A Latent Variable Disease Progression Model for Duchenne Muscular Dystrophy

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Background & Objectives

- Duchenne muscular dystrophy (DMD) is a rare X-linked pediatric disease characterized by a complete lack of dystrophin production, resulting in muscle deterioration and progressive lower body muscle weakness. This leads to nonambulation typically by early teenage years, followed by upper body muscle deterioration and ultimately death by the late 20s.
- The 6-minute walk test (6MWT) outcome has been used as a primary or secondary endpoint in trials to determine drug efficacy. The 6MWT has historically shown high variability both between patients and over time. Patients of the same age may have drastically different 6-minute walking distances (6MWD), and may progress with very different rates. Late stage clinical trials for DMD have had complications demonstrating efficacy using this highly variable endpoint.
- **The objective was to better understand DMD disease progression in boys as measured by the 6MWT through quantitative modeling using all publicly available individual level natural history and placebo literature data.**

Methods

1. Conduct a literature search for all publicly available individual level longitudinal natural history data of the 6MWT in boys both healthy and diagnosed with DMD (Table 1)
   (a) Digitize data using GraphClick version 3.0.3
2. Fit a hierarchical model to the data set using maximum likelihood in NONMEM version 7.4 with First Order Conditional Estimation
   (a) Explore covariates of steroid administration and interventional trial effects
   (b) Perform simulation-based visual prediction check (VPC) using 1000 Monte Carlo (MC) replicates of the data
   (c) Perform a simulation-based check of the model's predictive ability at one year (because a typical length of trial/time of interim data analysis in DMD trials) from the same 1000 MC simulations.
      i. Group by age bins to analyze predictive ability

Reference	Reported N	Reported Age Statistics	Data Type	Inclusion criteria minimum walking distance
Brehm et al. 2014[1]	14	Mean: 8.72 years. Range: 6-12.5 years	DMD natural history	>= 150 meters
Goemans et al. 2013[2]	65	Mean: 9.5 years. Range 5.1-15.3	DMD natural history	none
Henricson et al. 2012[3]	22	Median: 9 years. Range 4-12	healthy controls	none
McDonald et al. 2010[4]	15	Range 4-12 years	DMD natural history	>= 10 meters
McDonald et al. 2013[5]	57	Mean: 8 years. Range: 5-15 years	DMD & BMD placebo-treated patients, Ataluren trial NCT00592553	>= 75 meters
Mercuri et. al 2016[6]	96	Mean: 8.73 years	DMD natural history	>= 75 meters

Table 1: Studies identified from literature search and included in data collection; summary statistics; and inclusion criteria.

Results

- The modeling data set included 16 healthy boys and 219 DMD patients. 8.72, 51.4 and 39.9% of the DMD subjects had one, two and three or more 6MWT measures, respectively. 44.0% of the DMD subjects came from the Mercuri et al [6] study.
- The model was first fit to the healthy subject data. Then, those population parameter estimates were fixed and the entire data set was used for estimation of parameters for DMD subjects.
- A one compartment indirect response model represented the 6MWT and an exponential function represented the latent disease process. Latent disease stimulated the dissipation rate constant of the 6MWT, causing the 6MWT to decline for DMD patients. The healthy and DMD populations shared the dissipation rate constant (K_{OUT}), but a covariate ($KCOV$) was included on the production rate constant (K_{IN}) to allow for separate estimates for the two populations.
- A change point for the production rate constant (K_{IN}) of the 6MWT was implemented with the MTIME function in NONMEM. This allowed for estimation of a lag time for production. This time was estimated to be 1.75 years old, which seems a logical age when toddlers may begin walking a measurable distance over 6 minutes.
- The parameters K_{OUT}, K_{IN}, and MTIME were estimated using only the healthy subjects, which was a small data set, resulting in less precise parameter estimates. DMD parameters were precisely estimated because there was a larger amount of DMD data to use in estimation.
- The observed data, population predicted mean and individual model predictions for both the healthy and DMD subjects are shown in Figure 1. Diagnostic plots in Figures 2-4 only include DMD subjects. Individual and population model predictions indicated a reasonable fit of the model to the data (Figures 1, 2).
- Visual predictive checks demonstrated that the model-simulated data were representative of the observed 6MWT outcomes (Fig 3). Predictive checks at one year indicated that the model reasonably described the 6MWT one year post-baseline (Fig 4).
- Conclusions about steroid administration and interventional trial effects were inconclusive due to lack of covariate information and suitable amounts of data in each covariate group.

Results

NONMEM model code:

```
$PK
IF (PATIENT.EQ.0)
  KOUT= THETA(1)
  KCOV = 1
  ALPHA = 0
  BETA = 0

IF (PATIENT.EQ.1)
  KOUT= THETA(1)*EXP(ETA(1))
  KCOV = THETA(6)
  ALPHA = THETA(4)*EXP(ETA(3))
  BETA = THETA(5)*EXP(ETA(4))

where PATIENT=0 for healthy
subjects and PATIENT=1 for DMD
subjects

MTDIFF = 1
MTIME(1)= THETA(2)

KIN1 = 0 KIN2 = THETA(3)*KCOV*
  EXP(ETA(2))
KIN = KIN1*(1-MPAST(1)) +
  KIN2*(MPAST(1))

IF(TIME.EQ.0) DIS = 0
IF(TIME.GT.0) DIS = (ALPHA*
  EXP(TIME*BETA))
A_0(1) = 0

$DES
DADT(1)=KIN-(KOUT *A(1)*
(1+DIS))
```

Results

Parameter	Final Estimate	Relative SE,%
K_{OUT}	0.48 months^{-1} (BSV: 5.40% healthy, 16.7% DMD)	141 (109, 18.3)
K_{IN}	321 $\frac{meters}{month}$ (BSV: 2.97%)	138 (166)
$MTIME$	1.75 years	323
$KCOV$	0.63	1.32
α	9.85E-06 (BSV: 32.2 %)	28 (43.7)
β	0.995 (BSV: 19.3%)	1.64 (12.8)
SD of residual error	42.0 meters	5.99

Table 2: Model parameter estimates and percent relative standard errors.

Results

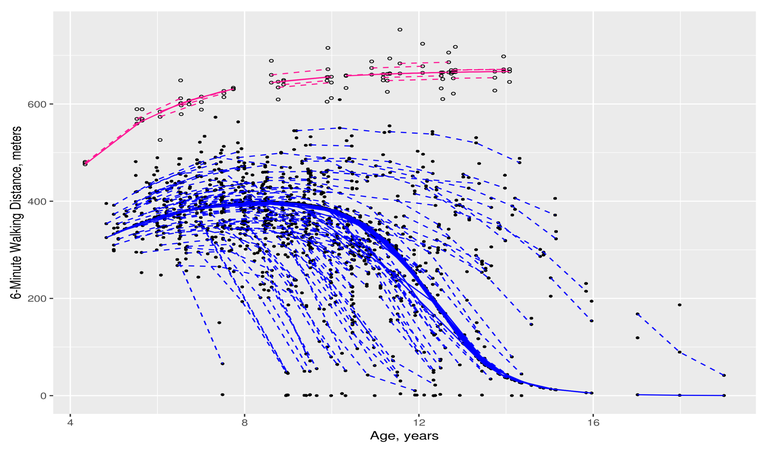

Figure 1: Latent variable disease progression model population predictions (solid lines), individual predictions (dashed lines) and observed measures (points) of the 6MWT in healthy boys and boys with DMD versus age. Pink lines and black open circles, healthy subjects. Blue lines and black closed circles, DMD subjects.

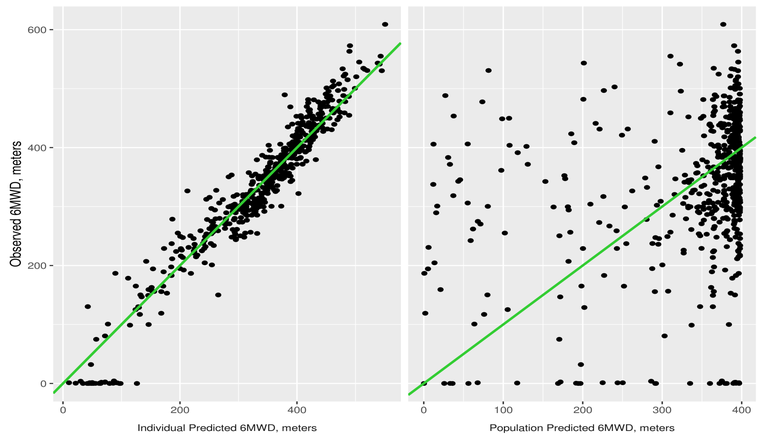

Figure 2: Observed versus individual predicted (left) and population predicted (right) 6MWT values in boys with DMD. Line of unity, green.

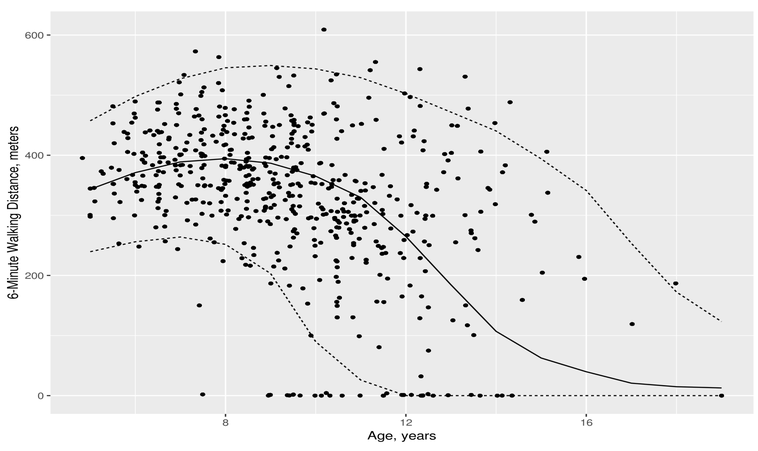

Figure 3: Visual predictive check of 6MWT measures of boys with DMD. Dashed lines: top and bottom, 95th and 5th simulated percentiles, respectively. Solid line: 50th simulated percentile. Solid circles: observed 6MWT.

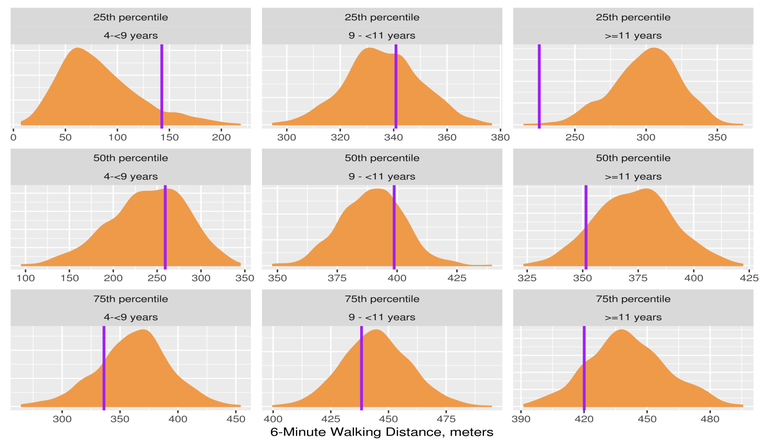

Figure 4: Visual predictive check of 25th, 50th and 75th quantiles of observed (purple lines) and simulated (orange distributions) of the 6MWT in boys with DMD at one year post-baseline by binned age groups.

Discussion & Conclusion

- A latent variable indirect response model reasonably described disease progression of DMD in boys as measured by the 6MWT with reasonable accuracy. Parameters fit to healthy subjects anchored the trajectory of the 6MWT, with the addition of a latent disease model for DMD subjects.
- Confidence in the model's predictive ability is demonstrated by simulation-based visual predictive checks.
- The model has potential to be used as a simulation tool to explore DMD clinical trial designs for future efficacy trials.

Hajjar JL et al. A Latent Variable Disease Progression Model for Duchenne Muscular Dystrophy. Poster presented at the American Conference on Pharmacometrics (ACoP9) 2018; Oct7-10, 2018; San Diego, CA. Poster T-011.

References

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[3] E. Henricson. *PLoS Curr*, 4:RRN1297, Jan 2012.

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[5] C. M. McDonald. *Muscle Nerve*, 48(3):343–56, Sep 2013.

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