
Walk 1 Block			0.512		
Hop		-0.469			
Crawl				-0.724	
Balance for 15 Minutes					0.647

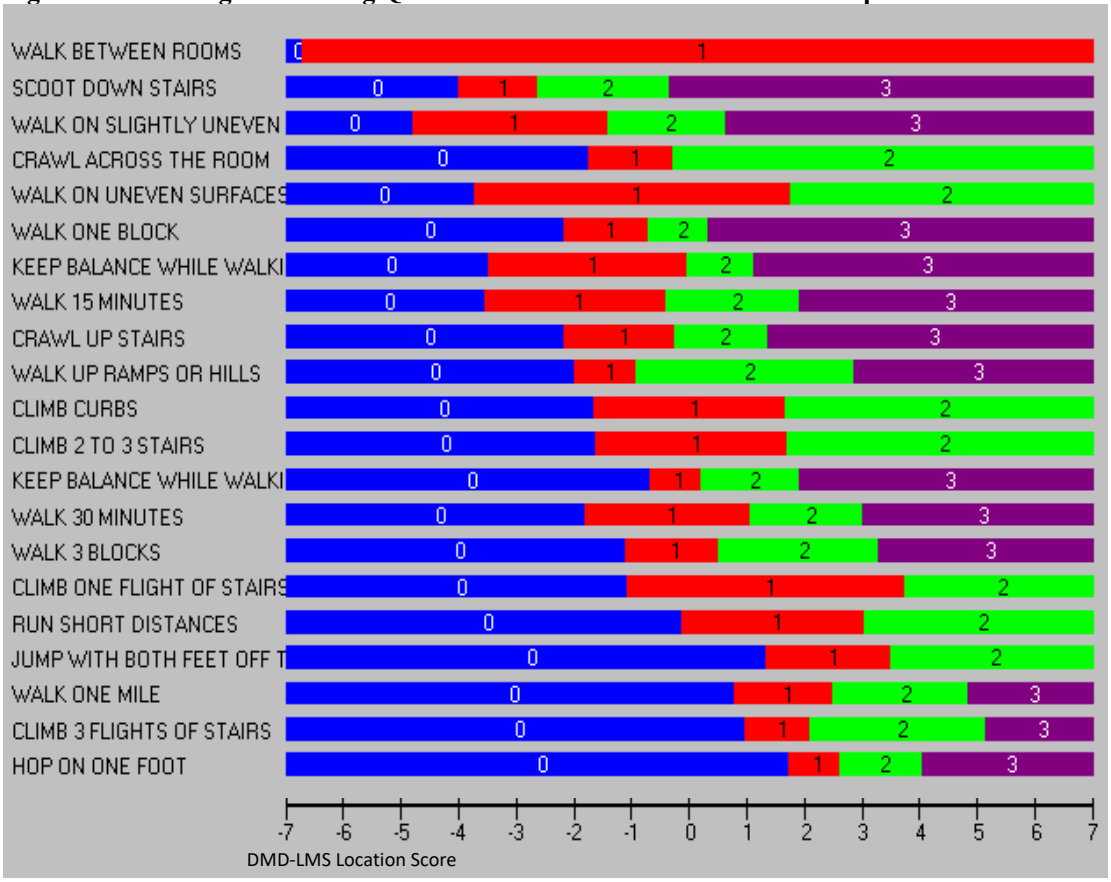
Person-Item Threshold Location: The person-item threshold distribution shown in **Figure 10** reflects the overall distribution of the population examined (persons in pink), in this case children and adolescents with Duchenne muscular dystrophy, over a continuous logit scale. The individuals' position on the scale represents their overall level of function in a latent construct representation of ambulatory mobility. The blue items then indicate the position of item thresholds, or points of change, between response categories for items included in the mobility domain list, and represent boundaries of the domain list's ability to readily differentiate between individuals at a given level of function. Points to the right indicate better function, points to the left indicate worse function. The distribution indicates that there was no notable ceiling or floor effect where respondents scored above or below the item ceilings, except where ambulation had been lost permanently. This suggests that the current list does an acceptable job of assessing differences in ambulatory ability across a range of ambulatory individuals who are mildly affected to those who are able to move about independently only by walking very short household distances or even crawling. Patients in this lower range of function are frequently described as non-ambulatory from the standpoint of day-to-day mobility.

Figure 10. Person-Item Threshold Distribution for the Walking and Moving Question Set



Threshold Ordering, Item Locations and Clinical "Face" Validity: Placing the questions in location order from easiest to most difficult yields the question set shown on the item location threshold map in **Figure 11**. Overall, these items represent a range of ambulatory mobility tasks that are progressively lost, starting with hopping on one foot, long distance and long duration walks and climbs, and running, followed by moderate distance and duration walks and climbs, followed by short walks, walks on uneven surfaces, and walking and crawling household distances. This is consistent with the clinical presentation and natural history of the disease and spans nearly the entire range of ambulatory function, suggesting that our construct has face validity as a representation of mobility.

Figure 11: Walking and Moving Question Set Item Location Threshold Map.



Final Instrument and Scoring: The final instrument, scoring sheet and linear score conversion table are included in the Appendix and are comprised of 21 items. The scored items comprise the formal assessment set. However, the construction of the scoring models can be based in part on removal of some daily activity tasks where scores may be highly correlated and could exert leverage over participant scores. Removal of some correlated items to improve scoring model accuracy might also reduce the tool's ability to inform researchers about patient performance of meaningful daily activities. Thus, the instrument itself can include non-scored items whose responses can be correlated with the calibrated items here, providing additional information about day to day abilities. This leaves room to insert other

non-scored experimental questions about other functional activities as the need arises. This approach also supports development of future scoring paradigms without losing the ability to calculate the "original" item score, thus enabling cross-mapping of this scoring model to other future models.

Changing and Maintaining Body Position Subscale

Model and Item Fit: The analysis included 137 scorable responses, excluding 3 scores with insufficient data. The person separation index of 0.97 demonstrates very good power of the overall model to individuate between respondents. Summary statistics show that using a revised subset of the updated response items to model a construct of ambulatory ability demonstrates a good item fit residual mean(SD) of -0.42(0.61), and a person fit residual mean(SD) of -0.29(0.43). Fit statistics for the final model are displayed in Table 30. Review of individual item fit (not shown) demonstrates that no items that would be expected to contribute to model misfit (with an item residual >|3.0|). Using more traditional methods, the 22 items show a Cronbach's Alpha internal consistency statistic that is excellent at 0.9854, with a Kaiser-Meyer-Olkin Sampling Adequacy measure of 0.972 and a Bartlett's Test of Sphericity Chi Square that is significant at <0.0001. Confirmatory principle components factor analysis demonstrates loading of the question set on two dimensions, with the first (ability to change position) explaining 79% of the variance and the second (neck strength/mobility) explaining an additional 5% for a total of 84%. Tests of internal consistency for the positional change dimension independently showed excellent Cronbach's Alpha statistic of 0.9889, a Kaiser-Meyer-Olkin Sampling Adequacy measures of 0.972, and Bartlett's Test of Sphericity Chi Squared that was significant at p<0.0001. Independent evaluation of the two-question neck strength/mobility dimension yielded values that were not in the typically acceptable ranges for internal consistency, suggesting that sole use of that dimension would not be advisable.

Table 30. Summary Test of Rasch Fit Statistics

Item Fit	Fit Residual Mean	SD
	-0.42	0.61
Person Fit	-0.29	0.43
Chi Squared Probability	0.507	
Degrees of freedom	44	
Person Separation Index (PSI)	0.97	

Individual Person Fit: Residuals values for person fit represent the difference between modelled responses and the individual's actual responses. Residual fit values < |3.0| can be considered acceptable. Residuals for individual person fit ranged from -1.53 to 1.67 (mean -0.28, SD 0.43) indicating that overall, individuals in the sample fit the model very well, with no responses falling outside the acceptable range.

Correlation of Residuals: Items in this domain-based list represent a latent construct of mobility in the context of a progressively debilitating disease measured using different representations (ie. Changing between standing, seated and supine positions or repositioning the body) of that mobility or lack thereof. Thus, we expect a moderate degree of covariation or dependency between variables, where a response on two items (ex. Get into bed, Get out of bed.) are both dependent on the underlying ability to transfer to and from a standing or seated position to a supine position. For purposes of this analysis, we were willing to accept a moderate degree of correlation (r<0.4) between items. Items exceeding our acceptable limit of moderate residual correlation are shown in **Table 31**. Of the items with moderately correlated residuals, questions related to similar functions of getting into and out of bed, changing positions in bed, and climbing into and out of a tub with or without a bench all represent similar in/out or stand/sit/stand type activities that nonetheless may use slightly different or opposing muscle groups to perform the tasks, and represent two motion patterns necessary to perform an important daily activity. Thus, we have selected to include these items in the model.

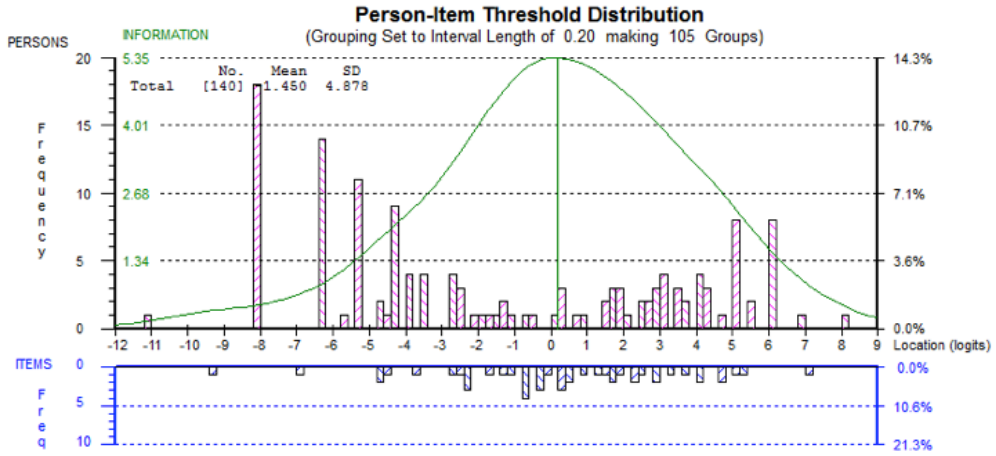
Table 31. Local Dependency for Changing and Maintaining Body Position Scale Items

Item	Get into bed.	Change positions in my bed.	Climb into a bathtub without a tub bench.	Transfer to a tub bench.
Get out of bed.	0.448			
Climb out of a bathtub without a tub bench.			0.566	
Transfer from a tub bench.				0.656
Turn myself during the night.		0.675		

Person-Item Threshold Location: The person-item threshold distribution shown in **Figure 12** reflects the overall distribution of the population examined (persons in pink), in this case children and adolescents with Duchenne muscular dystrophy, over a continuous logit scale. The individuals' position on the scale represents their overall level of function in a latent construct representation of transfer and positional mobility. The blue items then indicate the position of item thresholds, or points of change, between response categories for items included in the mobility domain list, and represent boundaries of the domain list's ability to readily differentiate between individuals at a given level of function. Points to the right indicate better function, points to the left indicate worse function. The distribution indicates that cumulatively there was a ceiling effect for 0.7% of participants and a floor effect for 1.4%. This suggests that

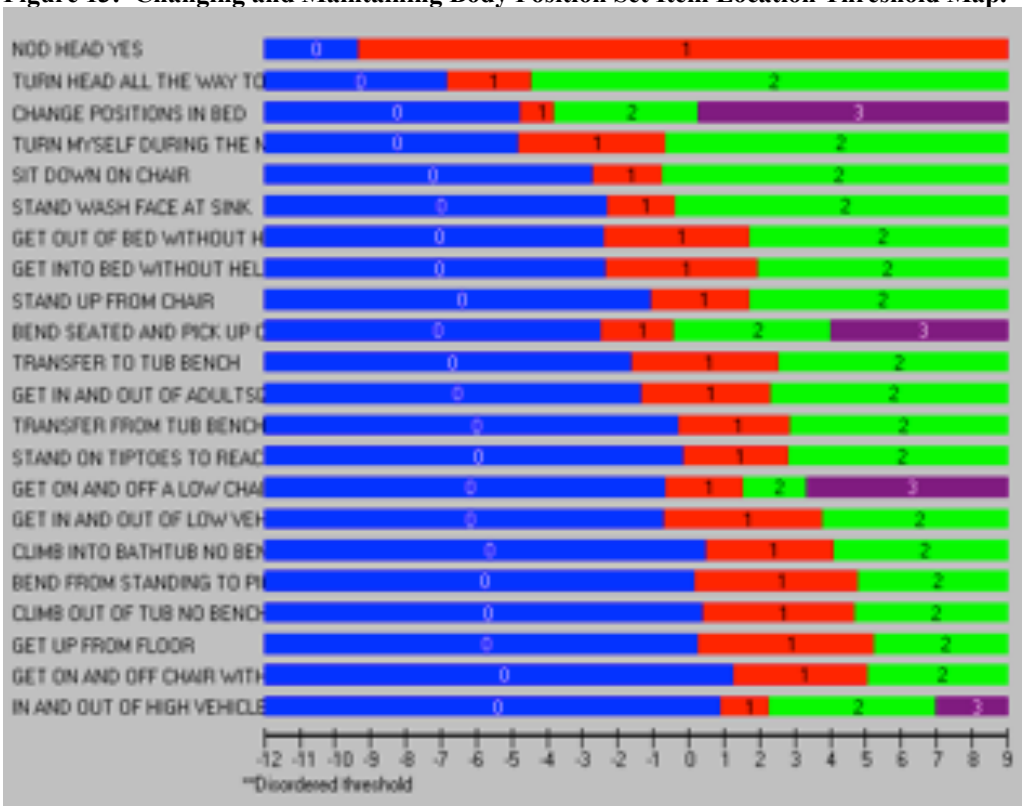
the current list does an acceptable job of assessing differences in transfer and positional stability across a range of ambulatory and non-ambulatory individuals across the range of early and mild to severe and advanced disease.

Figure 12. Person-Item Threshold Distribution for the Changing and Maintaining Body Position Set



Threshold Ordering, Item Locations and Clinical "Face" Validity: Placing the questions in location order from easiest to most difficult yields the question set shown on the item location threshold map in **Figure 13**. Overall, these items represent a range of positional transfer mobility tasks that are progressively lost, starting with climbing in and out of high vehicles, standing from a chair without using the arms, and standing from supine, followed by sit to stand and stand to sit transfers, to turning in bed, to moving the head and neck. This is consistent with the clinical presentation and natural history of the disease and spans nearly the entire range of ambulatory and non-ambulatory function, suggesting that our construct has face validity as a representation of mobility.

Figure 13: Changing and Maintaining Body Position Set Item Location Threshold Map.



Final Instrument and Scoring: The final instrument, scoring sheet and linear score conversion table are included in the appendix and are comprised of 30 items in total, including the 22 scored items listed above. The scored items comprise the formal assessment set. However, the construction of the scoring models can be based in part on removal of some daily activity tasks where scores may be highly correlated and could exert leverage over participant scores. Removal of some correlated items to improve scoring model accuracy

might also reduce the tool's ability to inform researchers about patient performance of meaningful daily activities. Thus, the instrument itself can include non-scored items whose responses can be correlated with the calibrated items here, providing additional information about day to day abilities. This leaves room to insert other non-scored experimental questions about other functional activities as the need arises. This approach also supports development of future scoring paradigms without losing the ability to calculate the "original" item score, thus enabling cross-mapping of this scoring model to other future models.

Carrying, Moving and Handling Objects Subscale

Model and Item Fit: The analysis included 129 scorable responses, excluding three extreme scores. The person separation index of 0.97 demonstrates excellent power of the overall model to individuate between respondents. Summary statistics show that using a revised subset of the updated response items to model a construct of ambulatory ability demonstrates a good item fit residual mean(SD) of -0.38(0.55), and a person fit residual mean(SD) of -0.2(0.76). Fit statistics for the final model are displayed in Table 32. Review of individual item fit (not shown) demonstrates that no items would be expected to contribute to model misfit (with an item residual >|3.0|). Using more traditional methods, the 33 items show a Cronbach's Alpha internal consistency statistic that is excellent at 0.9857, with a Kaiser-Meyer-Olkin Sampling Adequacy measure of 0.974 and a Bartlett's Test of Sphericity Chi Square that is significant at $p<0.0001$. Confirmatory principle components factor analysis demonstrates loading of the question set on three dimensions, with the first (mid/low-force) explaining 68% of the variance, the second (upper/high-force) explaining 8% of the variance, and the third (distal/hand function) explaining an additional 3% for a total of 79%. Tests of internal consistency for the upper, mid and distal dimensions independently showed excellent Cronbach's Alpha statistics of 0.9553, 0.9827 and 0.9499, Kaiser-Meyer-Olkin Sampling Adequacy measures of 0.942, 0.974 and 0.928 respectively, and Bartlett's Test of Sphericity Chi Squared that were all significant at $p<0.0001$.

Table 32. Summary Test of Rasch Fit Statistics

Item Fit	Fit Residual Mean	SD
	-0.38	0.55
Person Fit	-0.2	0.76
Chi Squared Probability	0.060	
Degrees of freedom	66	
Person Separation Index (PSI)	0.97	

Individual Person Fit: Residuals values for person fit represent the difference between modelled responses and the individual's actual responses. Residual fit values < |3.0| can be considered acceptable. Residuals for individual person fit ranged from -2.44 to 2.82 (mean -0.20, SD 0.76) indicating that overall, individuals in the sample fit the model very well, with no responses falling outside the acceptable range.

Correlation of Residuals: Items in this domain-based list represent a latent construct of mobility in the context of a progressively debilitating disease measured using different representations (ie. Lifting and manipulating objects, reaching parts of the body and using the hands) of that mobility or lack thereof. Thus, we expect a moderate degree of covariation or dependency between variables. For example, the acts of pulling/pushing open heavy doors are both dependent on the underlying ability to raise the arm against gravity and exert some degree of force. For purposes of this analysis, we were willing to accept a moderate degree of correlation (ie. <0.4) between items. Items exceeding our acceptable limit of moderate residual correlation are shown in **Table 33**. Of the items with moderately correlated residuals, questions related to opening and closing doors, raising the arm above the shoulder, and fine motor and hand strength combinations showed some moderate correlation but represented different levels of effort or capacity that are meaningful in day to day life. Thus, we have selected to include these items in the model.

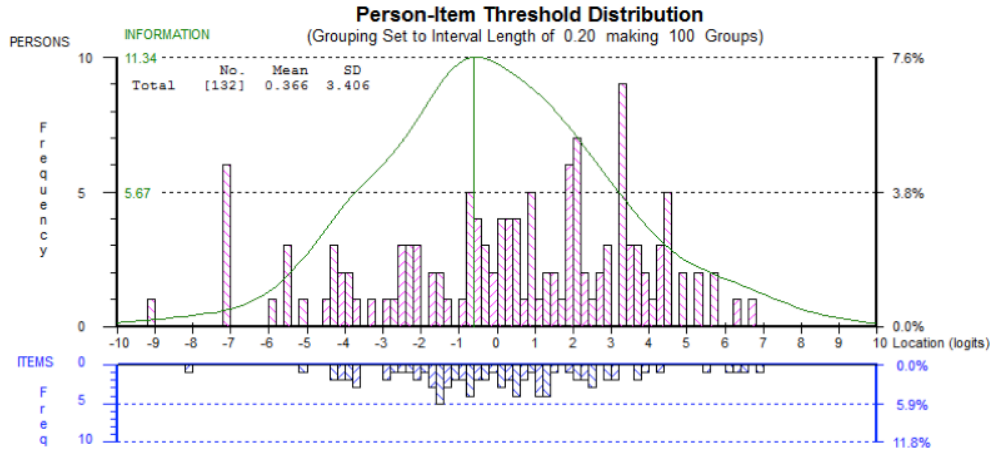
Table 33. Local Dependency for Moving, Carrying and Handling Objects Scale Items

Item	Pull open heavy doors.	Open small containers like snack bags or vitamins.	Press buttons on an elevator.
Push open heavy doors.	0.528		
Scratch my head.			0.57
Use a knife to spread butter or jelly on bread.		0.408	

Person-Item Threshold Location: The person-item threshold distribution shown in **Figure 14** reflects the overall distribution of the population examined (persons in pink), in this case children and adolescents with Duchenne muscular dystrophy, over a continuous logit scale. The individuals' position on the scale represents their overall level of function in a latent construct representation of upper extremity mobility. The blue items then indicate the position of item thresholds, or points of change, between response categories for items included in the mobility domain list, and represent boundaries of the domain list's ability to readily differentiate between individuals at a given level of function. Points to the right indicate better function, points to the left indicate worse function. The distribution indicates that there was no notable ceiling effect where respondents scored above the item ceilings, and only a small floor effect with <1% of the population scoring below the floor of the instrument. This suggests that the current list does an acceptable job of

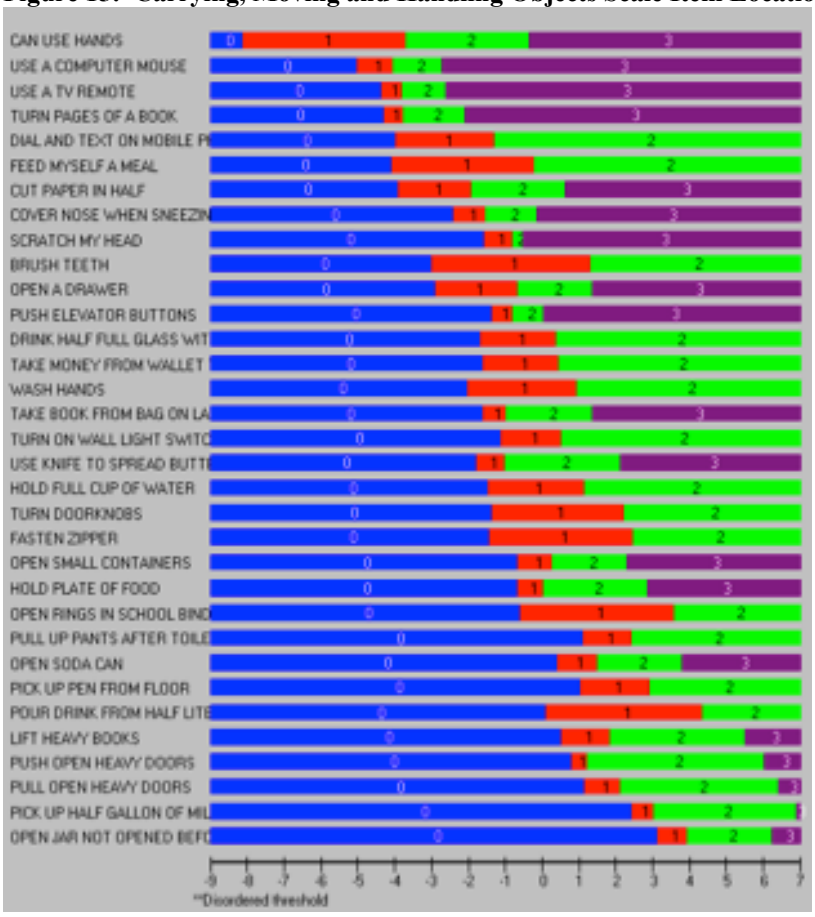
assessing differences in upper extremity ability across a range of individuals who are mildly affected to those who are severely restricted in the ability to move their upper extremities or use their hands for most functional tasks.

Figure 14. Person-Item Threshold Distribution for the Carrying, Moving and Handling Objects Scale Items



Threshold Ordering, Item Locations and Clinical "Face" Validity: Placing the questions in location order from easiest to most difficult yields the question set shown on the item location threshold map in **Figure 15**. Overall, these items represent a range of upper extremity mobility tasks that are progressively lost, starting with tasks requiring significant shoulder strength such as opening a closed jar and lifting heavy drink cartons, through items requiring elbow flexion strength such as holding plates of food or drink, to small distal manual tasks such as using a TV remote or computer mouse. This is consistent with the clinical presentation and natural history of the disease and spans nearly the entire range of upper extremity function, suggesting that our construct has face validity as a representation of mobility.

Figure 15: Carrying, Moving and Handling Objects Scale Item Location Threshold Map.



Final Instrument and Scoring: The final instrument, scoring sheet and linear score conversion table are included in the appendix and are comprised of 50 items in total, including the 33 scored items listed above. The scored items comprise the formal assessment set. However, the construction of the scoring models can be based in part on removal of some daily activity tasks where scores may be highly correlated and could exert leverage over participant scores. Removal of some correlated items to improve scoring model accuracy might also reduce the tool's ability to inform researchers about patient performance of meaningful daily activities. Thus, the instrument itself can include non-scored items whose responses can be correlated with the calibrated items here, providing additional information about day to day abilities. This leaves room to insert other non-scored experimental questions about other functional activities as the need arises. This approach also supports development of future scoring paradigms without losing the ability to calculate the "original" item score, thus enabling cross-mapping of this scoring model to other future models.

The DMD-LMS as a Whole Instrument

Model Fit, Test-Retest Reliability and Internal Consistency: A summary of model fit and internal consistency characteristics of the whole instrument, the three subscales and their individual dimensions is presented below in Table 34. Taken as a whole, the 76 items show a Cronbach's Alpha internal consistency statistic that is excellent at 0.9933, with a Kaiser-Meyer-Olkin Sampling Adequacy measure of 0.971 and a Bartlett's Test of Sphericity Chi Square that is significant at $p<0.0001$. We measured the 1-month test-retest reliability of the instrument in 87 participants. This yielded an intraclass correlation coefficient (ICC) of 0.993 for the entire instrument, and ICC's for the Walking and Moving, Changing and Maintaining Body Position and Carrying, Moving and Handling Objects subscales of 0.989, 0.987 and 0.983 respectively, indicating a high degree of test-retest reliability. There was a small sample of participants from 10-17 years of age where both the boy with DMD and their parent or caregiver completed the devices in tandem. Correlation of the between parent- and child-completed measures for the Walking and Moving, Changing and Maintaining Body Position and Carrying, Moving and Handling Objects subscales were 0.9732, 0.9582 and 0.9807, respectively.

Table 34: Model Fit and Consistency of the DMD-LMS Total and Subscale Scores.

Domain/Subscale	Person Separation Index	Item-Trait Chi2	Person Mean (SD) Fit Resid	Intraclass Correlation Coefficient (1-month)	Cronbach's Alpha	K-M-O Sampling Adequacy	Bartlett's Sphericity Chi2
DMD-LMS (whole instrument)				0.993	0.9933	0.971	25652.8 (DF 2850, p<0.0001)
Walking and Moving	0.9525	39.45 (DF 42, p=0.583)	-0.04 (0.22)	0.9895	0.9899	0.957	9986.1 (DF 253, p<0.0001)
Changing and Maintaining Body Position	0.9666	43.15 (DF 44, p=0.507)	-0.28 (0.42)	0.987	0.9854	0.972	8707.9 (DF 231, p<0.0001)
Changing Position					0.9889	0.972	8579.0 (DF 190, p<0.0001)
Head and Neck ROM / Strength					0.1683	0.5	13.4 (DF 1, p<0.0001)
Carrying, Moving and Handling Objects	0.9732	84.67 (DF 66, p=0.060)	-0.19 (0.75)	0.9826	0.9857	0.974	8756.6 (DF 435, p<0.0001)
Upper / Weighted					0.9553	0.942	2220.3 (DF 45, p<0.0001)
Mid / Unweighted					0.9827	0.974	5201.6 (DF 136, p<0.0001)
Distal / Hand					0.9499	0.928	1375.6 (DF 15, p<0.0001)

Calculating the Subscale and Total Instrument Scores: To calculate subscale scores, scorable questions items are assigned the point value noted in each subscale's Scoring Structure Table (see appendix) and then summed. Once the sum of the scorable items is obtained, the linearized score is determined using the subscale's Score Sheet (see appendix). The total instrument score is a simple sum of the 3 linearized subdomain scores.

Discriminant Ability of the Instrument and Subscales: Upon beginning the survey, participants were asked the following series of brief yes/no questions about their (or their child's) functional abilities that was designed to mirror the functional "milestone" scale previously reported by our group (19,34) as a way to stratify participants by level of disease severity:

Can your child with DMD (or you if you have DMD) do the following things without help?

- Stand up from lying on the floor without help?
- Climb at least 4 stairs without help?
- Stand up from a chair without help?
- Walk at least 10 meters (about 30 feet) without help?
- Reach your arms all the way over your head without help?
- Breathe OK during the day without some type of ventilator or bi-pap machine?

Based on responses to these questions, we classified participants into 7 functional milestone categories:

1. Ambulatory, can stand from supine, can climb stairs, can rise from a chair
2. Ambulatory, cannot stand from supine, can climbs stairs, can rise from a chair
3. Ambulatory, cannot stand from supine, cannot climb stairs, can rise from a chair

4. Ambulatory, cannot stand from supine, cannot climb stairs, cannot rise from a chair
5. Non-ambulatory, with overhead reach
6. Non-ambulatory, without overhead reach, no daytime ventilation (typically corresponding to FVC>30%)
7. Non-ambulatory, without overhead reach, daytime ventilation (typically corresponding to FVC<30%)

In addition, we asked the question "Are you/your son with DMD taking steroids (i.e. glucocorticoids or corticosteroids) for strength maintenance?". This was classified into a binary yes/no category representing current steroid use.

Comparison of Adjacent Group Means for Total Score and Subscale Scores*:* We calculated differences in initial baseline mean scores between adjacent levels of the "milestone" classes to evaluate the ability of the DMD-LMS and its subscales to discriminate between levels representing worsening disease severity from near-typical function in early childhood to late-stage disease. The results of those tests are shown in Table 35 and Figures 16 - 19 below. Classes 3 and 4 presented a problem, in that the period of time in which participants cannot climb stairs, and either can or cannot rise from a chair independently but can still ambulate to some degree is relatively brief in the overall context of the lifespan. Because of this, there were a small number of participants (3 and 4, respectively) who were given the Class 3 or Class 4 categorizations. Thus, while scores on the instrument and subscales decreased from Class 2 to Class 3, the number of Class 3 participants (only 4) was not sufficient to indicate statistically-significant differences in scores between individuals who can and cannot rise from a chair. This may be resolved with additional data collection in the future. Using this method, the instrument otherwise demonstrated significant score contrasts between *all* other adjacent levels, either in the Total Score or subscale scores.

Table 35

Ability of DMD-LMS Total and Domain Subscale Scores to Discriminate Between Different Levels of Patient Milestone Function

Functional Class		Walking and Moving	Changing and Maintaining Body Position	Carrying, Moving and Handling Objects	Total Score
1 vs. 2	*Level 1 Score (mean, SD)*	**78.3, 11.9**	**79.7, 9.3**	79.3, 9.6	**240.3, 25.8**
	Level 2 Score (mean, SD)	**63.0, 6.2**	**70.5, 4.6**	77.2, 7.9	**210.6, 13.1**
	Score Difference (mean, SE)	**15.2, 7.0**	**9.2, 5.5**	2.1, 5.7	**29.7, 15.2**
	p-value	**0.017**	**0.0487**	*NS*	**0.0284**
2 vs. 3	*Level 2 Score (mean, SD)*	63.0, 6.2	70.5, 4.6	77.2, 7.9	210.6, 13.1
	Level 3 Score (mean, SD)	54.3, 10.7	61.5, 8.5	74.8, 11.0	208.1, 15.2
	Score Difference (mean, SE)	8.7, 7.1	8.9, 5.5	2.4, 7.8	2.5, 12.6
	p-value	*NS*	*NS*	*NS*	*NS*
3 vs. 4	*Level 3 Score (mean, SD)*	**54.3, 10.7**	61.5, 8.5	74.8, 11.0	208.1, 15.2
	Level 4 Score (mean, SD)	**27.3, 20.2**	54.2, 12.0	69.8, 13.6	151.3, 45.0
	Score Difference (mean, SE)	**27.0, 13.2**	7.3, 7.7	4.9, 10.1	56.8, 34.5
	p-value	**0.05**	*NS*	*NS*	*NS*
4 vs. 5	*Level 4 Score (mean, SD)*	**27.3, 20.2**	**54.2, 12.0**	69.8, 13.6	**151.3, 45.0**
	Level 5 Score (mean, SD)	**5.2, 10.3**	**41.1, 8.3**	61.8, 8.4	**105.4, 20.7**
	Score Difference (mean, SE)	**22.07, 7.20**	**13.1, 5.3**	8.0, 5.5	**45.9, 15.1**
	p-value	**0.0029**	**0.0109**	*NS*	**0.0032**
5 vs. 6	*Level 5 Score (mean, SD)*	**5.2, 10.3**	**41.1, 8.3**	**61.8, 8.4**	**105.4, 20.7**
	Level 6 Score (mean, SD)	**0.9, 3.2**	**27.7, 8.7**	**44.9, 13.5**	**73.3, 21.8**
	Score Difference (mean, SE)	**4.3, 1.8**	**13.4, 2.2**	**17.0, 3.2**	**32.1, 6.0**
	p-value	**0.0111**	**<0.00001**	**<0.00001**	**<0.00001**
6 vs. 7	*Level 6 Score (mean, SD)*	0.9, 3.2	**27.7, 8.7**	**44.9, 13.5**	**73.3, 21.8**
	Level 7 Score (mean, SD)	0	**19.7, 8.3**	**21.0, 11.2**	**40.8, 19.3**
	Score Difference (mean, SE)	0.9, 0.9	**8.0, 2.7**	**23.9, 4.7**	**32.5, 7.6**
	p-value	*NS*	**0.0025**	**<0.00001**	**<0.00001**

Figure 16

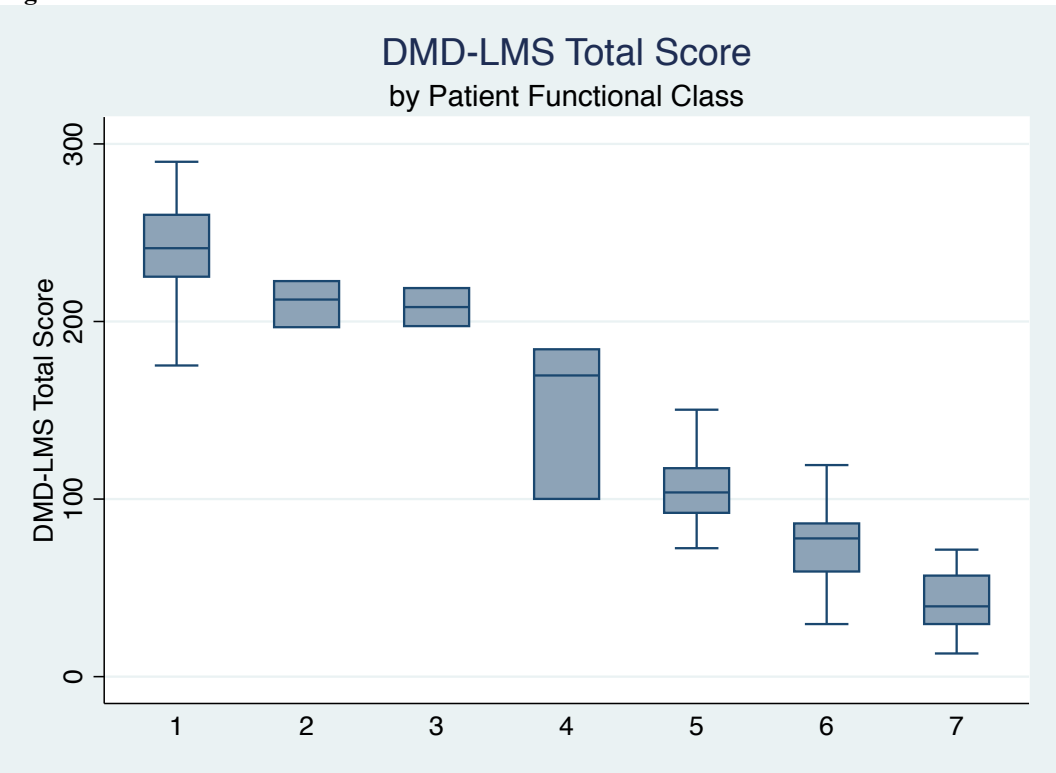


Figure 17

Figure 18

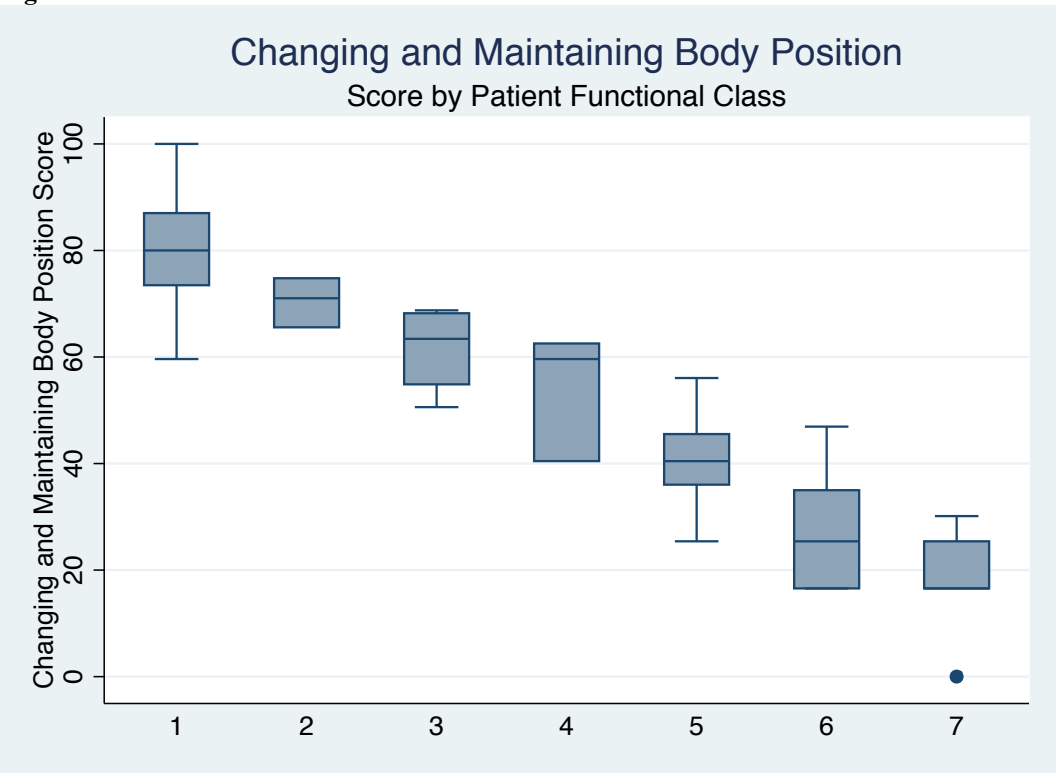
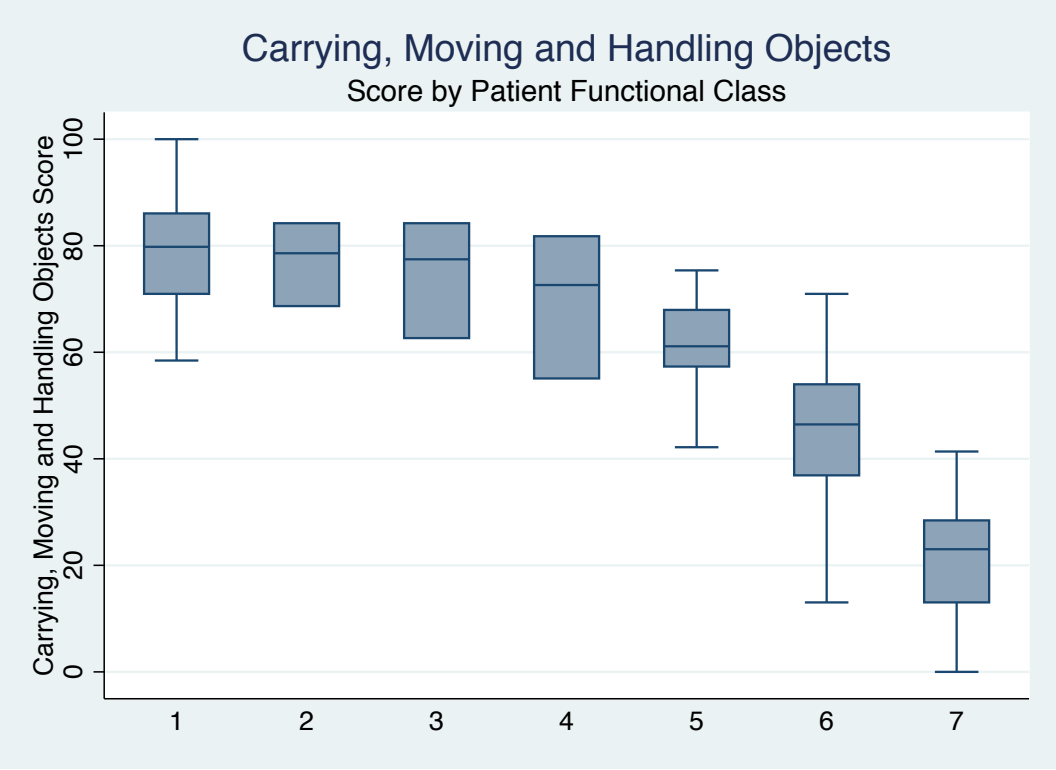


Figure 19



Linear Discriminant Analysis to Classify Participants into Functional Milestone Categories: While comparing mean instrument *scores* alone for adjacent functional groups is important, it ignores some of the richness in the data provided in the *patterns* of responses to collections of calibrated items in the instrument. We conducted canonical linear discriminant analysis, one of the more common statistical methods used in unsupervised machine learning, to determine whether the information in our instrument validation dataset was sufficient to correctly discriminate between participants in our seven functional milestone groups. The "hit ratios" indicating percentage of correct classifications for the individual subscale items and the full set of items are shown below in Table 36. The *Walking and Moving* subscale items collectively did an excellent job of correctly classifying ambulatory participants, as well as those with no ambulatory ability. The items performed less well at correctly classifying non-ambulatory participants in the Class 5-6 groups, although they did correctly classify participants as ambulatory or non-ambulatory. The items in the *Changing and Maintaining Body Position* question set did a similarly excellent job at correctly classifying most ambulatory participants, and correctly classified them as ambulatory or non-ambulatory but performed less well at differentiating between degrees of non-ambulatory function. The *Carrying, Moving and Handling Objects* items together performed well at correctly classifying most participants in all categories. For the *Total Score*, we included item responses from all three subscales in the analysis, which yielded a model with four statistically significant latent discriminant functions. The model correctly classified 100% of participants from categories 1-5, 87.5% of category 6 participants, and 100% of category 7 participants for an excellent overall "hit ratio" of 96%. The misclassified Category 6 participants were all classified by the model into the more severe Category 7 group. This indicates that the information provided in by the collection of question items, taken in its entirety across all three domains is sufficient to determine a participant's level of overall mobility using a clinically-relevant classification method with subtle differences between groups.

Table 36.

Canonical LDA "Hit Ratios" Reflecting Ability of DMD-LMS Total and Subscale Items Response Patterns to Define Clinically-Relevant Functional Milestone Groups

Functional Class	Walking and Moving	Changing and Maintaining Body Position	Carrying, Moving and Handling Objects	Total Score
1	98%	95%	91%	100%
2	100%	100%	100%	100%
3	100%	100%	100%	100%
4	100%	66%	100%	100%
5	25%	80%	95%	100%
6	3%	55%	83%	88%
7	100%	72%	100%	100%
OVERALL	94%	78%	94%	96%

Comparison of Steroid-Treated and Non-Treated Participant Responses for Total Score and Subscale Scores: For the *Walking and Moving* subscale, on average controlling for age the measured effect of steroid use was 17.3 (SE 7.7, $p=0.028$) points. For the *Changing and Maintaining Body Position* subscale, on average controlling for age the measured effect of steroid use was 12.8 (SE 3.6, $p<0.0001$) points. For the *Carrying, Moving and Handling Objects* scale, on average controlling for age the measured effect of steroid use was 15.1 (SE 3.1, $p<0.0001$) points. Overall for the *Total Score*, on average controlling for age the measured effect of steroid use was 46.8 (SE 11.7, $p<0.0001$) points. These results demonstrate that the instrument is sensitive to detection of a steroid-like treatment effect.

Part 2 Conclusion

There is a clear need to examine responses in person-reported outcomes of function and mobility relative to clinically-derived milestones. They represent the same concept, and thus we expect them to be strongly related to one another – this is the point. One of the key challenges in drug development[33] as stated by the FDA is a lack of validated person-reported outcomes that can be used to demonstrate that 1) individuals in clinical trials can demonstrate "noticeable" differences in function, and 2) that by creating a set of questions relating to more community-based functions, we can tie observed differences or changes in clinically-measured function back to performance of those daily community-based functions. There are a host of promising and novel therapeutic agents currently being tested in DMD. Presently none of these drugs are expected to make major improvements in function, but may slow or stabilize progression of disease over short-term and potentially make improvements over the long-term.

A better understanding of community-based functions relative to clinically-measured outcomes places maintenance of stability of the disease in the context of activities of daily living that are important to the patients and their roles as active and participatory members of family, peer groups and society as a whole. This will lead to a better understanding of the natural history of Duchenne muscular

dystrophy sources of variation between patients, and will improve our ability to predict the course of disease for groups of patients and individuals based on measurements at a given point in time. Doing so will improve our ability to predict and prepare families and patients for the necessary course of clinical care, and furthermore will help us to identify clinical trial cohorts in a much more refined manner.

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Appendix – DMD-LMS Instruments and Scoring

DMD Life-Time Mobility Scale (DMD-LMS) v.1.0

Instructions

The DMD-LMS is a series of statements to help measure your / your child's **current** level of mobility in three areas of daily living: *Walking and Moving*, *Changing and Maintaining Body Position*, and *Carrying, Moving and Handling Objects*.

The survey will ask you if you think you / your child **could have** performed a set of daily tasks within the past 7 days **without help**. The tasks will be related to walking, changing positions, and using the arms and hands. Some of the tasks might be hard, some of them might be easy. Some tasks might not be possible **without help**. Your choices will be that you / your child could do the task with no difficulty, with some difficulty, with a lot of difficulty, or you could not do it.

You / your child may not have completed the specific task listed in the past 7 days. If so, use your best judgement to select the answer that best reflects your or your child's **current** level of mobility for the task **without help:**

1. With no difficulty 2. With some difficulty 3. With a lot of difficulty 4. Could not do it

Walking and Moving				
In the past 7 days:	**1. With no difficulty**	**2. With some difficulty**	**3. With a lot of difficulty**	**4. Could not do it**
1. I could run short distances without help.	❑	❑	❑	❑
2. I could walk for 30 minutes without help.	❑	❑	❑	❑
3. I could walk for 15 minutes without help.	❑	❑	❑	❑
4. I could walk more than a mile without help.	❑	❑	❑	❑
5. I could walk three blocks without help.	❑	❑	❑	❑
6. I could walk one block without help.	❑	❑	❑	❑
7. I could walk between rooms without help.	❑	❑	❑	❑
8. I could walk up three flights of stairs without help.	❑	❑	❑	❑
9. I could walk up one flight of stairs without help.	❑	❑	❑	❑
10. I could walk up 2-3 stairs without help.	❑	❑	❑	❑
11. I could walk up and down ramps or hills without help.	❑	❑	❑	❑
12. I could walk up and down curbs without help.	❑	❑	❑	❑
13. I could jump with both feet off the ground without help.	❑	❑	❑	❑
14. I could hop on one foot without help.	❑	❑	❑	❑
15. I could walk on rough, uneven surfaces (such as lawns, gravel driveway) without help.	❑	❑	❑	❑
16. I could walk on slightly uneven surfaces (such as cracked pavement) without help.	❑	❑	❑	❑
17. I could crawl across a room without help.	❑	❑	❑	❑
18. I could keep my balance while walking for 30 minutes without help.	❑	❑	❑	❑
19. I could keep my balance while walking for 15 minutes without help.	❑	❑	❑	❑
20. I could crawl up a flight of stairs without help.	❑	❑	❑	❑
21. I could scoot down a flight of stairs without help.	❑	❑	❑	❑

DMD-LMS Walking and Moving Scoring Structure 1.1

Item	Max Score	With No Difficulty	With Some Difficulty	With A Lot of Difficulty	Can't Do
Run short distances.	2	2	1	1	0
Walk for 30 minutes.	3	3	2	1	0
Walk for 15 minutes.	3	3	2	1	0
Walk more than a mile.	3	3	2	1	0
Walk 3 blocks.	3	3	2	1	0
Walk 1 block.	3	3	2	1	0
Walk between rooms.	1	1	1	1	0
Walk up 3 flights of stairs.	3	3	2	1	0
Walk up 1 flight of stairs.	2	2	1	1	0
Walk up 2-3 stairs.	2	2	1	1	0
Walk up and down ramps.	3	3	2	1	0
Walk up and down curbs.	2	2	1	1	0
Jump with both feet off the ground.	2	2	1	1	0
Hop on one foot.	3	3	2	1	0
Walk on rough, uneven surfaces.	2	2	1	1	0
Walk on slightly uneven surfaces.	3	3	2	1	0
Crawl across a room.	2	2	1	1	0
Keep my balance while walking 30 min.	3	3	2	1	0
Keep my balance while walking 15 min.	3	3	2	1	0
Crawl up stairs.	3	3	2	1	0
Scoot down stairs.	3	3	2	1	0

DMD-LMS Walking and Moving Score Sheet 1.1

Linearized Score	Raw Score
100.2	53.0
97.5	52.0
94.7	51.0
92.4	50.0
90.2	49.0
92.5	50.0
86.0	47.0
84.0	46.0
82.2	45.0
80.4	44.0
78.7	43.0
77.0	42.0
75.5	41.0
73.9	40.0
72.4	39.0
71.0	38.0
69.5	37.0
68.2	36.0
66.8	35.0
65.4	34.0
64.2	33.0
62.9	32.0
61.6	31.0
60.3	30.0
59.1	29.0
57.9	28.0
56.6	27.0
55.4	26.0
54.2	25.0
53.0	24.0
51.8	23.0
50.6	22.0
49.4	21.0
48.2	20.0
47.0	19.0
45.7	18.0
44.5	17.0
43.2	16.0
42.0	15.0
40.7	14.0
39.3	13.0
37.9	12.0
36.5	11.0
35.0	10.0
33.5	9.0
31.8	8.0
30.0	7.0
28.1	6.0
26.0	5.0
23.8	4.0
21.0	3.0
17.5	2.0
12.0	1.0
0.0	0.1

Changing and Maintaining Body Position				
In the past 7 days:	**1. With no difficulty**	**2. With some difficulty**	**3. With a lot of difficulty**	**4. Could not do it**
1. I could sit down on a chair without help.	❑	❑	❑	❑
2. I could stand up from a chair without help.	❑	❑	❑	❑
3. I could bend over from a seated position and pick up something off the floor without help.	❑	❑	❑	❑
4. I could get down on my knees without holding on to something.	❑	❑	❑	❑
5. I could bend over from a standing position and pick up something off the floor.	❑	❑	❑	❑
6. I could get into bed without help.	❑	❑	❑	❑
7. I could get out of bed without help.	❑	❑	❑	❑
8. I could change positions in my bed without help.	❑	❑	❑	❑
9. I could get up from the floor without help.	❑	❑	❑	❑
10. I could get in and out of an adult sized chair without help.	❑	❑	❑	❑
11. I could get on and off a chair without help and without using my arms.	❑	❑	❑	❑
12. I could get on and off a low chair without help.	❑	❑	❑	❑
13. I could get on and off a toilet without help.	❑	❑	❑	❑
14. I could climb into a bathtub without a tub bench without help.	❑	❑	❑	❑
15. I could climb out of a bathtub without a tub bench without help.	❑	❑	❑	❑
16. I could transfer to a tub bench without help.	❑	❑	❑	❑
17. I could transfer from a tub bench without help.	❑	❑	❑	❑
18. I could sit on a bench without back support for 15 minutes without help.	❑	❑	❑	❑
19. I could sit on a bench without back support for 30 minutes without help.	❑	❑	❑	❑
20. I could sit in a regular chair without help and without holding on.	❑	❑	❑	❑
21. I could stand on my tiptoes to reach for something without help.	❑	❑	❑	❑
22. I could turn my head all the way to the side to look at someone or something without help.	❑	❑	❑	❑
23. I could turn myself during the night without help.	❑	❑	❑	❑
24. I could stand while washing my hands and face at a sink without help.	❑	❑	❑	❑
25. I could get in and out of a low vehicle (car) without help.	❑	❑	❑	❑
26. I could get in and out of a high-clearance vehicle (SUV or truck) without help.	❑	❑	❑	❑
27. I could nod my head "yes" without help.	❑	❑	❑	❑
28. I could lift my head up when I lay on my back without help.	❑	❑	❑	❑
29. I could balance while sitting on the toilet without help.	❑	❑	❑	❑
30. I could wipe/clean myself after using the toilet without help.	❑	❑	❑	❑

DMD-LMS Changing and Maintaining Body Position Scoring Structure 1.1

Item	Max Score	With No Difficulty	With Some Difficulty	With A Lot of Difficulty	Can't Do
Sit down on a chair.	2	2	1	1	0
Stand up from a chair	2	2	1	1	0
Bend over seated and pick something off the floor.	3	3	2	1	0
Bend over standing and pick something off the floor.	2	2	1	1	0
Get into bed.	2	2	1	1	0
Get out of bed.	2	2	1	1	0
Change positions in bed.	3	3	2	1	0
Get up from the floor.	2	2	1	1	0
Get in and out of an adultsized chair.	2	2	1	1	0
Get into and out of a chair without using the arms.	2	2	1	1	0
Get on and off a low chair.	3	3	2	1	0
Climb into a bathtub with no tub bench.	2	2	1	1	0
Climb out of a bathtub with no tub bench.	2	2	1	1	0
Transfer to a tub bench.	2	2	1	1	0
Transfer from a tub bench.	2	2	1	1	0
Stand on tiptoes to reach for something.	2	2	1	1	0
Turn my head all the way to the side.	2	2	1	1	0
Turn myself during the night.	2	2	1	1	0
Stand while washing my hands and face at a sink.	2	2	1	1	0
Get in and out of a low vehicle (car).	2	2	1	1	0
Get in and out of a high clearance vehicle (SUV or truck)	3	3	2	1	0
Nod my head "yes".	1	1	1	1	0

DMD-LMS Changing and Maintaining Body Position Score Sheet 1.1

Linearized Score	Raw Score
100.0	47.0
94.0	46.0
90.0	45.0
86.9	44.0
85.0	43.0
83.3	42.0
81.7	41.0
80.0	40.0
78.5	39.0
77.0	38.0
75.6	37.0
74.3	36.0
73.0	35.0
71.7	34.0
70.4	33.0
69.2	32.0
68.0	31.0
66.8	30.0
65.7	29.0
64.5	28.0
63.4	27.0
62.3	26.0
61.2	25.0
60.1	24.0
59.0	23.0
57.9	22.0
56.9	21.0
55.8	20.0
54.7	19.0
53.6	18.0
52.5	17.0
51.4	16.0
50.3	15.0
49.2	14.0
48.0	13.0
46.8	12.0
45.6	11.0
44.3	10.0
43.0	9.0
41.6	8.0
40.0	7.0
38.5	6.0
36.3	5.0
33.5	4.0
29.5	3.0
25.0	2.0
18.0	1.0
0.0	0.0

Carrying, Moving and Handling Objects				
In the past 7 days:	**1. With no difficulty**	**2. With some difficulty**	**3. With a lot of difficulty**	**4. Could not do it**
1. I could use my hands.	❑	❑	❑	❑
2. I could cover my nose when sneezing without help.	❑	❑	❑	❑
3. I could brush my teeth without help.	❑	❑	❑	❑
4. I could cut a piece of paper in half with scissors without help.	❑	❑	❑	❑
5. I could dial and text on a cell phone without help.	❑	❑	❑	❑
6. I could cut up different textures of food without help.	❑	❑	❑	❑
7. I could turn doorknobs without help.	❑	❑	❑	❑
8. I could button up (a shirt for example) without help.	❑	❑	❑	❑
9. I could pick up a gallon of milk with one hand and set it on the table without help.	❑	❑	❑	❑
10. I could take a book out of a bag on my lap without help.	❑	❑	❑	❑
11. I could fasten a zipper without help.	❑	❑	❑	❑
12. I could feed myself a meal without help.	❑	❑	❑	❑
13. I could drink from a half-full glass without a straw without help.	❑	❑	❑	❑
14. I could hold a full cup of water in my hand without help.	❑	❑	❑	❑
15. I could hold a plate full of food without help.	❑	❑	❑	❑
16. I could lift heavy books without help.	❑	❑	❑	❑
17. I could turn a light switch on/off on the wall at a standard height without help.	❑	❑	❑	❑
18. I could take money from a wallet from my pocket to pay for something without help.	❑	❑	❑	❑
19. I could open the rings in school binders without help	❑	❑	❑	❑
20. I could open a can of soda without help.	❑	❑	❑	❑
21. I could open a pack of chips (crisps) without help.	❑	❑	❑	❑
22. I could open a drawer without help.	❑	❑	❑	❑
23. I could open a fridge door without help.	❑	❑	❑	❑
24. I could pull open heavy doors without help.	❑	❑	❑	❑
25. I could push open heavy doors without help.	❑	❑	❑	❑
26. I could open a jar that has never been opened before without help.	❑	❑	❑	❑
27. I could open a jar that has been opened before without help.	❑	❑	❑	❑
28. I could open small containers like snack bags or vitamins without help. (regular screw top)	❑	❑	❑	❑
29. I could turn the pages of a book without help.	❑	❑	❑	❑
30. I could bring a phone to my ear without help.	❑	❑	❑	❑
31. I could pick up a pen from the floor without help.	❑	❑	❑	❑
32. I could pick up small objects from the table without help.	❑	❑	❑	❑
33. I could pour a drink from a half-liter bottle without help. LINKS:	❑	❑	❑	❑
34. I could pour a half gallon of milk without help.	❑	❑	❑	❑
35. I could press buttons on an elevator without help.	❑	❑	❑	❑

36. I could pull up my trousers after using the toilet without help.	❑	❑	❑	❑
37. I could put a jacket on without help.	❑	❑	❑	❑
38. I could reach out to shake hands without help.	❑	❑	❑	❑
39. I could scratch my head without help.	❑	❑	❑	❑
40. I could screw the cap off a bottle that has not been opened before without help.	❑	❑	❑	❑
41. I could sign my name without help.	❑	❑	❑	❑
42. I could use a TV remote control without help.	❑	❑	❑	❑
43. I could type on a computer with a keyboard without help.	❑	❑	❑	❑
44. I could use a knife to spread butter or jelly on bread without help.	❑	❑	❑	❑
45. I could use a computer mouse without help.	❑	❑	❑	❑
46. I could use a computer track pad without help.	❑	❑	❑	❑
47. I could wash my hands without help.	❑	❑	❑	❑
48. I could wipe my nose without help.	❑	❑	❑	❑
49. I could write several lines without help.	❑	❑	❑	❑
50. I could play video games with a hand-held controller without help.	❑	❑	❑	❑

DMD-LMS Carrying Moving Handling Objects Scoring Structure 1.1

Item	Max Score	Dimension	With No Difficulty	With Some Difficulty	With A Lot of Difficulty	Can't Do
Use my hands.	3	Distal/Hand	3	2	1	0
Cover my nose when sneezing.	3	Mid/Low Force	3	2	1	0
Brush my teeth.	2	Mid/Low Force	2	1	1	0
Cut a piece of paper in half with scissors.	3	Distal/Hand	3	2	1	0
Dial and text on a cell phone.	2	Distal/Hand	2	1	1	0
Turn doorknobs.	2	Mid/Low Force	2	1	1	0
Pick up a gallon of milk with one hand and set it on the table.	3	Upper/High Force	3	2	1	0
Take a book out of a bag on my lap.	3	Upper/High Force	3	2	1	0
Fasten a zipper.	2	Mid/Low Force	2	1	1	0
Feed myself a meal.	2	Mid/Low Force	2	1	1	0
Drink from a half-full glass without a straw.	2	Mid/Low Force	2	1	1	0
Hold a full cup of water in my hand.	2	Mid/Low Force	2	1	1	0
Hold a plate full of food.	3	Mid/Low Force	3	2	1	0
Lift heavy books.	3	Upper/High Force	3	2	1	0
Turn a light switch on/off on the wall at a standard height.	2	Mid/Low Force	2	1	1	0
Take money from a wallet from my pocket.	2	Mid/Low Force	2	1	1	0
Open the rings in school binders.	2	Upper/High Force	2	1	1	0
Open a can of soda.	3	Upper/High Force	3	2	1	0
Open a drawer.	3	Mid/Low Force	3	2	1	0
Pull open heavy doors.	3	Upper/High Force	3	2	1	0
Push open heavy doors.	3	Upper/High Force	3	2	1	0
Open a jar that has never been opened before.	3	Upper/High Force	3	2	1	0
Open small containers like snack bags or vitamins.	3	Upper/High Force	3	2	1	0
Turn the pages of a book.	3	Distal/Hand	3	2	1	0
Pick up a pen from the floor.	2	Mid/Low Force	2	1	1	0
Pour a drink from a half-liter bottle.	2	Upper/High Force	2	1	1	0
Press buttons on an elevator.	3	Mid/Low Force	3	2	1	0
Pull up my trousers after using the toilet.	2	Upper/High Force	2	1	1	0
Scratch my head.	3	Mid/Low Force	3	2	1	0
Use a TV remote control.	3	Distal/Hand	3	2	1	0
Use a knife to spread butter or jelly on bread.	3	Mid/Low Force	3	2	1	0
Use a computer mouse.	3	Distal/Hand	3	2	1	0
Wash my hands.	2	Mid/Low Force	2	1	1	0

DMD-LMS Carrying Moving Handling Objects Score Sheet 1.1

Linearized Score	Raw Score
108.00	85.0
102.00	84.0
98.00	83.0
94.00	82.0
91.00	81.0
88.50	80.0
86.90	79.0
85.40	78.0
84.10	77.0
82.80	76.0
81.50	75.0
80.40	74.0
79.20	73.0
78.20	72.0
77.10	71.0
76.10	70.0
75.20	69.0
74.20	68.0
73.30	67.0
72.40	66.0
71.60	65.0
70.70	64.0
69.90	63.0
69.10	62.0
68.35	61.0
67.60	60.0
66.85	59.0
66.10	58.0
65.40	57.0
64.70	56.0
64.00	55.0
63.35	54.0
62.70	53.0
62.00	52.0
61.35	51.0
60.70	50.0
60.10	49.0
59.45	48.0
58.85	47.0
58.20	46.0
57.60	45.0
57.00	44.0
56.40	43.0
55.80	42.0
55.20	41.0
54.65	40.0
54.05	39.0
53.45	38.0
52.90	37.0
52.30	36.0
51.70	35.0
51.15	34.0
50.55	33.0
50.00	32.0
49.40	31.0
48.80	30.0
48.20	29.0
47.65	28.0
47.05	27.0
46.45	26.0
45.85	25.0
45.25	24.0
44.60	23.0
44.00	22.0
43.35	21.0
42.70	20.0
42.05	19.0
41.40	18.0
40.70	17.0
40.00	16.0
39.30	15.0
38.55	14.0
37.80	13.0
37.00	12.0
36.20	11.0
35.30	10.0
34.40	9.0
33.40	8.0
32.30	7.0
31.00	6.0
29.20	5.0
27.00	4.0
23.50	3.0
20.00	2.0
15.00	1.0
0.00	0.0