

PROJECT HERCULES: THE CHALLENGES OF ESTIMATING MULTI-STATE MODEL TRANSITIONS IN RARE DISEASES: CREATING A NATURAL HISTORY MODEL FOR DUCHENNE MUSCULAR DYSTROPHY (DMD)

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Theme 5: Achieving the triple A's by 2030: Accessible, Available and Affordable Treatments for people living with a rare disease.

Introduction

About Duchenne

Duchenne Muscular Dystrophy (DMD) is a rare progressive disease that is often diagnosed in early childhood, and results in significantly reduced life expectancy. The disease almost always affects boys, and there is no current cure.

About Project HERCULES

Project HERCULES is an international multi-stakeholder collaboration led by Duchenne UK that is developing disease-level tools and evidence to support HTA and access decisions for new treatments for Duchenne Muscular Dystrophy.

About The Research

Due to the rarity of DMD, both the research literature and patient numbers are limited. This study aimed to fully characterise the natural history of DMD by synthesising data from clinical trials, digital extraction from the literature, and elicitation from stakeholders. A unified analysis was performed to represent the progression of a patient with DMD and to inform future economic decision models on potential treatments.

Methods

Natural history model

The proposed model in Figure 1 is the result of multiple stakeholder input from clinicians, patients and carers. State definitions were made in accordance primarily with clinical beliefs, while also bearing the (limited) data availability in mind.

Data sources

• Intermediate transitions:

Information on transitions from states 1 to 8 were available from clinical trials (mainly from placebo arms, made accessible by the C-Path Institute[1]).

• Mortality transitions:

No data was available on transitions to state 9: instead, a literature review was conducted identifying appropriate Kaplan-Meier survival curves, from which survival data was extracted via Guyot's algorithm[2].

• Transfer state (state 3) transitions:

Clinical trials did not report necessary information; instead, these transitions were informed by simulated data based on clinical, carer and patient elicitation.

Analysis

A parametric Markov multi-state model was fitted to the combined dataset with age as the time-scale, assuming constant rates of transition between states and supplemented by repetitively estimated mortality rates. The model fit was iterated until convergence of all transition rates. This was repeated for a steroid-user population.

Figure 1

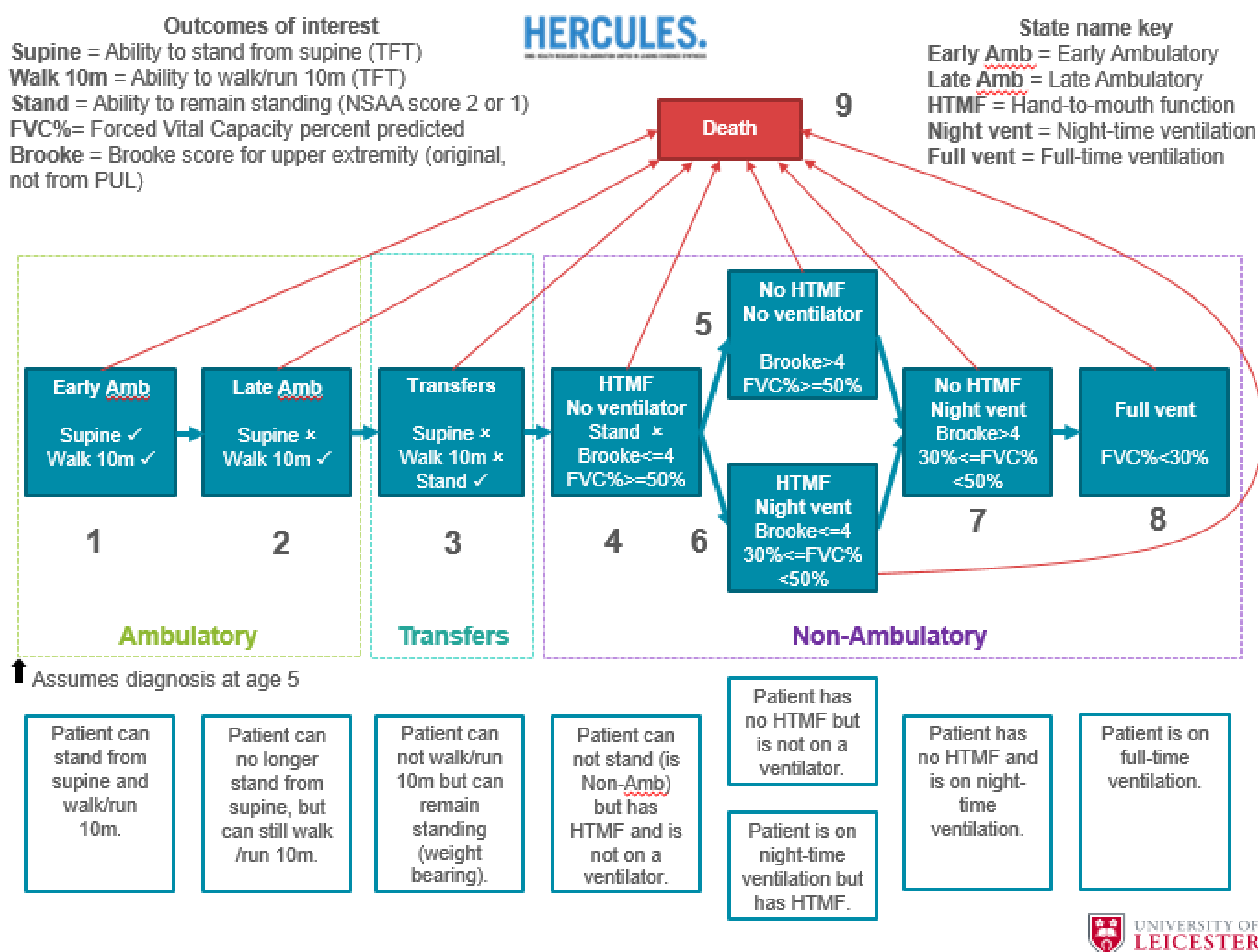


Figure 1: Proposed natural history model for Duchenne Muscular Dystrophy.

Figure 2

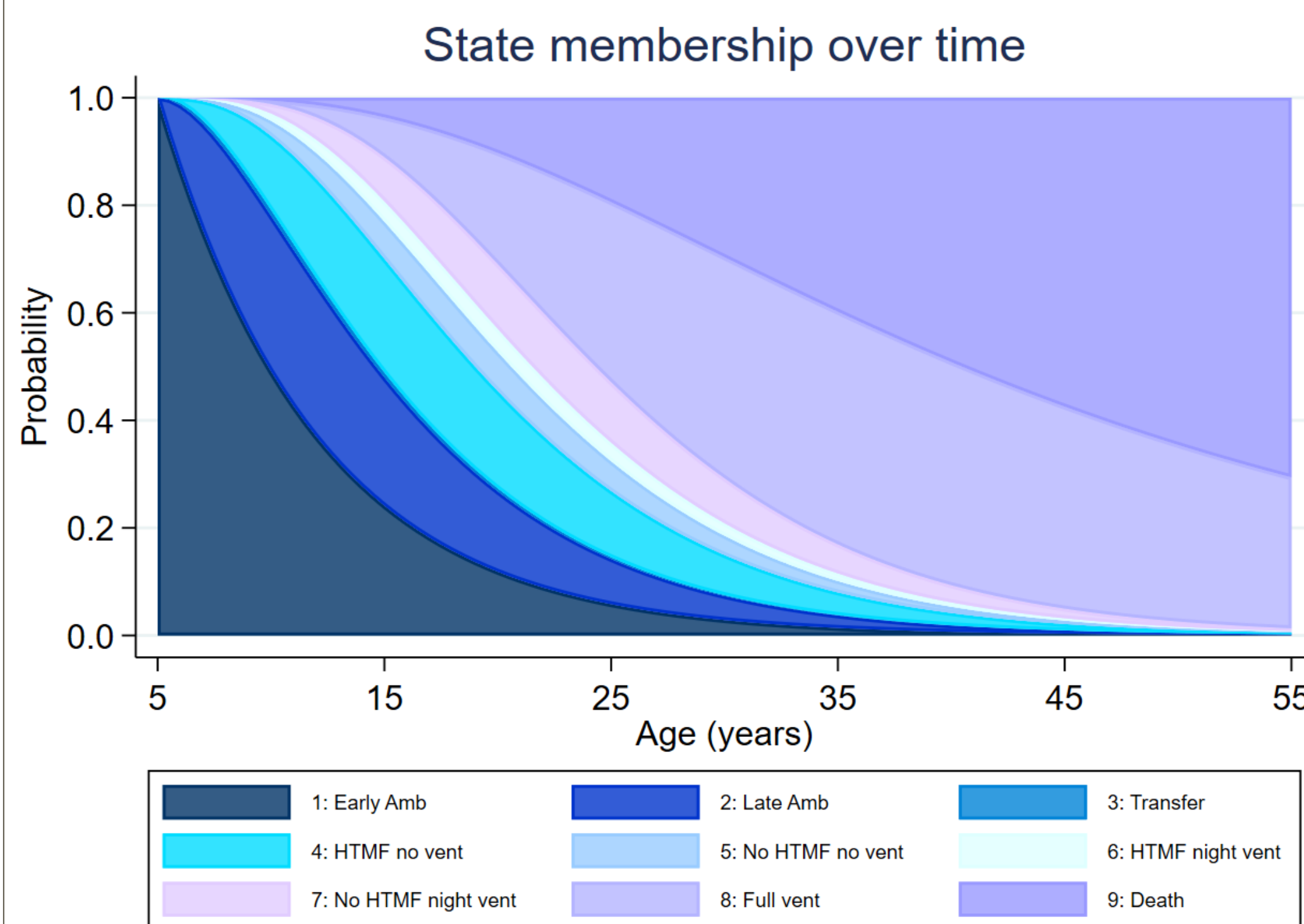


Figure 2: State occupancy probabilities for DMD.

Results

1005 patients from 11 studies were available for intermediate disease transitions. The average age a patient progressed to each health state was consistent with clinical opinion. Median survival of patients with DMD was estimated to be 40 years (see Figure 2), assuming DMD diagnosis at age 5. A longer length of stay in state 8 was estimated than prior belief expected, likely due to the clinical trial data (informing the intermediate transitions) and mortality data coming from different cohorts. Analysis on steroid users suggested longer times spent in later states, with slower transition rates.

Conclusion

Natural history model discussion

This study models the full natural history of DMD in a single unified analysis and highlights some of the challenges of working in a rare disease area. The model quantified vital measures such as length of stay in each state and life expectancy, which can readily inform future economic decision models. New treatments targeted at health states of DMD can be integrated into the natural history model.

Future work

The extracted mortality data will be supplemented by data from the Clinical Practice Research Datalink (CPRD), an electronic health record containing survival data on over 600 patients with DMD. Further elicitation will also be conducted on transitions in and out of state 3 to investigate and reduce uncertainty about the model fit. This study identifies the need to focus future data collection around the transfer state in clinical studies.

References

- [1] Critical Path Institute, Tucson, AZ. Available at: <https://c-path.org/programs/d-rsc/>
- [2] Guyot P, Ades AE, Ouwens JNM, Welton NJ. *BMC Med. Res. Meth.* 2012; 12:9

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