AN EVIDENCE-BASED EVENT MODEL FOR DUCHENNE MUSCULAR DYSTROPHY IN THE UNITED STATES

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BACKGROUND

- Duchenne muscular dystrophy (DMD) is a rare, severe neurodegenerative disease characterized by loss of ambulation (LOA), loss of upper body function, respiratory insufficiency, and early mortality
- While the typical natural history for DMD patients with respect to age of clinical events has been previously described, there is considerable heterogeneity within the population
- An extrapolation of the occurrence of clinical events to the United States (US) DMD population has not been described

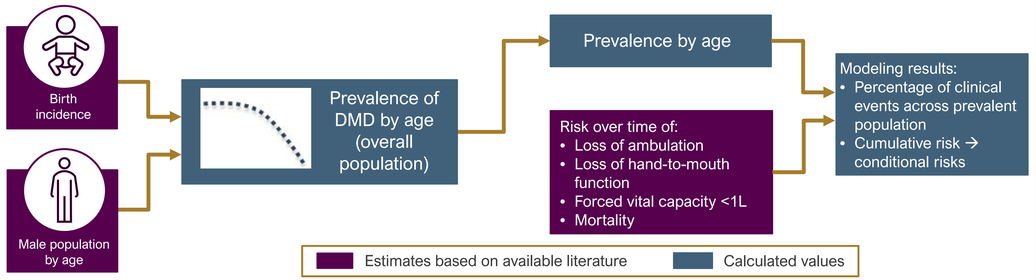
OBJECTIVE

To build an evidence-based model to extrapolate the impact of DMD natural history on the US prevalent population over five years and estimate the conditional risk of clinical events by age

METHODS

- Published data sources (reflecting contemporary standard of care) were identified that reported time-to-event Kaplan-Meier (KM) curves for the probability of DMD patients experiencing clinical events by age, including:
  - LOA, loss of unweighted hand-to-mouth function (HTMF), reaching forced vital capacity less than 1 liter (FVC1L), and mortality
- Parametric curves were derived from digitized KM curves by minimizing the sum of squared errors
  - Analysis 1 used McDonald et al[1] for non-fatal events and Phillips et al[2] for mortality
  - Analysis 2 also used McDonald et al[1] for non-fatal events (with a different parameter fit for LOA) and Passamano et al[3] for mortality
  - For LOA and HTMF, KM curves were stratified by patients receiving glucocorticoids for at least a year. Based on published data this was assumed to be 82% of the DMD population[1]
- A prevalence model, which has been previously described, was developed in Excel which estimated the distribution of current US DMD patients by age[4] (left side, Figure 1)
- Risks of key clinical milestones were projected onto this population to model (right side, Figure 1):
  - Proportion of the prevalent DMD population having already experienced key clinical milestones
  - Conditional probability of experiencing the event over a 1- to 5-year time horizon for patients who remain event-free at a given age

Figure 1: Clinical model schematic



RESULTS

- For the current US prevalent DMD population (distributed across ages) it is estimated that:
  - 50.2% – 58.7% are ambulatory, 70.5% – 80.3% have retained HTMF, and 77.8% – 88.5% have FVC above 1L
  - Over the next five years, 18.3% – 21.3% will lose ambulation, 15.2% – 17.2% will lose unweighted HTMF, 13.4% – 14.8% will transition to FVC1L, and 20.4% – 23.0% will pass away (Table 1)
- Median age was 12 years old for LOA in both analyses, 18 for loss of HTMF, 21 for transitioning to FVC1L, and ranged from 21 to 22 years for death over the two analyses
- For an 8-year-old ambulatory patient the conditional probability of LOA is 7.7% – 8.6% over one year, and 48.7% – 52.7% over five years (Table 2). However, 13.2% – 14.5% of 18-year-olds are still ambulatory, 6 years after the median age of LOA
- The 1-year conditional risk of LOA for still-ambulatory patients increases with age (Table 3) from 7.7% – 8.6% for ambulatory 8-year-olds to 21.3% – 24.4% for ambulatory 16-year-olds

Table 1: Estimated percentage of prevalent US DMD population transitioning to key milestones over the next 5 years

	LOA	Loss of HTMF	Transition to FVC1L	Mortality
1 Year	3.6% – 4.2%	2.8% – 3.1%	2.4% – 2.4%	4.1% – 4.7%
2 Years	7.2% – 8.4%	5.7% – 6.4%	4.9% – 5.2%	8.2% – 9.3%
3 Years	10.9% – 12.7%	8.8% – 9.8%	7.6% – 8.1%	12.3% – 13.9%
4 Years	14.6% – 17.0%	12.0% – 13.4%	10.4% – 11.4%	16.3% – 18.5%
5 Years	18.3% – 21.3%	15.2% – 17.2%	13.4% – 14.8%	20.4% – 23.0%

Table 2: Conditional risk of LOA for ambulatory patients

Time Horizon	LOA for an Ambulatory 8-Year Old
1 Year	7.7% - 8.6%
2 Years	17.4% - 19.5%
3 Years	28.0% - 31.3%
4 Years	38.7% - 42.6%
5 Years	48.7% - 52.7%

Table 3: 1-year conditional risk of LOA by baseline age

Baseline Age	Conditional Risk
8	7.7% - 8.6%
9	10.5% - 12.0%
10	12.9% - 14.6%
11	14.8% - 16.5%
12	16.3% - 17.6%
13	17.9% - 18.3%
14	19.1% - 19.7%
15	21.9% - 20.1%
16	21.3% - 24.4%

DISCUSSION

- DMD is a severe disease that represents a substantial burden under natural history
- This analysis highlights the considerable variability of outcomes around the median age
  - While many sources highlight LOA by age 12,[5] sources do not always highlight how many patients may lose ambulation noticeably before then and how many patients may still be ambulatory after age 12
- Increasing 1-year risk of LOA with each year for still-ambulatory patients shows the inevitability of disease progression. This trend is consistent for other DMD milestones explored
- This framework can be adapted for new evidence, additional events, and a range of baseline ages
- A strength of this study is the use of a range of published sources describing real-world evidence for clinical outcomes to develop the model, reflecting a range of related outcomes by age. Use of both cumulative and conditional probabilities allows for exploration of the range of trajectories that may occur, in addition to the most common ages at clinical event occurrence
- Limitations include reliance on robustness of published data, limited published risk data, and presumed independence of events

CONCLUSIONS

- The use of KM curves in estimating the risk of DMD patients experiencing clinical events by age demonstrates the substantial variation in the timing of these events
- Although DMD is a rare condition, extrapolating the clinical event estimates to the national DMD population highlights the gravity of disease burden

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