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## Implementation of Motor Function Measure score percentile curves - Predicting motor function loss in Duchenne muscular dystrophy

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### A B S T R A C T

The Motor Function Measure is a standardized scoring system to evaluate motor function and monitor disease progression in neuromuscular diseases such as Duchenne muscular dystrophy. There are no available reference percentile curves for this measure. The aim of this analysis was to generate Motor Function Measure percentile curves for ambulant and non-ambulant patients affected by Duchenne Muscular Dystrophy, providing the opportunity to better evaluate the status and progression of an individual patient compared to other patients in the same age group. Data of patients aged between 6 and 15 years (819 measurements) was obtained from the international Motor Function Measure database. Age-dependent percentile curves were estimated using a “Generalized additive model for location, scale and shape” as suggested by the World Health Organisation Multicentre Growth Reference Study Group. Percentile curves for the Motor Function Measure total score and its sub-scores for patients with and without treatment with glucocorticoids are presented. Mean scores decline with age. Patients treated with glucocorticoids have higher mean values compared to glucocorticoid-naïve patients at the same age. The percentile curves with the online tool extend the clinical utility of the Motor Function Measure by facilitating the interpretation of individual standing and disease progression.

#### Keywords:

Muscular dystrophy  
Duchenne  
Neuromuscular diseases  
Disease progression  
Motor skills disorder  
Reference values

### 1. Introduction

Duchenne muscular dystrophy (DMD) is the most frequent neuromuscular disorder in paediatric neurology, affecting about 1 of 5800–6000 male births [1]. The disease is characterized by a subsequent decline of motor function, including loss of ambulation, which varies significantly between individuals [2]. Treatment with glucocorticoids is proven to be beneficial but effectiveness is limited and there are substantial side effects. Therefore, there is still an unmet medical need for an effective treatment in DMD and the

evaluation of new treatment options is urgent. Nevertheless, the conduct of clinical trials with the valid assessment of potential beneficial medical compounds in patients with DMD is difficult for many reasons [3,4]. Apart from a wide phenotypical spectrum in patients with DMD, in young affected boys motor development and motor decline are overlapping. After an initial phase of improvement, a plateau phase is reached followed by motor decline. This is an individual process and therefore some boys of the same age are still gaining motor abilities when others already show a decline in motor function. Being able to compare the development of individual motor function within a historical group of glucocorticoid treated and –untreated patients of different ages would greatly help to find subtle changes from a trajectory line. This could essentially help patients by facilitating individual clinical care, as individual changes in motor performance are clearly visible during

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## Abbreviations

|     |                             |
|-----|-----------------------------|
| D1  | Dimension 1                 |
| D2  | Dimension 2                 |
| D3  | Dimension 3                 |
| DMD | Duchenne Muscular Dystrophy |
| MFM | Motor Function Measure      |

the entire course of disease. Furthermore, it could serve as a useful tool to select boys with similar curves of evolution in order to demonstrate drug efficacy in clinical studies in a sub-population of patients with DMD.

Therefore, we suggest the use of percentile curves of the Motor Function Measure (MFM) in boys with DMD. The MFM is a well-established test, which is validated in patients from 6 to 60 years and is suitable for both ambulant and non-ambulant patients [5]. Even though there are several clinical scores assessing motor function in DMD, we chose this measure as it is widely used as an important endpoint in clinical studies and in clinical practice. It is composed of three different dimensions; dimension 1 (D1) for standing and transfers, dimension 2 (D2) for axial and proximal motor capacity and dimension 3 (D3) for the distal motor capacity. Using the MFM in serial assessments, a profile of physical impairment can be established to document changes over time [6]. By plotting the MFM scale versus age Vuillerot et al. have shown a mean decrease of 17.2% of the D1 in ambulant DMD-patients between the age of 6 and 12 years. Loss of ambulation usually occurs within 1 year when reaching the cut-off of 40% D1 or 70% total score [5]. These are important findings for a cohort of patients with DMD but the individual course is left out of consideration.

The aim of this analysis was to generate MFM percentile curves for ambulant and non-ambulant patients with DMD providing the opportunity for medical caregivers, physiotherapists and clinical researchers to improve the evaluation of status and progression of motor function in individual patients or patient groups. Percentile curves for patients with and without corticosteroid treatment are presented.

## 2. Material and methods

The study is an observational, retrospective, cohort study. Consent of participants providing data to the database was obtained according to the Declaration of Helsinki and local ethics committee in Switzerland approved the analysis of data.

### 2.1. Motor Function Measure

The Motor function measure (MFM) scale was created to assess and monitor severity and progression of motor function in children and adults with neuromuscular disorders [7]. It consists of 32 items that are grouped in three functional domains. Domain 1 (D1): standing position and transfer includes 13 items; Domain 2 (D2): axial and proximal motor function includes 12 items and; Domain 3 (D3): distal motor function comprises 7 items. Dependent on the assessed persons maximal abilities, the specific items are graded with a number between 0 (= cannot initiate the exercise or maintain the starting position) and 3 (performs the task fully and normally). The total score as well as its sub-scores are depicted as a percentage of the maximal possible score; the higher the total score, the less severe the impairment.

### 2.2. MFM registry

Data of patients with DMD was obtained retrospectively from the international MFM registry (<https://mfm-nmd.org/the-mfm-database/?lang=en>). The database was established in 2007 in Montpellier, France and is authorized by the French Data Protection Authority (CNIL). Since, data of MFM from children and adults with suspected or identified neuromuscular disorders were recorded by registered clinicians, after patients were informed locally about the registry and have given informed consent. Only MFM data assessed by specifically trained physiotherapists is evaluated in this trial. To date, 44 centres from France, Belgium, Switzerland, Argentine and Lebanon have contributed.

### 2.3. Patients

MFM scores of children with a diagnosis of DMD recorded in the MFM registry before July 2019 were analysed retrospectively. Inclusion criteria were (i) definite diagnosis of DMD (molecular biology or muscle biopsy), (ii) male gender, (iii) an age between 6 and 15 years at the conduct of the MFM and (iv) a minimum of two MFM tests at two different time points. We identified 146 patients who fulfilled the inclusion criteria.

### 2.4. Descriptive statistics

The MFM total score and its sub-scores (D1, D2, D3) are presented graphically (E-Fig. 1). For the MFM sub-score D1, representing standing and walking, the number and proportion of patients with loss of free ambulation is presented as Kaplan-Meier curve by glucocorticoid use and age groups (E-Fig. 2). The age groups include the lower but not the upper boundary (i.e. 6 – 7 year includes patients aged 6 or more but younger than 7).

### 2.5. Age-dependent percentile curves

Age-dependent percentile curves are estimated using a “Generalized additive model for location, scale and shape” as suggested by the WHO Multicentre Growth Reference Study Group using the R-package *gamlss* software [8,9]. The MFM total score as well as all MFM sub-scores were assumed to follow a beta inflated distribution, since the score as well as the sub-scores provide values between zero and one hundred including the endpoints of the range. Thus, data was divided by 100 in order to transform the range to 0–1. Age was included as fixed effect using a P-spline with 3° of freedom; patient ID was included as random effect.

## 3. Results

### 3.1. Group characteristics

A total of 789 eligible MFM measurements of 146 ambulant and non-ambulant patients with DMD were identified in the registry at the time of analysis in July 2019. 61 boys were ambulant at the time of first MFM registered. 67 boys were steroid-naïve over the whole observation period. The number of MFM measurements per patient ranged from 2 in 37 patients to 17 in one patient. The median number of measurements was 4.

Time intervals within two consecutive MFM ranged from two days to 2388 days (6.5 years). The median time interval between the MFM tests are 6.6 months (1st quartile 5.5 months; 3rd quartile 11.9 months). 388 measurements were performed on boys whilst being treated with glucocorticoids for at least 6 months (= patients treated with corticosteroids), 305 measurements were performed on glucocorticoid-naïve patients and 96 on patients with

corticosteroid treatment for less than 6 months (= patients without corticosteroids).

### 3.2. Descriptive statistics

MFM total score and its sub-score values in patients with DMD decline with age. We analysed data separately for patients with and without glucocorticoid treatment. Patients with DMD on glucocorticoids being treated for more than 6 months have higher mean total MFM values compared to patients without or short term glucocorticoid treatment at the same age. Similarly, mean MFM sub-scores (D1, D2, D3) are higher in patients affected by DMD with glucocorticoid use compared to patients without treatment. Patterns of motor function decline are comparable in the MFM sub-scores compared to the total score. However, the decline of performance starts earlier in life for the D1 sub-score than the total MFM score, while the decline of the D3 sub-score starts later than the decline observed for the total MFM score (E-Fig. 1).

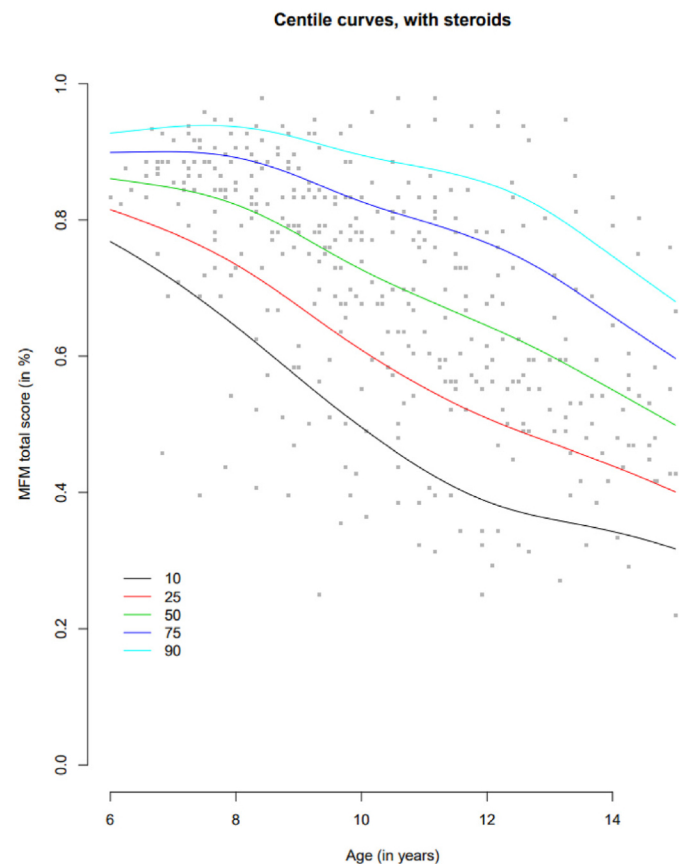
In E-Fig. 2 the number and proportion of patients with loss of ambulation is presented with a Kaplan-Meier curve by anytime use of steroids. The proportion of patients with total loss of ambulation at any age is lower in the group treated with glucocorticoids compared to the group of patients without glucocorticoid treatment.

### 3.3. Treatment-dependent percentile curves

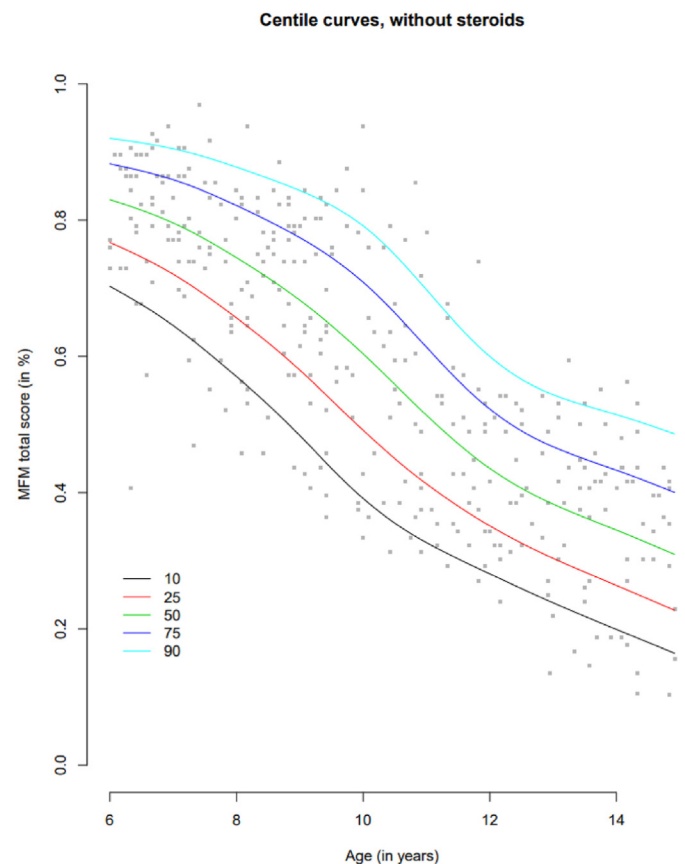
Percentile curves for patients with DMD were generated for the

total MFM score and the MFM sub-scores D1, D2 and D3 (Fig. 1 and 2). These percentile curves were modelled separately for patients with and without standard treatment of glucocorticoids. MFM measurements performed on glucocorticoid-naïve patients and on patients with corticosteroid treatment for less than 6 months were allocated to the non-corticosteroid-treated group. Measurements performed on boys whilst being treated with glucocorticoids for at least 6 months were allocated to the corticosteroid treated group. Therefore, MFM measurements of individual patients could switch groups over time. The upper, middle, and lower curves represent 10%, 25%, 50%, 75% and 90% percentiles. Fig. 1 shows the percentile curves for patients with glucocorticoid treatment for the MFM total score, Fig. 2 for children without glucocorticoid treatment. Between Figs. 1 and 2 a clear difference in the shape of the percentile curves is seen. In boys without corticosteroid treatment we see a nearly linear and parallel motor decline that slows around the age of eleven. In corticosteroid treated boys the disease course is more stable until the age of 12. Thereafter, the patients on the higher percentile curves comparatively accelerate in motor decline. The percentile curves for the MFM sub-scores D1, D2, and D3 for DMD groups with and without glucocorticoids are shown in Fig. 3.

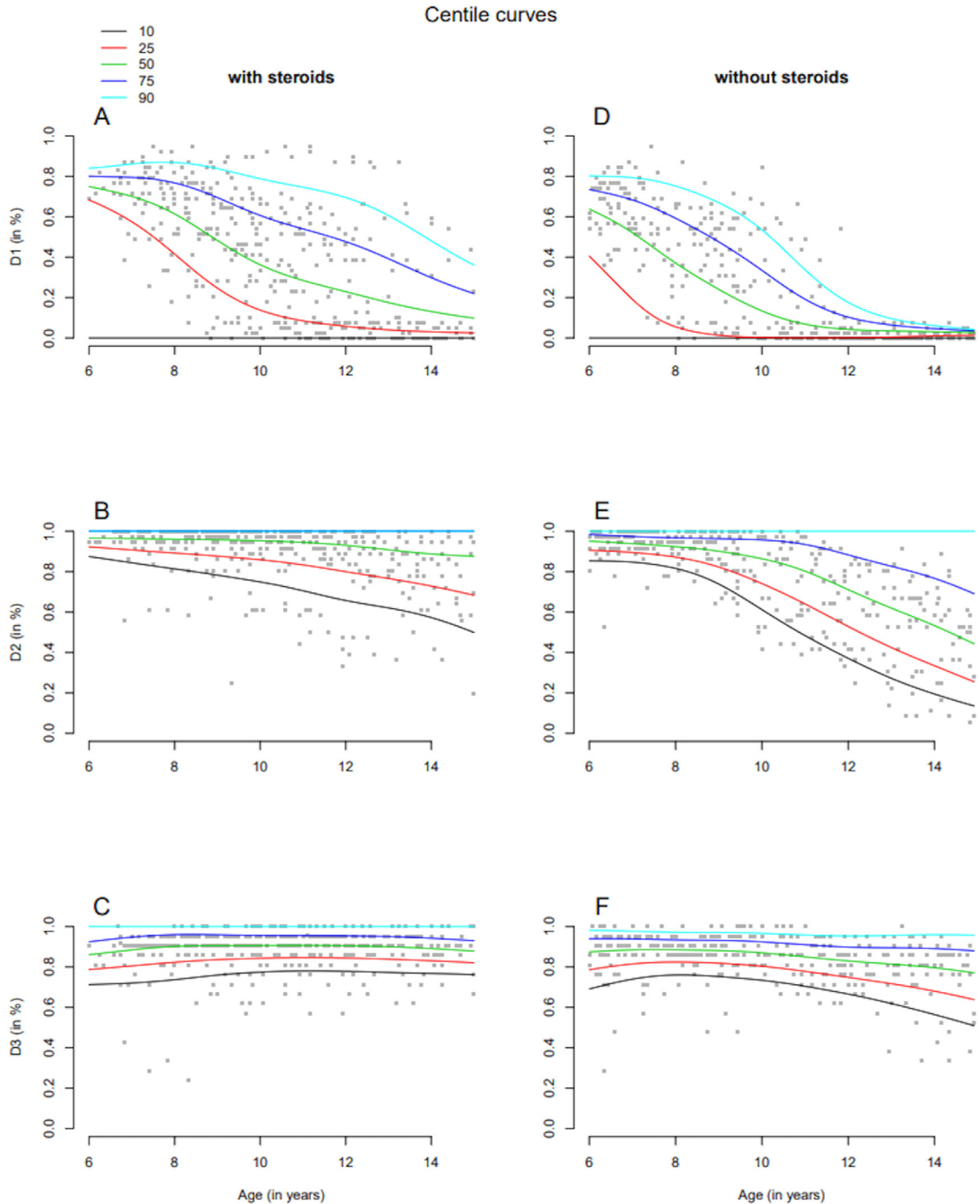
To simplify the evaluation we have created an online tool to calculate the percentile rang of an individual DMD assessment that can be used by caregivers and involved medical staff: <https://mfm-nmd.org/calculation-of-mfm-percentiles-in-dmd/?lang=en> Age, use of corticosteroids and MFM total and sub-score values are the parameters needed to calculate percentiles.



**Fig. 1.** MFM total score percentile with corticosteroids. Motor function measure total score percentile curves for patients with DMD treated with glucocorticoids. The upper, middle, and lower curves represent 10%, 25%, 50%, 75% and 90% percentiles.



**Fig. 2.** MFM total score without corticosteroids. Motor function measure total score percentile curves for patients with DMD without glucocorticoid treatment. The upper, middle, and lower curves represent 10%, 25%, 50%, 75% and 90% percentiles.



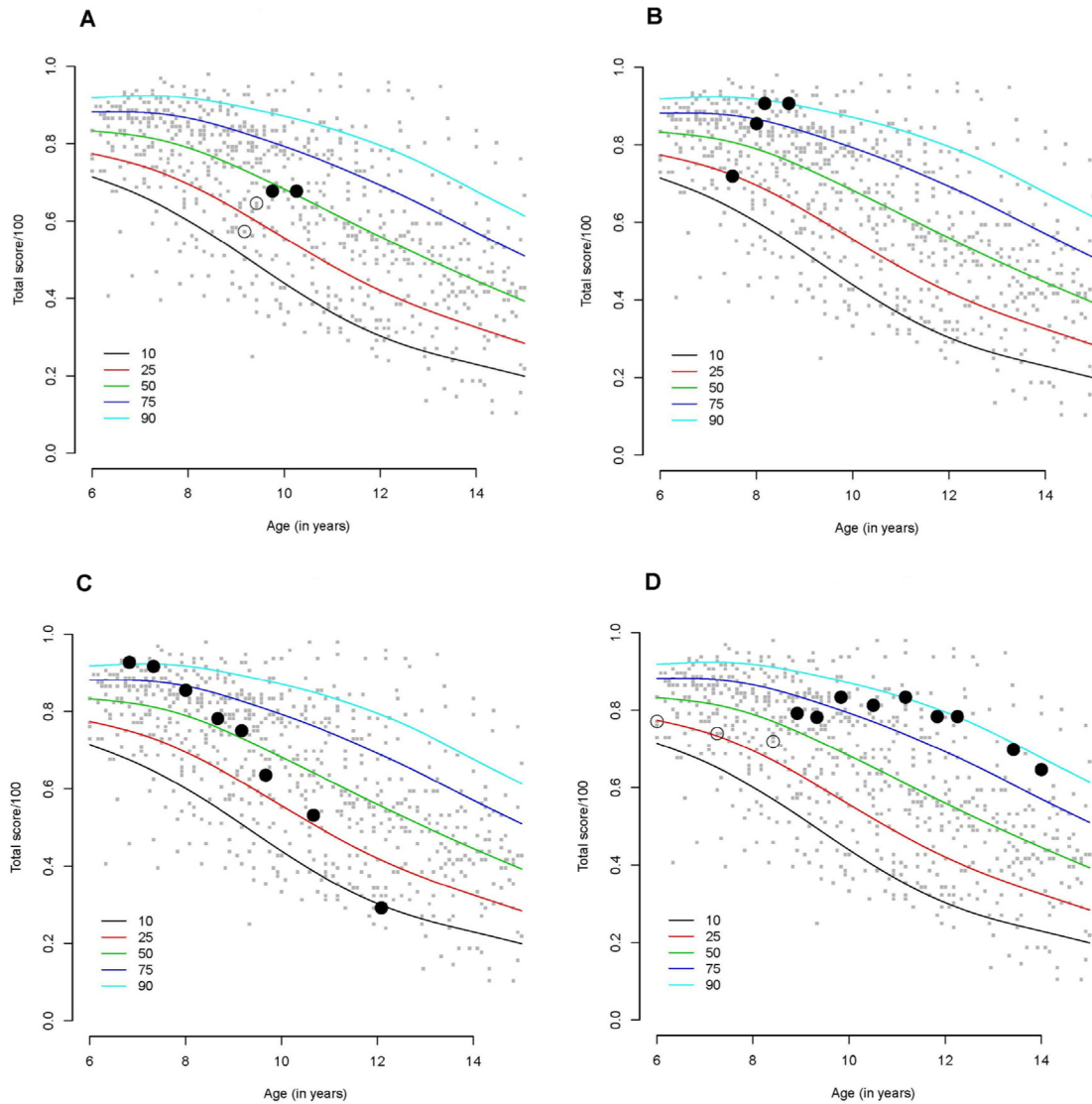
**Fig. 3.** Centile curves for MFM D1, D2, D3 sub-scores in patients with and without corticosteroids. Percentile curves for patients with DMD under glucocorticoid treatment for the MFM sub-scores D1 (A), D2 (B), and D3 (C) and patients with DMD without glucocorticoid treatment for the MFM sub-scores D1 (D), D2 (E), and D3 (F) are presented.

### 3.4. Individual MFM courses

The MFM courses of individual patients with DMD contributing MFM data to generate the percentile curves were additionally assessed. For each patient all MFM total data points are plotted on the same percentile curves irrespective of a change in glucocorticoid intake. Fig. 4 shows illustrating examples of MFM D1, arbitrarily chosen by the corresponding author (PH). Full data is available online.

## 4. Discussion

Up to date no percentile curves for the MFM were available, with the MFM mainly being investigated for reliability as an outcome parameter in clinical DMD trials [10]. The implementation of the percentile curves with online accessibility from the MFM homepage allows for medical care givers and physiotherapists a better evaluation of motor function of individual patients with DMD. Further, each patient can be compared to other same aged patients



**Fig. 4.** Individual MFM courses.

Arbitrarily chosen MFM total score courses of 4 individual patients with DMD to highlight individual disease courses. Empty circles indicate MFM scores at time points without corticosteroid treatment; full circles indicate MFM scores under treatment with corticosteroids. A and B illustrate similar curves of evolution with gain and stabilisation of motor function at different ages. C illustrates early downward crossing of percentiles despite good motor performance at a young age and D illustrates a positive effect of corticosteroid treatment.

at one point in time and their data can be analysed for change in function over time as previously achieved for a patient population with cerebral palsy [11]. Using MFM percentile curves, it will be possible to select patient groups with similar curves of evolution in order to demonstrate drug efficacy in a sub-population of patients with DMD. Currently, therapeutic investigations in children with DMD aim to include patients in a stable phase of motor performance after gaining and before losing motor function. This selection is mainly done by choosing patients according to a prespecified age and walking distance in the 6-Minute Walk Test. But looking at some individual courses of MFM development (Fig. 4) upward or downward or crossing of percentiles, indicating still ongoing gain or accelerated loss of motor function, occurs at individual age and motor performance. Therefore, formulating inclusion criteria for clinical trials according age and motor performance at a single time point might be misleading. The presented percentile curves might allow to better choose candidates for future clinical trials and allows smaller and shorter trials to be informative. Additionally, treatment effects of new medical treatment or physical therapy can be

visualised in every individual boy and assessed together in a cohort of patients. The MFM percentile curves can serve as assessment in the evaluation of motor function at every stage of the disease as the MFM reflects all dimensions of motor function (standing and transfers, axial and proximal motor capacity and distal motor capacity) independent from walking abilities. As previously stated by The Duchenne Regulatory Science Consortium [12] a clearer understanding of the variability in disease progression of patients with DMD is urgently needed. With increasing data it might become possible to evaluate MFM trajectories across same aged patients with different gene mutations.

Randomized controlled trials (RCTs) have shown that corticosteroid use in patients affected by DMD improve muscle function for up to six months and muscle strength for up to two years [13]. Our analysis confirmed that patients with DMD treated with corticosteroids show better muscle function and walking abilities compared to patients without corticosteroid use at the same age. We hypothesise that the different aspect of the MFM total score percentiles in corticosteroid treated and untreated boys with DMD

is due to a broad individual therapeutic effect of medical treatment. Therefore, the percentiles curves of both groups are not identical in shape but the percentile curves of corticosteroid treated patients show a “belly”, where at the age of 12 years maximal treatment effect in excellent responders is seen. The proportion of patients with total loss of ambulation at any age is lower in the group using glucocorticoids compared to the group of patients without glucocorticoid treatment. Comparable to the literature [14], patients with DMD without glucocorticoid treatment lose ambulation about two years earlier than corticosteroid using patients affected by DMD.

The major limitation of our analysis is the relatively small number of data used to construct these curves and the broad range of the number of MFM measures per patient. Therefore, the curves have to be interpreted carefully at the moment. We will update the curves on a regular basis aiming to achieve a larger data set and more reliable percentile curves in the future. Furthermore, there are different glucocorticoid treatment regimens that can influence these results. However, if more data is available, it will be easy to update the curves in order to get an even more accurate trajectory.

## 5. Conclusion

We believe that these online assessable MFM percentile curves provide a useful and easy applicable tool to monitor individual disease progression in children with DMD. With emerging new treatment options, the percentile curves will be an important aid to select patients with similar curves of progression for clinical trials and to monitor treatment effects on estimated evaluation of motor function.

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## Ethics approval

The data used in the present study required no extra clinical examinations, tests, or treatments than those given regularly. Participants (or their legal representatives) gave their signed informed consents to the collection, storage, and anonymous analysis of the data. Additionally, local ethical committee (Ethikkommission Nordwest-und Zentralschweiz) gave its approval for the re-use of biological material and health-related data for research in encrypted form.

## Declaration of competing interest

The authors state that they do not have any conflicts of interest to declare.

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