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ARTICLE

Development of a model-based clinical trial simulation platform to optimize the design of clinical trials for Duchenne muscular dystrophy

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Abstract

Early clinical trials of therapies to treat Duchenne muscular dystrophy (DMD), a fatal genetic X-linked pediatric disease, have been designed based on the limited understanding of natural disease progression and variability in clinical measures over different stages of the continuum of the disease. The objective was to inform the design of DMD clinical trials by developing a disease progression model-based clinical trial simulation (CTS) platform based on measures commonly used in DMD trials. Data were integrated from past studies through the Duchenne Regulatory Science Consortium founded by the Critical Path Institute (15 clinical trials and studies, 1505 subjects, 27,252 observations). Using a nonlinear mixed-effects modeling approach, longitudinal dynamics of five measures were modeled (NorthStar Ambulatory Assessment, forced vital capacity, and the velocities of the following three timed functional tests: time to stand from supine, time to climb 4 stairs, and 10 meter walk-run time). The models were validated on external data sets and captured longitudinal changes in the five measures well, including both early disease when function improves as a result of growth and development and the decline in function in later stages. The models can be used in the CTS platform to perform trial simulations to optimize the selection of inclusion/exclusion criteria, selection of measures, and other trial parameters. The data sets and models have been reviewed by the US Food and Drug Administration and the European Medicines Agency; have been accepted into the Fit-for-Purpose and Qualification for Novel Methodologies pathways, respectively; and will be submitted for potential endorsement by both agencies.

*See the Acknowledgments for the list of Cooperative International Neuromuscular Research Group investigators.

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STUDY HIGHLIGHTS

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Duchenne muscular dystrophy (DMD) is a rare disorder that progresses in a nonlinear fashion. It is challenging to design and conduct clinical trials to evaluate new therapies given the rare disease designation of DMD.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study describes the development of models that quantify DMD disease progression across the course of disease as described using a series of different measures, accounting for known sources of variability.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

We identified significant covariates affecting the dynamics of disease progression and showed how they affected the progression of various measures in individuals at various stages of disease. We developed a model-based clinical trial simulation platform.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

Our analysis enhances the understanding of DMD progression. This will inform future clinical trial design with respect to selection of optimal measures in specific populations and may therefore minimize the size and length of trials without limiting the ability of those trials to demonstrate if therapies are effective.

INTRODUCTION

Duchenne muscular dystrophy (DMD) is a fatal X-linked genetic disorder that primarily affects males, caused by mutations in the gene that encodes dystrophin. These mutations result in no or very low production of functional dystrophin. Dystrophin is a protein that connects the cytoskeleton of a muscle fiber to the extracellular matrix, thus providing strength and stability to the muscle. Lack of dystrophin leads to progressive replacement of muscle with fat and fibrotic tissue, affecting skeletal, cardiac, and smooth muscles. Clinically it results in loss of ambulation and upper body function; progressive loss of respiratory capacity, and subsequently respiratory function; and cardiomyopathy. DMD affects about one in every 5000 newborn boys with initial symptoms apparent at the age of 2–3 years.[1] The progressive loss of muscle tissue leads to loss of ambulation by the age of 8–14 years. People with DMD typically require ventilatory support by the age of 20 years as a result of respiratory failure, and premature death occurs in the third or fourth decades of life.[2–5]

There is no cure for DMD, but current treatment options help to alleviate symptoms, slow the rate of progression, and increase the life expectancy of individuals with DMD.[1] Current standard of care of individuals with DMD include use of corticosteroids (deflazacort or prednisone/prednisolone), which improve skeletal muscle strength initially, reduce the loss of muscle strength over time, and therefore delay the loss of ambulation. However, corticosteroids also cause adverse effects such as weight gain, growth retardation, behavioral issues, osteoporosis, and hirsutism.[6,7] Only deflazacort (Emflaza®; PTC Therapeutics Inc.) is approved for DMD by the US Food and Drug Administration (FDA), whereas prednisone/prednisolone are used off label. Recent advances in mutation-specific therapies resulted in conditional approval of ataluren (Translarna™; PTC Therapeutics Inc.) for individuals with DMD with nonsense mutations by the European Medical Agency (EMA) and accelerated approval of several oligonucleotide therapies that target specific mutation groups by the FDA based on increased production of the dystrophin protein. These include eteplirsen (Exondys51®; Sarepta Therapeutics) for individuals with DMD with mutations that are amenable to the skipping of exon 51, golodirsen (Vyondys53®; Sarepta Therapeutics) and viltolarsen (Viltepso®; NS Pharma, Inc.) for mutations amenable to the skipping of exon 53, and casimersen (Amondys45®; Sarepta Therapeutics) for mutations amenable to the skipping of exon 45.[8,9]

There is a clear need for development of additional therapies for DMD, but numerous challenges remain in developing informative clinical trials. As DMD is a rare disease, there is a limited number of primarily pediatric patients available to participate in clinical trials. With multiple therapies being tested in parallel and therapy approaches that target only subsets of individuals with specific mutations, recruitment becomes even more challenging. Unless the newborns undergo genetic tests

for detecting DMD, it is often challenging to identify the symptoms of DMD during the early years before significant muscle loss, when some potential therapies may be most effective. There is considerable variability in the rate at which disease progresses in individuals with DMD, which makes clear demonstration of clinical effects difficult. Known factors contributing to this variability include the localization of mutation, presence of modifier genes, and differences in standard of care. Measurement of disease progression is also challenged by the fact that many test results are affected by the effort and motivation of the subject, which can vary, particularly in young children.[10,11,13] Furthermore, the progression of these measures is nonlinear in nature, that is, younger boys often show improvements in certain functions and then subsequently lose that function over time with increased progression of the disease.[14–16] Most functional tests can be measured only at specific stages of disease, as over time individuals living with DMD lose the ability to perform the required function (e.g., once boys become nonambulatory they cannot complete a walk test). Under these circumstances, it is challenging to extrapolate the trajectories of disease severity in individuals with DMD without having quantitative models that explain the nonlinear nature of various measures.

The FDA's guidance on DMD clinical trials does not define a specific clinical measure or measures that should be used in all clinical trials, and scientific consensus is that different measures may be more appropriate to use at different stages of disease and for therapies targeting different disease pathomechanisms or different body systems.[17] Many different potential measures have been used in trials to date and have shown sensitivity to change at specific disease stages. However, no measure has been developed that is appropriate for use across the disease continuum, as those most sensitive to change in younger subjects, such as the NorthStar Ambulatory Assessment and some timed function tests, cannot be performed by subjects later in the disease who can no longer walk.[14–16] Thus, to understand the effect of a therapy on disease progression across the spectrum of disease it is essential to look at a battery of different assessments in subjects who retain different levels of function. To design and conduct clinical trials in this disease it is therefore of utmost importance to have a quantitative way of understanding the rate of change of different measures in the DMD population as a whole and to understand as best as possible the sources of variability in the rate of progression. This can allow informed selection of inclusion/exclusion criteria coupled to the selection of outcome measures to help design clinical trial protocols that will demonstrate the effectiveness of a therapy in the course of a clinical trial.[10]

The Duchenne Regulatory Science Consortium (D-RSC) brings together multiple stakeholders including drug sponsors, academic researchers, regulators, and patient advocacy groups to promote the sharing of patient-level data, collaborate on modeling and simulation efforts, and to drive community acceptance of the drug development tools resulting from these efforts.[11] By leveraging the D-RSC database, which has been extensively curated and integrated, our objective was to develop models of different clinical measures used in clinical trials to inform the design of future trials for DMD. We developed a disease progression model-based clinical trial simulation (CTS) platform based on models of the following five different clinical measures: the NorthStar Ambulatory Assessment (NSAA), forced vital capacity (FVC), and velocity of completion of three timed motor function tests (TFTs): stand from supine, four-stair climb, and 10 m (or 30 ft) walk-run. These measures were selected based on the availability of data from past trials, proposed use in future trials, and potential regulatory acceptance through discussions with the consortium members (representatives of companies developing therapies for DMD, clinicians and academic scientists and advisors from regulatory agencies).

METHODS

Data

Longitudinal subject-level data were integrated from 15 studies in patients with DMD (Table 1). The models were developed using 11 primarily North American studies that shared data with the consortium. Additional non-US data from four data sets were used to confirm that the models were representative of a global population of patients. Both the model-building and model-validation data sets included data from both clinical trials and natural history studies and included people from age 4 to end-stage disease. Data standardization was completed using data standards published by the Clinical Data Interchange Standards Consortium.[12]

Dependent variables, time metric, and covariates

Selection of the measures to model was based on availability of data in the database, perceived value of the measures in regulatory decision making (based on consortium discussions), and an attempt to include at least one measure that could be used in most stages of disease. The five functional measures selected were (1) NSAA, a 17-item rating scale used to measure functional motor abilities in ambulant

TABLE 1 Characteristics of the studies included in the final analysis and external validation data sets

Study	*n*	Age range (years)	Analysis purpose	Study type	Race (%)	Mutation (%)	Steroids use (%)
UC Davis (DMD-1000)	60	4–31	Primary analysis	Observational	Missing (100)	Missing (100)	Naïve (100)
UC Davis 2 (DMD-1000A)	24	4–14	Primary analysis	Observational	Asian (4.2), Other (8.3), White (87.5)	Missing (100)	Naïve (100)
CCHMC (DMD-1002)	96	4–17	Primary analysis	Observational	Asian (2.1), Other (11.4), White (86.5)	a_other_del (24), del_3-7 (4.2), dup (13.5), missing (12.5), skip_44 (4.2), skip_45 (10.4), skip_51 (10.4), skip_53 (7.3), small_mut (3.1), stop (10.4)	Current steroid user (100)
CINRG DNHS (DMD-1003)	440	4–34	Primary analysis	Observational	Asian (17.5), Other (8.6), Unknown (2.3), White (71.6)	a_other_del (11.6), del_3-7 (1.1), dup (3), missing (41.1), skip_44 (4.5), skip_45 (9.3), skip_51 (14.3), skip_53 (6.4), small_mut (2.3), stop (6.4)	Naïve (17) Current steroid user (68) Past steroid user (15) Deflazacort (33) Prednisone/prednisolone (36) Switched steroid at least once (84)
Santhera (DMD-1004)	34	10–19	Primary analysis	RCT	Other (5.9), White (94.1)	Missing (100)	Not available (91) Past (9)
Lilly (DMD-1005)	116	7–15	Primary analysis	RCT	Asian (12.9), Other (4.3), White (82.8)	dup (17.2), missing (75), small_mut (6), stop (1.7)	Current (100) Deflazacort (52) Prednisone/prednisolone (48)
CHOP (DMD-1006)	42	5–24	Primary analysis	Observational	Other (9.5), White (90.5)	a_other_del (21.4), del_3-7 (2.4), dup (2.4), missing (7.1), skip_44 (4.8), skip_45 (7.1), skip_51 (9.5), skip_53 (7.1), small_mut (4.8), stop (33.3)	Past (100)
Imaging DMD (DMD-1007)	91	5–18	Primary analysis	Observational	Missing (100)	Missing (100)	Naïve (2) Current (98) Deflazacort (64) Prednisone/prednisolone (32) Other/unknown (2)
PTC 007 (DMD-1009)	57	5–16	Primary analysis	RCT	Missing (100)	stop (100)	Naïve (5) Current (70) Not available (25) Deflazacort (30) Prednisone/prednisolone (39) Other (25) Switched steroid at least once (42)

TABLE 1 (Continued)

Study	*n*	Age range (years)	Analysis purpose	Study type	Race (%)	Mutation (%)	Steroids use (%)
PTC 020 (DMD-1010)	115	7–15	Primary analysis	RCT	Asian (5.2), Missing (8.7), Other (11.3), White (74.8)	stop (100)	Naïve (1) Current (99) Deflazacort (42) Prednisone/prednisolone (58) Switched steroid at least once (43)
CINRG steroid (DMD-1011)	64	4–12	Primary analysis	RCT	Missing (100)	Missing (100)	Current (100)
Biomarin 114044 (DMD-1015)	61	5–17	External validation	RCT	Missing (100)	del 38–50 (1.6), del 45–50 (25.8), del 46–50 (0.5), del 47–50 (1.7), del 48–50 (11.8), del 49–50 (33.6), del 50 (8.4), del 52 (16.6)	Naïve (58) Current (42)
Biomarin 114117 (DMD-1016)	18	5–11	External validation	RCT	Missing (100)	del 45–50 (38.9), del 48–50 (16.7), del 49–50 (5.6), del 50 (22.2), del 52 (16.7)	Naïve (17) Current (83)
Biomarin 114876 (DMD-1017)	16	6–12	External validation	RCT	Missing (100)	del 45–50 (56.3), del 47–50 (6.3), del 48–50 (25), del 49–50 (6.3), del 50 (6.3)	Naïve (6) Current (94)
Biomarin natural history (DMD-1018)	269	3–21	External validation	Observational	Missing (8), American Indian (9.3), Asian (2), Black (1.5), White (75), Multiple (2), Unknown (1.7)	Missing (100)	Naïve (4) Current (89) Past (7)

Abbreviations: CCHMC, cincinnati children's hospital medical center; CHOP, children's hospital of Philadelphia; CINRG, the Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; DNHS, DMD natural history study; PTC, PTC Therapeutics Inc.; RCT, randomized controlled trial; UC, University of California.

individuals with DMD and expressed as a bounded ordinal variable (0–34); (2) FVC, the total volume of air that can be forcibly exhaled from the lungs after taking the deepest breath possible (i.e., during the forced expiratory volume test); (3) velocity stand, calculated as the inverse of time to stand from supine position; (4) velocity climb, calculated as the inverse of the time to climb four standardized stairs; and (5) velocity walk-run, calculated as the distance divided by time taken to walk or run 10 m or 30 ft on a flat surface.[18] We chose to use FVC versus percent-predicted FVC as it is the raw measurement that is recorded on an instrument and therefore the most reliable measure to use when combining data from multiple studies. Different sites and studies use different equations to calculate percent-predicted FVC, making data integration across studies challenging. However, raw FVC data could be acquired from all studies, allowing integration of like data from each study. The covariates used to calculate percent-predicted FVC were investigated in the model development, so the effects of these variables are incorporated. Furthermore, percent-predicted FVC is variable in people with DMD as the calculation of percent-predicted FVC requires an accurate measure of height, which is challenging in individuals who cannot stand and may have scoliosis. Some studies use ulnar length to calculate predicted height, and some attempt to estimate standing height, adding error to the calculation of percent predicted between studies and even in subjects within a study. In addition, the use of steroids by people living with DMD can affect both height and weight and further complicate the interpretation of predicted normal FVC. After discussion with experts in the field, it was concluded that the use of raw FVC measurements and inclusion of the variables that are used to transform FVC to percent-predicted FVC as potential covariates would provide the most accurate models.

The longitudinal modeling analysis time metric was years of age of individuals at each assessment, as the functional measures are affected by age, stage of disease, and the process of development. The age range to be modeled was selected based on availability of data and the reliability of the measure in subjects of different ages (e.g., FVC values measured in children <5 years of age might not be reliable).

Depending on the data availability, various patient and study characteristics were tested as covariates: baseline age (BAGE; age at start of study), baseline disease severity (BSCORE; measure score at start of study), race, steroid use, genetic mutation, and study type (natural history versus clinical trial study; Table 1).

Disease progression model development

The overall model development process for the five measures is shown in Figure 1. Given the nonlinear dynamics of the measures, several mathematical functions were tested including quadratic, Bateman, and sigmoid I_{max} functions (see Supplementary Material S1.1, Appendix S1). Base model structure selection was based on a series of criteria, including the Akaike information criterion, scientific plausibility, and visual inspection of model diagnostic plots. Two levels of random variability, that is, interindividual variability (IIV) and residual variability (RV), were incorporated. IIV was described using a log-normal or logit distribution on structural parameters where applicable. Various error model structures such as additive, proportional, and combined models were tested (see Supplementary Material S1.2, Appendix S1). In addition, IIV on RV was tested for NSAA to account for an additional layer of variability in the scores of NSAA within individuals.

Selection of covariates was based on prior information from the literature and using an automated stepwise covariate modeling (SCM) approach using forward addition and backward elimination with p values of 0.05 and 0.01, respectively. Continuous covariates were incorporated into the model using a power function centered by their median values, whereas categorical covariates were incorporated using a proportional effect. Covariate effects on the mean time-course of all five measures were simulated for a patient with BAGEs of 4 years (NSAA and TFTs) or 5 years (FVC), with the median BSCORE value in the final analysis data sets using typical parameter estimates of the final model.

Model evaluation was done by a series of criteria, including visual inspection of standard goodness-of-fit (GOF) plots based on predictions and residuals, precision of parameter estimates, successful minimization of the model, and η shrinkage. Bootstrap analysis was performed using 1000 resampled data sets for estimating the precision of parameters. Simulation-based diagnostics were conducted on the final base and covariate models using both the model development and external validation data sets by inspecting visual predictive checks (VPCs) based on 500 simulated data sets. Model development was conducted in NONMEM® (Version 7.4.1; Icon Development Solutions) using stochastic approximation expectation-maximization for TFTs and first-order conditional estimation with interaction for the other measures (i.e., NSAA and FVC); model execution was done using Perl-speaks-NONMEM (Version 2.9.9; Uppsala University). Data preprocessing and postprocessing and data visualization were done in R (Version 3.6.0; R Foundation for Statistical Computing).

Missing dependent variable and covariates

Imputation of missing dependent variables or covariates was not performed. Missing dependent variables as a result

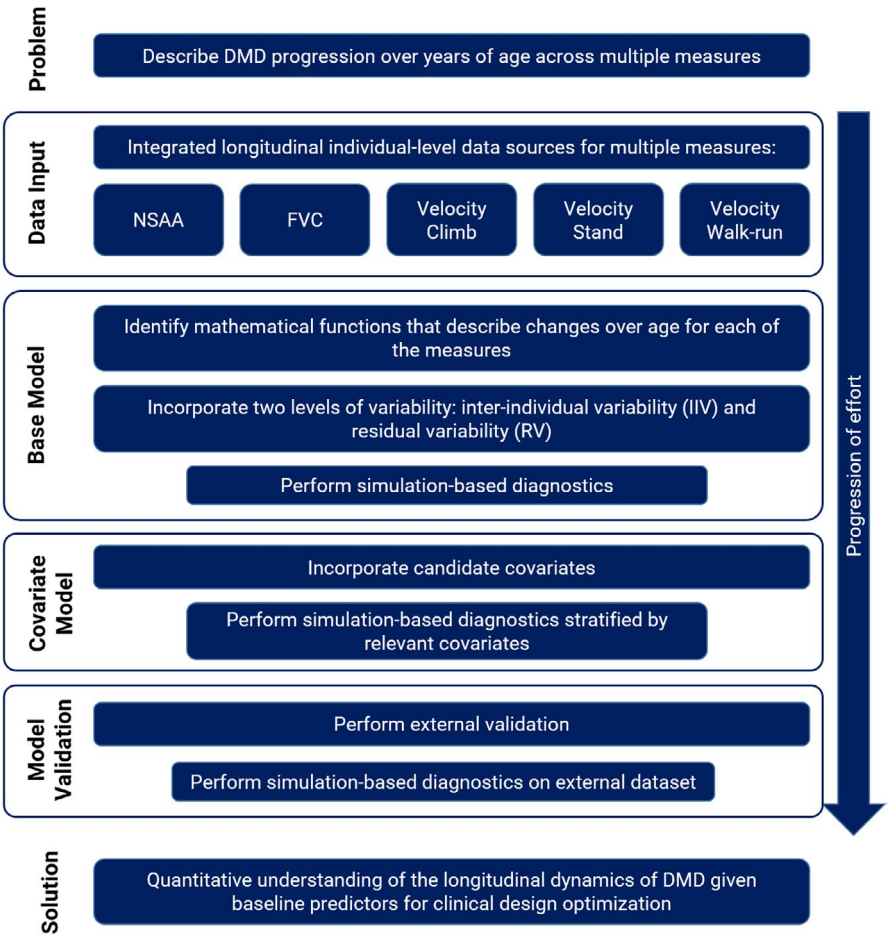

FIGURE 1 Overall model development and validation strategy. DMD, Duchenne muscular dystrophy; FVC, forced vital capacity; NSAA, North Star Ambulatory Assessment

of an inability to perform a test because of disease severity were censored and evaluated using the likelihood-based M4 method.[19] Inability to perform a test was defined in each study if the individual was unable to complete the test in a given time. Regrouping of some of the covariates was performed, for example, individuals with groups of mutations noted to cause slower progression—that is, those categorized as deletions in exons 3–7 (del 3_7) or those that could be corrected by skipping exon 44 (skip-44) were categorized "del 3_7/skip-44," whereas all others, including those with missing information, were grouped as "the others." For race, based on exploratory plots from base model, subjects were grouped as Asian or the others (which included those with missing race information); for steroid use, the grouping was done based on steroid use at baseline (naïve or missing vs. people who were recorded to have used steroids at baseline). Missing covariates were combined with "the others" category in the final data set.

CTS platform

The developed disease progression models were used as a backbone of the CTS platform that can be used to optimize clinical trial enrichment and design for evaluating new therapies in DMD through simulation. Along with each of the final models, the CTS platform incorporates (i) trial design characteristics (e.g., number of subjects per each arm, trial duration, and frequency of assessment), (ii) inclusion/exclusion criteria based on identified covariates, and (iii) hypothetical treatment effects based on user selected magnitudes of changes on the final parameters to envision active comparator arms. The CTS platform was developed in R (Version 3.6.0) using the Shiny library.

RESULTS

Data summary

The primary modeling analysis data set included 1141 individuals (aged 4–34 years) diagnosed with DMD and 19,996 observations of all five measures. The external validation data set included 364 individuals (aged 4–21 years) diagnosed with DMD and 7256 observations. For FVC, subjects older than 5 years were included in this analysis. For other measures (i.e., NSAA, velocity climb, stand, and walk-run), subjects older than 4 years were included.

Characteristics of the studies included are shown in Table 1. For additional details on the exclusion of data, see Supplementary Material S1.3, Appendix S1.

Base disease progression model

The multiplication of the Chapman-Richards growth and sigmoid I_{max} functions (Equation 1) was selected as the base model structure that best captured the time course for all measures.[20,21]

$$\text{Score}_i = G_{\max,i} \times (1 - e^{-g_i \times \text{Age}_i}) \times \left(1 - \left(\frac{\text{DP}_{\max,i} \times \text{Age}_i^{\gamma_i}}{\text{DP}_{50,i}^{\gamma_i} + \text{Age}_i^{\gamma_i}}\right)\right),$$

$$\text{DP}_{\max,i} = \frac{\exp(\text{LDP}_{\max,i})}{1 + \exp(\text{LDP}_{\max,i})} \quad (1)$$

where Age_i is the age of individual i during the course of study when the corresponding measure value, that is, Score_i is recorded; $G_{\max,i}$ represents a maximum possible score for individual i; g_i denotes an empirical growth scaling parameter for the individual i; $\text{DP}_{\max,i}$ represents a maximum fractional decrease from $G_{\max,i}$ in score for individual i, which is modeled in the logit domain to constrain between 0 and 1 where $\text{LDP}_{\max,i}$ can range between $\pm\infty$;$\text{DP}_{50,i}$ represents an approximate age at which the score is half of its maximum decrease for individual i; and γ_i denotes the Hill coefficient or shape factor for individual i. Logit transformation of NSAA scores was done to constrain the values between 0 and 34. Parameter estimates of final base models of all measures were shown in Supplementary Material S1.4–S1.8, Appendix S1. The base models were developed further using the SCM approach for covariate selection, that is, BSCORE, BAGE, mutation groups (skip_44/del_3-7 or others), race (Asians or others), study type (natural history or clinical trial), and steroid users (naïve or users).

Final disease progression models

NorthStar Ambulatory Assessment

The NSAA model was developed based on aggregated individual-level data from four studies with 476 individuals aged 4–22 years and 2550 observations (Supplementary Material S1.9, Appendix S1). BSCORE, BAGE, and study type were found to have significant effects on DP_{50}, whereas steroid use at baseline and specific mutation groups (skip_44/del_3-7) were found to have significant effects on g. The estimated age at which the NSAA score is half of its maximum decrease (DP_{50}) was found to be 10.9 years with a maximum fractional decrease ($\text{DP}_{\max}$) of 90.7%. Correlations between parameters DP_{50}, g, and γ were also estimated. Inclusion of these covariates explained about 54% and 34% of variability on DP_{50} and g, respectively. Final parameter estimates are shown in Table 2, and covariate effects of the mean time-course of NSAA is shown in Figure 3.

TABLE 2 Final parameter estimates of North Star Ambulatory Assessment model

Parameter	Final model estimate (%RSE)	Bootstrap estimates, $n = 1000$; median (95% CI)
Fixed effects		
$\text{LDP}_{\max}$	2.25 (8)	2.201 (1.587–2.87)
$\text{DP}_{\max}$	0.904	0.90
$G_{\max,typ}$	34 Fixed	34 Fixed
$\text{DP}_{50,typ}$, years	10.8 (1)	10.804 (10.434–11.148)
g_{typ}	0.375 (6)	0.364 (0.323–0.414)
γ_{typ}	6.55 (7)	6.823 (5.862–7.967)
Additive error	0.377 (3)	0.381 (0.355–0.405)
$\theta^{\text{DP}_{50}}_{\text{BAGE}}$	0.654 (6)	0.646 (0.559–0.73)
$\theta^{\text{DP}_{50}}_{\text{BSCORE}}$	0.625 (6)	0.613 (0.521–0.732)
$\theta^{\text{DP}_{50}}_{\text{study type}}$	0.1 (24)	0.099 (0.058–0.151)
$\theta^{g}_{\text{Mutation}}$	0.82 (23)	0.89 (0.296–1.763)
$\theta^{g}_{\text{Steroid use}}$	−0.126 (63)	−0.16 (−0.305 to 0.008)
Random effects (%RSE) [%Shrinkage]		
IIV DP_{50}	12 (8) [29]	12 (10.3–14)
$\omega\left(\text{DP}_{50}, g\right)$, % correlation	−73 (19.4)	−67.5 (−86.6 to −46.9)
IIV g	39.7 (11) [42]	38.5 (29–47.5)
IIV γ	59 (7) [29]	58 (50.7–64.3)
IIV additive error	51.59 (5) [25]	51.6 (45.8–57.5)

Note: Steroid use at baseline was included in the model as a covariate although the CI contained zero because of both the proximity to zero and of the clinical importance of steroid use.

Abbreviations: θ^{a}_{b}, covariate effect on parameter "a" due to covariate "b"; a_{typ}, typical value of parameter "a"; BAGE, baseline age; BSCORE, measure score at baseline; CI, confidence interval; IIV, interindividual variability; RSE, relative standard error.

Forced Vital Capacity

The FVC model was developed based on aggregated individual-level data from seven studies with 782 individuals aged 5–20 years and 4293 observations (Supplementary Material S1.10, Appendix S1). BAGE, specific mutation groups (skip_44/del_3-7), and race (Asian or others) were found to be significant on DP_{50}, whereas BSCORE, BAGE, and the mutation groups (skip_44/del_3-7) were found

TABLE 3 Final parameter estimates of forced vital capacity model

Parameter	Final model estimate (%RSE)	Bootstrap estimates, $n = 1000$; median (95% CI)
Fixed effects		
LDP_{max}	1.37 (4)	1.432 (0.989–1.945)
DP_{max}	0.79	0.80
$G_{max,typ}$	4.78 (0.6)	4.774 (4.729–4.819)
$DP_{50,typ}$, years	17.4 (2)	17.471 (16.82–18.12)
g_{typ}	0.0438 Fixed	0.043 (0.043–0.043)
γ_{typ}	10.8 (6)	10.855 (9.639–12.459)
Additive error	0.101 (2)	0.101 (0.076–0.123)
Proportional error	0.0715 (1)	0.071 (0.052–0.086)
$\theta^{DP_{50}}_{BAGE}$	0.374 (8)	0.367 (0.317–0.418)
$\theta^{DP_{50}}_{Mutation}$	0.187 (29)	0.199 (0.079–0.394)
$\theta^{DP_{50}}_{Race}$	−0.0769 (39.3)	−0.079 (−0.138 to −0.02)
$\theta^{G_{max}}_{BAGE}$	−0.679 (3)	−0.676 (−0.708 to −0.641)
$\theta^{G_{max}}_{BSCORE}$	0.844 (2)	0.843 (0.804–0.881)
$\theta^{G_{max}}_{Mutation}$	0.0574 (24)	0.057 (0.005–0.112)
Random effects (%RSE) [%Shrinkage]		
IIV G_{max}	8.2 (4) [27]	8.1 (7.2–9)
IIV DP_{50}	17.8 (5) [36]	17.4 (15–19.9)
IIV γ	59 (7) [50]	58.7 (49.2–68.6)

Abbreviations: θ^{a}_{b}, covariate effect on parameter "a" due to covariate "b"; a_{typ}, typical value of parameter "a"; BAGE, baseline age; BSCORE, measure score at baseline; CI, confidence interval; IIV, interindividual variability; RSE, relative standard error.

to have a significant effect on G_{max}. The estimated age at which the FVC is half of its maximum decrease (DP_{50}) was found to be 17.4 years with a maximum fractional decrease (DP_{max}) of 79%. A combined error model was used to explain the RV. Final parameter estimates are shown in Table 3, and covariate effects of the mean time-course of FVC is shown in Figure 3.

Velocity climb

The velocity climb model was developed based on aggregated individual-level data from nine studies with 842 individuals aged 4–20 years and 5366 observations (Supplementary Material S1.11, Appendix S1). BSCORE, BAGE, specific mutation groups (skip_44/del_3-7), and race (Asian or others) were found to be significant on DP_{50}, whereas BSCORE and BAGE were found to have a significant effect on G_{max} and γ. The estimated age at which the velocity climb score is half of its maximum decrease (DP_{50}) was 10.8 years, whereas the estimated DP_{max} found to be 1, indicating that there is 100% decline in measure value. A combined error model was used to explain the RV. Final parameter estimates are shown in Table 4, and covariate effects of the mean time-course of velocity climb is shown in Figure 3.

Velocity stand

The velocity stand model was developed based on aggregated individual-level data from eight studies with 677 individuals aged 4–20 years and 4365 observations (Supplementary Material S1.12, Appendix S1). BSCORE, BAGE, and specific mutation groups (skip_44/del_3-7) were found to be significant on DP_{50}, and BSCORE was found to have a significant effect on G_{max} and γ. The estimated age at which the velocity stand score is half of its maximum decrease (DP_{50}) was 10.6 years, and the estimated DP_{max} was found to be 100%. A combined error model was used to explain the RV. Final parameter estimates are shown in Table 4, and covariate effects of mean time-course of velocity stand is shown in Figure 3.

Velocity walk-run

The velocity walk-run model was developed based on aggregated individual-level data from eight studies with 825 individuals aged 4–20 years and 5056 observations (Supplementary Material S1.13, Appendix S1). BSCORE, BAGE, and specific mutation groups (skip_44/del_3-7) were found to have significant effects on DP_{50}, and BSCORE and BAGE were found to have significant effects on G_{max} and γ. In addition, study type (natural history or clinical trial) was added as covariate on γ. The estimated age at which the velocity walk-run score is half of its maximum decrease (DP_{50}) was 12 years with an estimated DP_{max} of 100%. A combined error model was used to explain the RV. The estimated correlation between DP_{50} and γ was found to be −47%. Final parameter estimates are shown in Table 4, and covariate effects of the mean time-course of the velocity walk-run is shown in Figure 3.

Model evaluation

Disease progression models of the five measures were evaluated using internal and external validation approaches. Visual inspection of standard GOF plots revealed no visible bias, and VPC plots showed good agreement between the observed and predicted data (see

TABLE 4 Final parameter estimates of three timed motor functions test models

Parameter	Velocity climb		Velocity stand		Velocity walk-run	
	Final model estimate (%RSE)	Bootstrap estimates, $n = 1000$; median (95% CI)	Final model estimate (%RSE)	Bootstrap estimates, $n = 1000$; median (95% CI)	Final model estimate (%RSE)	Bootstrap estimates, $n = 1000$; median (95% CI)
Fixed effects						
LDP_{max}	20 Fixed	20	20 Fixed	20	20 Fixed	20
DP_{max}	1 Fixed	1	1	1	1 Fixed	1
$G_{max,typ}$	0.898 (1)	1.082 (0.925–1.973)	0.211 (2)	0.209 (0.2–0.234)	2.27 (1)	2.684 (2.455–3.197)
$DP_{50,typ}$, years	10.8 (1)	10.768 (10.584–10.976)	10.6 (1)	10.636 (10.357–10.925)	12 (1)	11.739 (11.486–12.03)
g_{typ}	0.0407 (1)	0.033 (0.017–0.039)	0.427 (11)	0.437 (0.327–0.563)	0.165 (1)	0.121 (0.093–0.141)
γ_{typ}	15.5 (3)	15.321 (14.214–16.625)	16.8 (5)	17.382 (14.623–19.945)	11.9 (4)	11.312 (10.255–12.482)
Additive error	0.0121 (5)	0.012 (0.01–0.014)	0.0115 (6)	0.011 (0.008–0.014)	0.107 (3)	0.109 (0.09–0.129)
Proportional error	0.184 (1)	0.182 (0.17–0.199)	0.192 (2)	0.199 (0.181–0.219)	0.0973 (2)	0.096 (0.086–0.106)
$\theta^{DP_{50}}_{BAGE}$	0.475 (4)	0.481 (0.422–0.548)	0.418 (6)	0.423 (0.34–0.504)	0.486 (5)	0.506 (0.441–0.57)
$\theta^{DP_{50}}_{BSCORE}$	0.0495 (22)	0.048 (0.029–0.066)	0.119 (13)	0.122 (0.091–0.156)	0.165 (13)	0.15 (0.11–0.187)
$\theta^{DP_{50}}_{Mutation}$	0.183 (16)	0.18 (0.079–0.295)	0.204 (24)	0.201 (0.047–0.408)	0.262 (15)	0.243 (0.14–0.372)
$\theta^{DP_{50}}_{Race}$	−0.074 (34)	−0.075 (−0.108 to −0.039)	N/A	N/A	−0.0967 (27)	−0.091 (−0.126 to −0.057)
θ^{γ}_{BAGE}	1.14 (9)	1.141 (0.851–1.518)	N/A	N/A	0.749 (14)	0.802 (0.555–1.066)
θ^{γ}_{BSCORE}	−0.696 (8)	−0.692 (−0.802 to −0.577)	−0.709 (14)	−0.728 (−0.955 to −0.302)	−1.33 (8)	−1.306 (−1.54 to −1.11)
$\theta^{\gamma}_{Study\ type}$	N/A	N/A	N/A	N/A	0.251 (34)	0.231 (0.07–0.422)
$\theta^{G_{max}}_{BAGE}$	−1.06 (3)	−1.082 (−1.185 to −1.001)	N/A	N/A	−0.545 (2.8)	−0.642 (−0.73 to −0.572)
$\theta^{G_{max}}_{BSCORE}$	0.93 (2)	0.933 (0.891–0.97)	0.893 (3)	0.875 (0.743–0.95)	0.96 (1.8)	0.971 (0.929–1.01)
Random effects (%RSE) [%Shrinkage]						
IIV G_{max}	15.3 (3) [30]	14.9 (12.2–18)	20.5 (4) [26]	22.4 (18.3–27.6)	8.7 (3) [29]	8.4 (6.9–9.8)
IIV DP_{50}	15.3 (3) [19]	15 (13.6–16.4)	16.6 (4) [23]	16.4 (14.6–18.1)	17.3 (4) [23]	16.2 (14.7–18)
IIV g	0 Fixed	0	0 Fixed	0	0 Fixed	0
IIV γ	47.7 (6) [45]	47.1 (40.3–53.4)	56.4 (9) [53]	58.5 (46.4–75.9)	48.3 (6) [46]	46.9 (40.1–53.9)
$\omega\left(DP_{50}, \gamma\right)$, % correlation	N/A	N/A	N/A	N/A	−47 (15)	−54.75 (−68.32 to −41.06)

Abbreviations: θ^{a}_{b}, covariate effect on parameter "a" due to covariate "b"; a_{typ}, typical value of parameter "a"; BAGE, baseline age; BSCORE, measure score at baseline; CI, confidence interval; IIV, interindividual variability; RSE, relative standard error.

Appendix S2). The VPC plots were also generated, which showed good predictive performance of the final models (see Figure 2 and Appendix S3). The VPC plots using external validation data sets are shown in Appendix S4. For TFTs, that is, velocity climb, stand, and walk-run, additional VPC plots of the fraction of missing observations resulting from disease severity versus age were also generated. These plots were generated for both the final analysis and external validation data sets and showed good predictive performance of the models (see Appendixes S3 and S4). All final model codes written in NONMEM are available in Appendix S5.

CTS platform

The CTS tool was developed by integrating the final disease progression models of all five measures, that

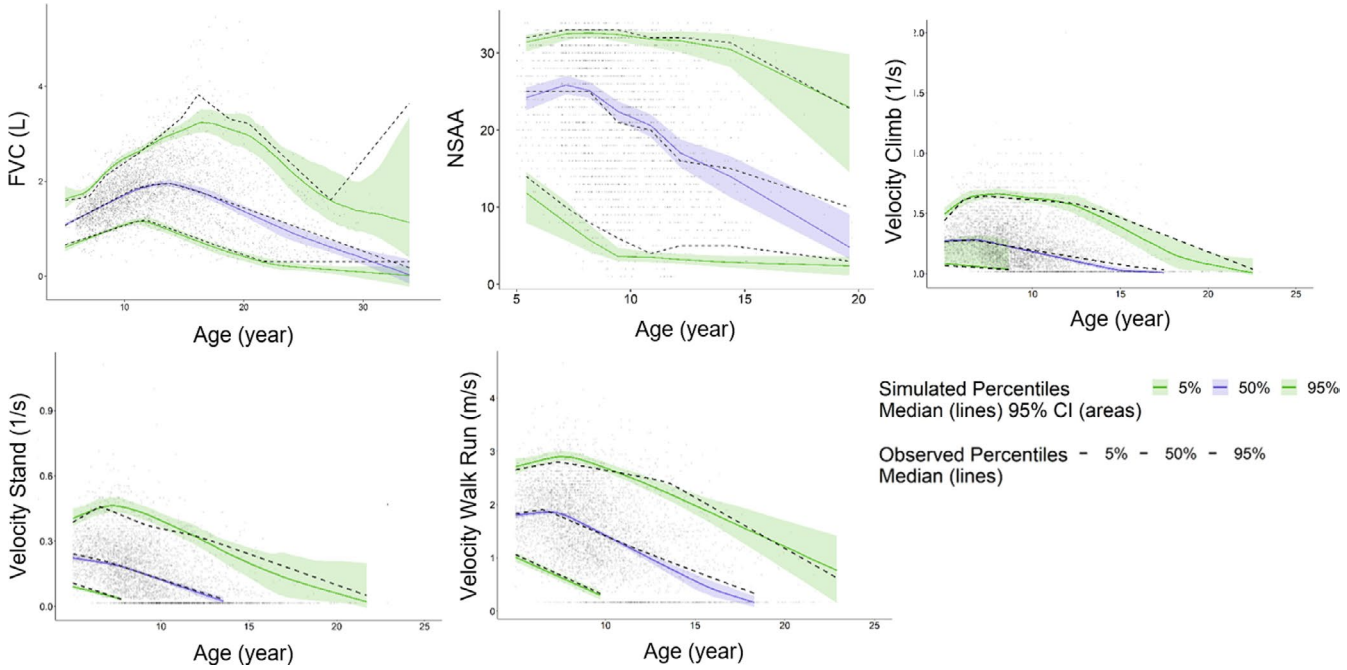

FIGURE 2 Visual predictive check for final models of all five measures. The visual predictive check plots show the median (dashed black line) and the 5th and 95th percentiles (lower and upper dashed lines, respectively) of the observed data. The blue shaded areas indicate the 90% CIs of the model prediction of the median, and the green shaded areas show 90% CIs of the model prediction for the 5th and 95th percentiles. The solid lines—blue for the median and green for the 5th and 95th percentiles—represent the model prediction. Black dots represent the observed data. CI, confidence interval; FVC, forced vital capacity; NSAA, North Star Ambulatory Assessment

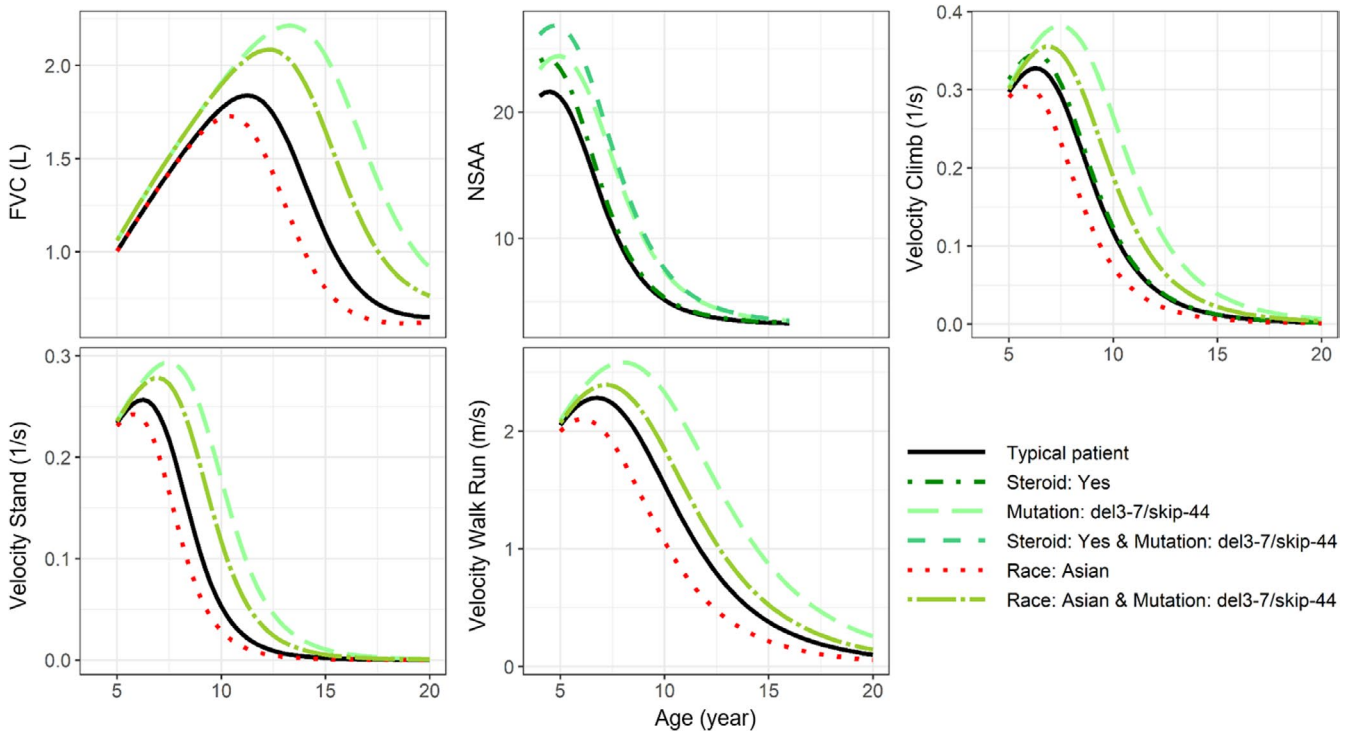

FIGURE 3 Predicted covariate effects on mean time-course of measures versus age. FVC, forced vital capacity; NSAA, North Star Ambulatory Assessment

is, NSAA, FVC, velocity climb, velocity stand, and velocity walk-run. CTSs can be performed for each of the five measures with user-chosen critieria for covariates, trial design parameters, and power calculation outputs. Because the current models were based on only placebo or natural history data, hypothetical treatment effects are

introduced to simulate active treatment arms, with user-chosen parameters for timing and magnitude of such effects. Once users select the patient characteristics, define treatment effect, and trial design characteristics, simulations can be conducted for placebo and treatment arms for selected measures with power calculations determined based on the patient population characteristics and trial design parameters. To accommodate the needs to understand disease progression in the study, an option to either run simulations based on age (i.e., time since birth) or trial time (i.e., time since the trial starts) was implemented.

DISCUSSION

To our knowledge, this is the first effort with the largest analysis data set in DMD that is used for the disease-drug-trial model development and validation purposes. In the current analysis, we developed disease progression models for DMD using the following five different functional measures: NSAA, FVC, velocity climb, velocity stand, and velocity walk-run. All models included both incline and decline phases where individuals with DMD initially gain function and then decline with age. However, the rate and degree to which these measures increase and the ages at which they start to decline vary across measures and individuals with DMD. Therefore, the selected base model structure, that is, a product of a Chapman-Richards growth function and a sigmoid I_{max} model, helps in capturing both the incline and decline phases while accounting for IIV. The structural parameters G_{max} and g of the model characterize the incline phase, whereas DP_{max}, DP_{50}, and γ characterize the decline phases of these measures. In the case of NSAA, the G_{max} parameter was fixed to the maximum possible score for an individual. The estimated parameter g, which represents the empirical growth scaling parameter for each individual, was found to be in the range of 0.04–0.4 across the measures, which explains the highly variable rate at which these measures increase.

The models accurately described well-established facets of disease progression. The estimated DP_{50} parameter represents the approximate age at which the score is half of its maximum decrease for each individual is between 10–12 years for NSAA and all three TFTs, whereas for FVC, this value is ~17 years, indicating that respiratory function declines at a slower rate compared with other measures. The estimated DP_{max} parameter that represents the maximum fractional decrease from G_{max} is in the range of ~0.8–1 for the various measures, indicating that there is typically complete loss of ability to complete these measures in the individuals with DMD. McDonald et al. reported that in individuals with DMD and not taking steroids, the peak median FVC was 1.85 L at the age of 12–12.9 years and dropped below 1 L by the age of 20–20.9 years.[14] The predictions from the developed model in a typical patient (not Asian or not having del3_7/skip-44 mutation groups) were in a similar range with a predicted median peak of1.95 L at the age of ~12 years, whereas it dropped below 1 L by the age of 22 years. For TFTs, Arora et al. reported that by the age of ~14 years, 50% of the individuals with DMD were unable to perform the TFTs.[15] Model predictions reveal that, by the age of 14–18 years, about 50% of individuals with DMD would not be able to do any TFTs considering the time cap of 30 s to perform the test.

BAGE and BSCORE, that is, the baseline values of each of the five measures, were found to be significant covariates on the DP_{50} parameter in the final models of all five measures. Although BAGE and BSCORE are correlated, both of these covariates were retained in the final model. Both covariates provide different but important information on disease severity in terms of ages and measure scores when individuals with DMD enter the study. Given the large variability in disease progression, different individuals with DMD at the same age could have a wide range of measure scores and vice versa. Thus, the inclusion of BAGE and BSCORE could help in accounting for these differences and precisely predicting the progression of the disease in individuals with different rates of progression who might be at different stages of disease. These covariates provide insights on baseline disease severity, which is related to disease progression. It is noteworthy that there are correlations between various mutations and disease severity, resulting in different DMD phenotypes.[22–24] In our analysis, the skip_44 (7% of total mutations) or del_3-7 mutation groups were found to be a significant covariate across all measures, which corresponds to a delayed onset of decline in the measure scores. The skip-44 mutation was also identified by Ricotti et al. as a significant covariate slowing the rate of decline in NSAA.[11] Wang et al. showed that individuals with DMD with del_3-7 mutation groups lost ambulation later than their age-matched peers, indicating slower disease progression.[25] In general, skip-44 constitutes about 7% of all mutations, whereas the del_3-7 mutation group was found to be ~4% in a study conducted in Spain.[13,26] Effect of race (Asian population) was found to be significant in FVC, velocity climb, and velocity walk-run measures, which showed early onset in decline of the measures score. However, differences in standard of care might be one of the reasons contributing to the early onset of the decline. Interestingly, the use of steroids was not a significant covariate in any measure except NSAA (Figure 3). This could be explained by confounding factors such as lack of dosing information and because steroid usage is only captured at baseline when individuals with DMD outside of clinical trials frequently

change their dosing regimens and go on and off steroids to reduce adverse effects.

Drug development in DMD is challenging because of a variety of factors, including a small patient population (exacerbated when proposed therapies can only treat genetic subtypes), measures that are nonlinear in nature and that are only sensitive to change in narrow windows of disease progression, and highly variable progression of the disease between individuals. Many proposed therapies for DMD are anticipated to slow the rate of progression rather than providing functional gains. Historically, such studies have often been performed over periods of 1 year or less, and no statistically significant effects could be detected. It should be noted that DMD studies that evaluate efficacy with durations of 18–24 months may significantly increase statistical power with modest increases in drug development time.[17] By using the proposed CTS platform, users will be able to simulate different trial designs using different lengths of trials, numbers of subjects, degrees of disease progression, measures, and starting populations of subjects along with their estimated drug effects to improve trial design moving forward and to improve the likelihood of detecting drug effects.

The CTS platform will help inform trial protocol development, including the selection of inclusion/exclusion criteria, stratification approaches, frequency of clinical assessments, trial duration, and sample size for studies evaluating therapeutic candidates for DMD. These strategies can inform phase II trials by helping select specific measures and populations where drug effects may be seen in a shorter period of time as well as phase III trials to optimize control arms and to inform innovative trial designs where multiple measures are considered.[9] These models and the CTS platform are being submitted to global regulatory authorities to seek endorsement from both the FDA and EMA through the Fit-for-Purpose and Qualification of Novel Methodologies pathways, respectively. Such acceptance from regulatory authorities provides confidence for sponsors who wish to use the CTS platform within the context of use, that is, insights into various trial enrichment strategies, including the selection of inclusion/exclusion criteria, stratification approaches, timing and selection of clinical assessments, trial duration, and sample size for studies evaluating therapeutic candidates for DMD. The platform is meant to increase the probability of success for evaluating new therapeutic candidates for DMD. In addition, the models could serve as a basis to inform placebo arms through historical controls, which could help in advancing trials more efficiently.

There are certain limitations in the developed disease progression models. As the data used in the model development had a minimum age of 4 years, the developed model cannot be reliably used to simulate the effects of therapies for those younger than the age of 4 years. As studies were conducted by different investigators at multiple sites and at multiple times, we are limited by the data that were collected in each study and the amount of granularity in each record. For example, a lack of complete information with respect steroid use (start/stop date of therapy) in these patients resulted in steroid use not being a significant covariate effect in all models, whereas it is well established that steroid use slows DMD progression. It is known that there are existing DMD modifier genes, and the presence of these would be expected to affect the rate of disease progression. However, this information was not collected in the databases used, so this variable could not be included. Furthermore, each database recorded dystrophin mutation data in a different format, limiting the granularity of the mutation information (capturing the mutation subtype of individuals) that could be included in the analysis to broad groups; additional granularity might improve the model performance.[10,11,27,28] However, the occurrence of these covariates, such as Asian race or the mutation groups skip-44/del3_7, are rare, which indicates that dilution of known covariate effect could be minimal. As mentioned previously, because of these data limitations, we could see some disagreement between model predictions and observed data in certain VPCs. These could be improved as we have more granularity in the covariate information and availability of data in later stages of disease. Lastly, additional work is needed to incorporate predictions of patient dropout into the models so that we can appropriately power studies.

In conclusion, the disease progression models developed for all five measures were able to accurately describe the observed longitudinal data from both clinical trials and natural history studies. These models were further tested through external validation that demonstrated the robustness of the final models. Some key demographic factors were also identified, explaining the variability in disease progression across individuals, such as mutation subgroups (skip-44 or del_3-7 groups), race (Asian or others), BAGE, and BSCORE. A model-based CTS platform was developed based on the developed disease progression models that incorporate all identified patient characteristics, which can be used for conducting simulations and thereby optimize clinical trial design for studies evaluating therapies for DMD.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

K.L., V.A., J.F.M., D.J.C., D.C., C.V., J.B., J.L., K.R., S.S., and S.K. wrote the manuscript. D.J.C., J.L., K.R., S.S., and S.K. designed the research. K.L., V.A., J.F.M., D.J.C., and S.K. performed the research. K.L., V.A., J.F.M., D.J.C., D.C., C.V., J.B., J.L., K.R., S.S., and S.K. analyzed the data.

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