Health State Transition Probabilities for Duchenne Muscular Dystrophy (DMD): Estimation from Published Data

MSR33

James Signorovitch[1], Andres Gomez-Lievano[1], Michaela Johnson[1], Nathaniel Posner[2], Valeria Merla[2], Hanane Akbarnejad[1], Yidan Ma[1], Stephen Dukacz[3], Zainab Aslam[2], Paul Cislo[2], Joseph C. Cappelleri[2]

[1] Analysis Group, Inc., Boston, MA, USA, [2] Pfizer, Inc., New York, NY, USA, [3] Pfizer, Inc., Toronto, ON, Canada

Objective

To estimate the distribution of time spent in each health state before progressing to the next for a condensed version of HERCULES Natural History Model (NHM) in DMD

Conclusions

Drawing on heterogeneous sources of published data and using the cumulant method to bridge the data gaps, we obtained new estimates of health state transition probabilities for the HERCULES NHM of DMD. These new estimates were consistent with multiple published sources and represent improvements to the previous estimates.

The congruence between our estimates and multiple published sources support the use estimates from this health state model as a basis for cost-effectiveness analysis and health technology appraisals in DMD.

Presenting author:

Nathaniel Posner
Director, HTA, Value & Evidence Strategy
Pfizer, Inc., New York, NY, USA
Nathaniel.Posner@pfizer.com

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Introduction

- Duchenne Muscular Dystrophy (DMD) is a rare, progressive genetic disorder that causes muscle degeneration and weakness, starting in early childhood and leading to a deterioration of mobility, independence, and ultimately, early mortality.[1]
- To inform health economic decision-making, a NHM of DMD disease progression across eight health states has been developed based on input from clinicians, patients, and caregivers by Project HERCULES.[2]
- The HERCULES model estimates the lifetime DMD disease trajectory through ambulatory and non-ambulatory health states; results from the model are, in part, a basis for health economic models that assess the lifetime costs and benefits of DMD treatment.[3]
- Estimation of transition probabilities for the HERCULES model, i.e., the rates at which DMD patients progress through the different health states, is critical for appropriate use in decision making. Inaccurate transition probabilities can lead to inaccurate technology appraisals.
- Previous estimates using traditional methods do not align with published literature on key milestones in NH.[3]
- Traditional approaches to estimating transitional probabilities have been limited by the sparseness of longitudinal data representing health state transitions, which is a common challenge, especially in rare disease.

Methods

Data sources (**Table 1**)

- Published aggregate data for the distribution of ages represented in each health state.
- Published time-to-event curves for specific health state transitions, identified via targeted literature review.

NHM

- A condensed 5-state version of the HERCULES NHM was used in the present study (**Figure 1**), in which the levels of ventilation support were used to define states 3-5.
- The model assumes sequential progression through health states, with no backwards transitions between states (**Figure 2**).

Estimation of transition probabilities

- Four candidate distributions were evaluated: exponential, gamma, lognormal and Weibull.
- Parameter estimation was based on a method of moments approach, exploiting a statistical property of Markov models: the additivity of cumulants.[4]
- Empirical moments, e.g., mean and variance, for the distribution of times between each health state transition were calculated from aggregate data on the distribution of ages in each health state (see **Box 1**).
- Variance-covariance matrices were estimated by applying a bootstrap re-sampling procedure.

Model selected

- For each fitted model, the age distribution of each health state transition was simulated to predict survival curves for each key DMD milestone event. The predicted curves were compared to published Kaplan-Meier (KM) using the Cramer von-Mises (CvM) distance.[5]

Box 1. Calculations

- The cumulants $c_n(X)$ of a random variable X, where the subscript "n" denotes the "order" of the cumulant, characterize distinct properties of X, and can be estimated in terms of the statistical moments (see **Equations (1a)-(1d)**)

From moments to cumulants	
$c_1(X) = Mean[X]$	Equation (1a)
$c_2(X) = Var[X]$	Equation (1b)
$c_3(X) = Skewness[X] * Var[X]^{\frac{3}{2}}$	Equation (1c)
$c_4(X) = ExcessKurtosis[X] * Var[X]^2$	Equation (1d)

- The nth order cumulant of times spent within states, $c_n(D_k)$, can be deduced from the cumulants of ages of entry, since $T_{k+1} = T_k + D_k$ for any health state k (see **Figure 2**),
- and T_k is independent of D_k (Markov property), using the additivity of cumulants:

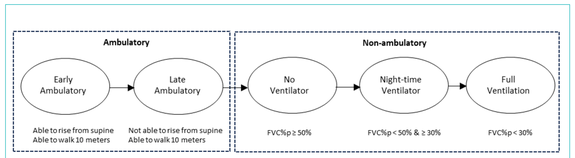
$$c_n(D_k) = c_n(T_{k+1}) - c_n(T_k) \qquad \text{Equation (2)}$$

- After computing the cumulants of the times between state transitions, $c_n(D_k)$, estimation of their statistical moments were computed using the same relations between cumulants and moments in **Equations (1a)-(1d)**.
- With the estimated moments of times between state transitions, their associated probability distributions were estimated for each health state using with the Method of Moments with four candidate parametric distributions (exponential, gamma, lognormal, Weibull).
- For each distribution function and health state, variance-covariance matrices were estimated applying a bootstrap re-sampling procedure.

Table 1: Data sources for summary age statistics and age-at-event curves for health states and DMD milestones

Study Name	Use case	Event outcome	Health state equivalent
Muntoni et al. 2013[6]	Deriving the moments of ages for states 1-4 (Table 2)	HERCULES health states	States 1-4
McDonald et al. 2018[7]	KM curve juxtaposition (Figure 3)	Loss of ability to stand from supine	State 2
McDonald et al. 2018[7]	KM curve juxtaposition (Figure 3)	Loss of ambulation	State 3
Bello et al. 2016[8]	KM curve juxtaposition (Figure 3)	Loss of ambulation	State 3
McDonald et al. 2018[7]	KM curve juxtaposition and derivation of moments for age of entry to state 5 (Table 2 and Figure 3)	Transition to FVC of 1L	State 5
Broomfield et al. 2021[9]	KM curve juxtaposition and derivation of moments for age of entry to Death (Table 2 and Figure 3)	Death	State 6
Broomfield et al. 2024[3]	KM curve juxtaposition (Figure 3)	HERCULES health states	States 2, 3, 5, 6

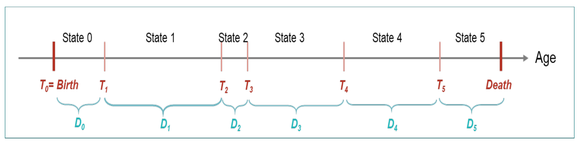
Figure 1: Health states and disease model used in the present study



Note: Death is the final state after Full Ventilation.

Abbreviations: FVC%p; Forced vital capacity percent predicted.

Figure 2: Times and ages associated with the transitions between states



Note: T_k denote "entry times" which are the ages at which patients enter a health state. D_k ($D_k = T_{k+1} - T_k$) denote "length of stay", "interarrival durations", or "sojourn times", which are the times spent within each state, and are mutually independent. The current study assumed patients enter the model through State 1 (Early Ambulatory) at birth, i.e., $T_1 = D_0 = 0$.

Results

- The estimated mean (standard deviation [SD]) duration times (in years) that patients spend within health states are 10.27 (2.42), 2.25 (2.02), 2.00 (2.23), 6.77 (5.46) and 8.23 (8.74) for states 1-5, respectively (**Table 2**).
- The best overall fit to the data was provided by the Weibull-based model, as quantified by the CvM distance between simulated age-at-event curves and published KM curves for equivalent DMD milestones (**Figure 3**). The estimated Weibull parameters are shown in **Table 3**.
- Simulated median transition ages in the Weibull-based model for key DMD milestones were 12.4 years (95% CI: 6.6, 19.0) for loss of ambulation, 20.4 years (95% CI: 11.1, 37.4) for start of full-time ventilation, and 27.6 years (95% CI: 14.1, 57.6) for death. These results are consistent with recent published literature.[7-11]
- Findings were similar across the gamma and lognormal distributions, with similar median ages at transition and alignment with published data. In contrast, models assuming an exponential distribution performed poorly and did not align with published data (**Figures 3** and **4**).

Table 2: Statistical moments characterizing time spent within health states

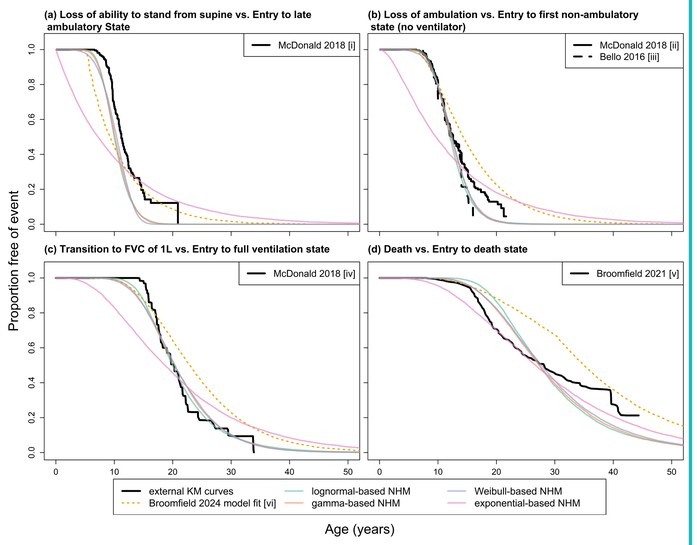
Health State	Mean Duration (years)	SD (years)	Skewness	Excess Kurtosis
Early Ambulatory	10.27	2.42	0.98	2.44
Late Ambulatory	2.25	2.02	-0.62	-8.97
No Ventilator	2.00	2.23	-0.16	-17.50
Night-time Ventilator	6.77	5.46	1.01	-3.06
Full Ventilation	8.23	8.74	-0.09	-3.10

Notes:
- Skewness quantifies a distribution's asymmetry. A 0 value denotes perfect symmetry (e.g., normal distributions). Typically, skewness within -1 to 1 suggests moderate asymmetry, while a skewness of 2 characterizes exponential distributions.
- Excess kurtosis, defined as kurtosis minus 3, gauges a distribution's tail weight relative to a normal distribution, which has an excess kurtosis of 0. Exponential distributions show a heavier tail with an excess kurtosis of 6.

Limitations

- This study relied on published aggregated data and a Markov model framework. Thus, the methods rely on several assumptions, including transition times between states are independent, health states are visited sequentially, no backward transitions are allowed, and the distribution of ages within each health state in the source data is representative and unbiased.

Figure 3. Juxtapositions of the fitted model assuming different distributions against benchmark KM curves from the published literature



For each DMD milestone (a-d), the distribution of ages entering a given health state from simulating the exponential-, gamma-, lognormal-, and Weibull-based models for the corresponding age-at-event are shown in red, orange, green, and violet colors, respectively. The curve from Broomfield 2024 model fit is shown as dotted line in yellow color. The KM curves from the published sources are shown as a black curve.

Notes:
[i] McDonald et al. (2018), Fig 1C, pooled data for patients with ≥1 year and <1 month of glucocorticoid use.
[ii] McDonald et al. (2018), Fig 1E, pooled data for patients with ≥1 year and <1 month of glucocorticoid use.
[iii] Bello et al. (2016), Fig 2, data for patients with other deletions mutations.
[iv] McDonald et al. (2018), Fig 4, data for patients who lost ambulation at ages 10-13 years.
[v] Broomfield et al. (2021), Fig 2B, data for patients born post-1990.
[vi] Broomfield et al. (2024), Fig 2, estimates from the fitted HERCULES NHM.

Table 3: Estimated parameters (alpha and beta) and standard errors (SE) for Weibull distribution characterizing the duration times (in years) spent within health states

Health State	Estimated alpha (SE)	Estimated beta (SE)
Early Ambulatory	4.85 (0.02)	11.20 (0.14)
Late Ambulatory	1.12 (0.08)	2.34 (0.40)
No Ventilator	0.90 (0.15)	1.90 (0.82)
Night-time Ventilator	1.25 (0.11)	7.27 (1.55)
Full Ventilation	0.94 (0.09)	8.01 (1.86)

Note: Standard errors were computed from the diagonal elements of the variance-covariance matrix estimated through bootstrap resampling method.

Figure 4. Survival curves of transition ages per health state resulting from assuming different probability distributions for time between transitions