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Concordance of patient-reported outcomes measurement information system (PROMIS) questionnaires between caregivers and children with DMD

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PROMIS includes patient-reported outcomes that quantify the impact of disease on physical, social, or cognitive function. While self-reporting is considered the gold standard, caregivers frequently report on behalf of patients in many disease states, including Duchenne muscular dystrophy (DMD). PROMIS Parent Proxy (PP) questionnaires are being used in DMD studies, with caregivers rating their child's functional ability. Agreement between caregiver and child on the PROMIS Mobility and Upper Extremity (UE) questionnaires remains largely unknown for the DMD community. This analysis evaluated the appropriateness of using caregivers of patients with DMD as proxies for these questionnaires. PROMIS Mobility (v1.0; n=41) and UE (v1.0; n=94) were administered to dyads at one USA health care center. Inter-rater reliability between caregivers and children on overall PROMIS raw scores was assessed using intraclass correlation coefficient (ICC). Degree of agreement between caregiver and child responses on individual PROMIS items was assessed using Gwet coefficient. ICC (95% CI) for overall PROMIS Mobility and UE scores are moderate 0.555 (0.304–0.735) and poor 0.413 (0.231–0.567), respectively. Caregiver and child ratings for each item showed substantial to perfect agreement for 10/23 (43%) and moderate agreement for 8/23 (35%) Mobility items. For UE, 17/29 items (59%) demonstrated substantial to perfect agreement and 7/29 (24%) moderate. Poor ICC observed for the UE overall score is likely attributable to differences in how corresponding items are scored between the PP and child questionnaire versions. Agreement was stronger within caregiver/child dyads when assessed item by item for both questionnaires, indicating substantial to perfect concordance for most items. This analysis found caregivers and their children have related yet unique perspectives. Based on these findings, caregivers can be considered suitable proxies for children when rating PROMIS Mobility and UE function.

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Accurate translation from Performance of Upper Limb (PUL) version 1.2 to 2.0 in Duchenne muscular dystrophy (DMD): a machine learning algorithm

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The Performance of Upper Limb (PUL) module measures upper limb motor performance in ambulant and non-ambulant DMD. Two versions of the PUL exist: the originally developed version (PUL 1.2) and a revised version (PUL 2.0). While PUL 2.0 is currently in broader use in clinical trials and practice, prior studies contain extensive historical data on PUL 1.2. A cross-walk between PUL 1.2 and PUL 2.0 is needed to make full use of historical data, e.g., for contextualization of outcomes in clinical trials and across periods of natural history. In this study, using data from 1137 visits from 208 patients in the DMD Italian Group database, we applied machine learning (LASSO) to predict PUL 2.0 total and domain scores from concurrently measured PUL 1.2 item scores. Models were fit in a training sample (858 visits, 166 patients) and predictions were evaluated in a held-out validation sample (279 visits, 42 patients). Mean age of patients at 1st visit in the training sample was 11.4 years; 64% of included patients were ambulatory at their 1st visit. In the held-out sample, PUL 1.2 item scores explained 98% of the variation in PUL 2.0 total scores, and the prediction error was 1.76 units; explained variation exceeded 95% for the shoulder, mid, and distal domain scores shoulder with prediction errors <1.1 units. These results are promising for accurate prediction of PUL 2.0 total scores from PUL 1.2 item scores and harmonization of PUL outcomes across multiple data sources. Future analyses are needed to benchmark prediction accuracy against the standard error of measurement of PUL 2.0 and to validate performance in an external data source.

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Centiles by age for the North Star ambulatory assessment and the associated timed items in glucocorticoid treated boys with Duchenne muscular dystrophy

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Clinical heterogeneity in motor function trajectory in boys with Duchenne Muscular Dystrophy (DMD) represents a significant hurdle to clinical monitoring. With this study we present the centiles by age for the North Star Ambulatory Assessment (NSAA), 10m walk/run (10MWR) and rise from floor (RFF) in corticosteroids (CS) treated boys with DMD, between 5 and 16 years. Participants were included from the NorthStar registry if they had genetically confirmed DMD, had initiated CS and were not enrolled in a clinical trial. Assessments where the participant completed the NSAA (all 17 items) or was recorded as non-ambulatory were included. Non-ambulant participants were assumed to have a NSAA total score of 0. The RFF and 10MWR velocities (RFFV and 10MWRV) were imputed as 0 if the corresponding item score was 0. The NSAA centiles were fitted using a GAMLSS model with a 0-1 inflated logit Normal family; a 0-inflated logit Normal was fitted to the RFFV and 10MWRV to generate the RFF and 10MWR centiles. We analysed 3987 NSAA assessments from 826 participants aged between 5 and 16 years. Of these, 27%, 46% and 30% of the NSAA, RFFV and 10MWRV values were imputed as 0 respectively. We visualise the 10th, 25th, 50th, 75th and 90th centiles for all three outcomes. The NSAA centiles show a peak score of 20, 26 and 30, with loss of ambulation at 10.7, 12.2 and 14.3 years for the 25th, 50th and 75th centiles, respectively, with the peaks occurring earlier in the lower centiles. The centiles show loss of rise from floor at 8.6, 10.1 and 11.9 years and a 10MWR of 0 at 8.9, 10.3 and 13.8 years for the 25th, 50th and 75th centiles, respectively. The NSAA, 10MWR and RFF centiles may provide insights for clinical monitoring of DMD boys, particularly in the late ambulatory stage where participants are uniformly declining. Future work will look to validate the centiles in national and international natural history cohorts and trial placebo arms.

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Digital outcome captures longitudinal degradation of upper-limb function in non-ambulant patients affected by neuromuscular disorders

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Precise upper limb function quantification is challenging but essential to judge efficacy of treatments for patients living with neuromuscular disorders. Lack of robust motor function endpoints has limited the number of clinical programs in this population and thus the access to innovative medication. The need for improving current outcomes and exploring innovative approaches, like wearable devices or video-based home assessment is consensual in the community. For ambulant patients affected by Duchenne muscular dystrophy (DMD), the EMA has recently qualified the first digital outcome as a primary endpoint in clinical trials: the stride velocity 95th percentile (SV95C). In this article we explore the possibility of using a similar outcome by measuring the motor function of the upper limbs in a population of non-ambulant patients affected with DMD and spinal muscular atrophy (SMA). Data for patients living with DMD was recorded in a natural history study including non-ambulant patients (N=16, age=13 ± 3 [8-19]). Comparison will be provided with data collected on non-ambulant patients affected by SMA. In both cases, patients wear two magneto-inertial measurement units, one on their wrist and one on their wheelchair. The digital outcome of interest quantifies the gestures where the patients develop the maximum energy with their upper limb, during the monthly recording period. It is called the 99th percentile of the total effort (TE99C). We compare the TE99C to the Performance of Upper Limb (PUL) scale in DMD and to the Motor Function Measurement (MFM32) in SMA. We evaluated the decrease of respectively PUL and MFM32 in the DMD and SMA studies and compared it to the evolution of TE99C. We will present the correlation between TE99C and the reference outcomes, as well as the longitudinal evolution of the different endpoints, in order to determine if the TE99C can constitute a valuable candidate to assess upper-limb motor function in neuromuscular disorders.

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