Received: 12 November 2020 | Revised: 9 November 2021 | Accepted: 12 November 2021

DOI: 10.1002/mus.27463

INVITED REVIEW

Answer questions and earn CME https://education.aanem.org/URL/JR92.

CME MUSCLE&NERVE WILEY

The impact of genotype on outcomes in individuals with Duchenne muscular dystrophy: A systematic review

Shelagh M. Szabo MSc[1] | Katherine L. Gooch PhD[2] | Alexis T. Mickle MSc[1] | Renna M. Salhany PharmD[2] | Anne M. Connolly MD[3]

[1]Broadstreet Heath Economics & Outcomes Research, Vancouver, British Columbia, Canada

[2]Sarepta Therapeutics, Inc, Cambridge, Massachusetts, USA

[3]Division of Neurology, Nationwide Children's Hospital, Ohio State University, Columbus, Ohio, USA

Correspondence
Anne M. Connolly, Division of Neurology, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205.
Email: anne.connolly@nationwidechildrens.org

Abstract

Duchenne muscular dystrophy (DMD) is associated with progressive muscle weakness, loss of ambulation (LOA), and early mortality. In this review we have synthesized published data on the clinical course of DMD by genotype. Using a systematic search implemented in Medline and Embase, 53 articles were identified that describe the clinical course of DMD, with pathogenic variants categorizable by exon skip or stop-codon readthrough amenability and outcomes presented by age. Outcomes described included those related to ambulatory, cardiac, pulmonary, or cognitive function. Estimates of the mean (95% confidence interval) age at LOA ranged from 9.1 (8.7-9.6) years among 90 patients amenable to skipping exon 53 to 11.5 (9.5-13.5) years among three patients amenable to skipping exon 8. Although function worsened with age, the impact of genotype was less clear for other outcomes (eg, forced vital capacity and left ventricular ejection fraction). Understanding the distribution of pathogenic variants is important for studies in DMD, as this research suggests major differences in the natural history of disease. In addition, specific details of the use of key medications, including corticosteroids, antisense oligonucleotides, and cardiac medications, should be reported.

KEYWORDS
Duchenne muscular dystrophy, exon skipping, genotype, natural history, pathogenic variants

Abbreviations: 6MWT, 6-minute walk test; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CARE, CAse REport statement and checklist; CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; FEV, forced expiratory volume; FVC, forced vital capacity; IQ, intelligence quotient; LOA, loss of ambulation; LVEF, left ventricular ejection fraction; MFM, Muscle Function Measure; NSAA, North Star Ambulatory Assessment; ORF, open reading frame; PECOS, Population, Exposure, Comparator, Outcomes, Study design; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RoB 2, Revised Cochrane Risk of Bias Tool for Randomized Trials; STRIDE-NMD, Strategic Targeting of Registries and International Database of Excellence—Neuromuscular Disorders; STROBE, Strengthening the Reporting of Observational studies in Epidemiology; TREAT-NMD, Translational Research in Europe—Assessment & Treatment of Neuromuscular Diseases; UDP, United Dystrophinopathy Project.

The objectives of this activity are to: 1) Understand and be able to evaluate the reasons that genotype might impact outcomes in individuals with Duchenne muscular dystrophy; 2) Understand and apply in clinical practice and research the relationships, if any, of genotype to ambulation, and to pulmonary, cardiac, and cognitive function; 3) Understand and apply to clinical practice and research the gaps in information that impact better understanding of genotype-phenotype relationships in Duchenne muscular dystrophy.

I have no conflicts of interest

1 | INTRODUCTION

Duchenne muscular dystrophy (DMD) is a neuromuscular disease that occurs primarily in males. It is caused by pathogenic variants in *DMD*, a gene that produces a large structural protein of muscle cells.[1] Individuals with DMD experience progressive muscle weakness, manifesting first as delayed motor function and gait abnormalities. This weakness then proceeds to loss of ambulation (LOA), loss of arm and hand function, respiratory impairment, cardiomyopathy, and premature death.[2,3] *DMD*, the largest known human gene, contains 79 exons spread over more than 2.4 million nucleotides. Deletions or duplications of exons that disrupt the open reading frame (ORF) account for approximately 70% of those with DMD.[1,4,5] The remaining 30%

are caused by ORF-disrupting small deletions, duplications, or insertions.[4,6] Locations of individual pathogenic variants are known to contribute to variability in patient phenotype due to the amount and function of dystrophin translated from the mutated gene.[7,8]

Understanding the impact of DMD genotype on natural history is important for prognosis,[7] because growing evidence, including from large, well-conducted clinical registries, suggests varying outcomes by genotype. This evidence is most convincing for progressive loss of lower limb and ambulatory function, as these are the outcomes for which the most data are available.[9-13] Wang et al, using self-report data from 765 registrants of the Duchenne Registry in the United States, reported age at LOA to vary according to the exon-skip amenability of underlying *DMD* pathogenic variants, and recognized that patients with variants amenable to skipping exon 44 had a milder phenotype.[12] Findings from the Cooperative International Neuromuscular Research Group (CINRG) registry were in agreement.[14]

Despite its importance, synthesizing genotype-phenotype data is challenging due to: (1) variability in outcome measures used across studies; (2) variability in the level of detail used to describe pathogenic variants; (3) heterogeneity between individuals, even of the same genotype, in the age at occurrence of key clinical milestones; and (4) genetic variation in other contributing genes.[15] Even the consistency of relationships between genotype and timing of LOA across studies has not been fully analyzed, which is challenging for two reasons. First, there is variability in research design and, second, clinical factors that were captured varied, including duration/type of corticosteroid use and presence of other genetic modifiers.[16,17] It is also unclear whether genotype and functional relationships for other major natural history milestones (eg, respiratory function or onset/severity of cardiomyopathy) hold true. Second, it has not been addressed how data from smaller studies may supplement estimates from large registries to provide insight into the genotype-specific timing of other natural history outcomes. The objective of this review was to assess and synthesize available data on the natural history of DMD by genotype.

2 | METHODS

A systematic review of the published literature was conducted to identify evidence on key clinical and functional outcomes relevant to understanding the natural history of DMD, presented according to genotype.

2.1 | Search strategy and study selection

Search strategies implemented in Medline and Embase were used to identify studies published between 1980 and May 4, 2020 that described the natural history and progression of DMD (Table S1). The systematic review design was guided by the study-specific PECOS (Population, Exposure, Comparator, Outcomes, Study design) criteria (Table S2) developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[18] Outcomes of interest in patients with DMD included measures describing the natural history (eg, age at LOA, or cognitive function by intelligence quotient [IQ]) or functional status (eg, the 6-minute walk test [6MWT]). Inclusion was limited to studies published in English, where outcomes data were presented according to individual mutations in the *DMD* gene or by genotype. To focus on patients at similar DMD disease stages, outcomes had to be presented within prespecified target age ranges to reduce heterogeneity. For example, a study sample with an age range of 6 years or less, or the standard deviation (SD) around the mean age estimate of 2.5 years or less. This age restriction was not applied to IQ, which remains relatively stable over time in DMD patients.[19]

Two of the authors (S.M.S. and A.T.M.) independently reviewed all abstracts identified by the search strategy against the PECOS criteria, and then reviewed the full texts of all potentially relevant abstracts. Availability of details on pathogenic variant or genotype status was considered within the full-text review stage rather than in the abstract review stage. Any discrepancies between reviewers were resolved by discussion to achieve consensus.

2.2 | Data extraction

Study characteristics extracted included authors, year, study duration, objective(s) and design, sample size, and inclusion and exclusion criteria. Patients' characteristics extracted included baseline demographics, pathogenic variant status, and details of corticosteroid and cardiac treatments.

Extracted natural history outcomes data included the percentage of patients experiencing an event of interest by time *t*, or the absolute or mean/median age at the event. Cross-sectional functional outcomes data of interest included the absolute or mean/median (with measures of dispersion) measure score at time *t* or age; and longitudinal functional outcomes data extracted (where available) included change over time among patients at different ages. All data were extracted according to DMD pathogenic variant or genotype. Most outcomes data were presented at the individual level; some estimates derived from groups of patients were also presented. Relevant outcomes data presented as survival curves were extracted using DigitizeIt version 2.3.2 software (I. Bormann, Braunschweig, Germany).

The strength of the available evidence was assessed using the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement for observational studies,[20] the CARE (CAse REport) statement and checklist for case studies,[21] the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB 2)[22] for clinical trials, and the Methodological Index for Non-Randomized Studies.[23]

2.3 | Classifying DMD genotype

Data on pathogenic variants associated with DMD were presented differently across studies. Some studies presented data on the specific variant, and others classified patients according to amenability to

theoretical exon skipping[7,24] or stop-codon readthrough (for nonsense mutations) therapies.[25-27] In the synthesis, pathogenic variant data were classified according to exon-skip or stop-codon readthrough amenability categories (as individual variants can be mapped to exon-skip amenability categories, but cannot be inferred from an exon-skip amenability category). Some variants are amenable to more than one exon-skipping category; for example, del 52 is amenable to therapies that skip exon 51 or exon 53.[7,24] Therefore, data from such patients could contribute to both exon-skip amenability groups (Table S3).

For synthesizing data on IQ, pathogenic variants were instead classified according to whether they would affect dystrophin isoform Dp140 ("Dp140^{-}" for those downstream of exon 44, which is considered predictive of cognitive involvement, vs "Dp140^{+}" for those upstream of exon 44).[28-30] Pathogenic variants beginning or ending in exon 44 were categorized as Dp140^{+} unless otherwise reported by the original investigators. Figure 1 is a schematic of the *DMD* gene, noting the two "hotspots" (regions with high mutation frequency) and the estimated proportion of individuals whose reading frames would be restored, hypothetically, by skipping the indicated exon within each hotspot. The Dp140^{-} and Dp140^{+} regions are also indicated.[7,19,31]

2.4 | Classifying corticosteroid and cardiac treatment

Although corticosteroid use is an important modifier of the natural history of DMD,[13,32] not all studies describe corticosteroid treatment. Some studies describe corticosteroid use at the individual level, whereas others describe use at the group level. In this review, patients have been classified as "corticosteroid-treated" if corticosteroid use was described at the group level and at least 80% of the population were treated. The overall syntheses are presented for all patients irrespective of corticosteroid treatment status, with a subgroup analysis performed based on grouped data where at least 80% were confirmed as corticosteroid-treated or individual patient data from corticosteroid-treated patients. Details of treatment regimens (eg, corticosteroid choice, schedule, or dose) were extracted (where available), but not considered in the synthesis due to lack of comparable reporting across studies.

Similarly, the use of cardiac medications, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and beta blockers, was inconsistently reported with respect to dose, duration, and treatment schedule, with different studies describing these at the individual level, group level, or not at all. Although it was therefore considered infeasible to analyze the cardiac outcome (according to left ventricular ejection fraction [LVEF]) by cardiac-treatment subgroups, these data are reported as footnotes in the corresponding figure.

2.5 | Synthesis and analysis

First, a list was compiled of all outcome measures reported according to pathogenic variant or genotype and age in published studies identified by the search strategy. Only outcomes reported in more than one study or among studies with more than 50 patients were considered further in the synthesis.

From that set of eligible studies, baseline demographics and clinical characteristics were summarized using counts/percentages and means/medians with dispersion. Mean age at LOA by genotype was estimated as a weighted average from individual and grouped data from patients of the same genotype. Median age at LOA was estimated from individual data, and for grouped data LOA was presented as reported by the original investigators. In terms of interpretation, for mean and median age at LOA, the denominator for outcomes calculated from individual data would be *only those who had lost ambulation*, due to how the data are reported in the literature. For grouped median data, the denominator included both those who *had, and who had not yet, lost ambulation*. For functional assessment data, mean (standard deviation) values were estimated from individual and grouped data (if available), and medians were calculated if sufficient

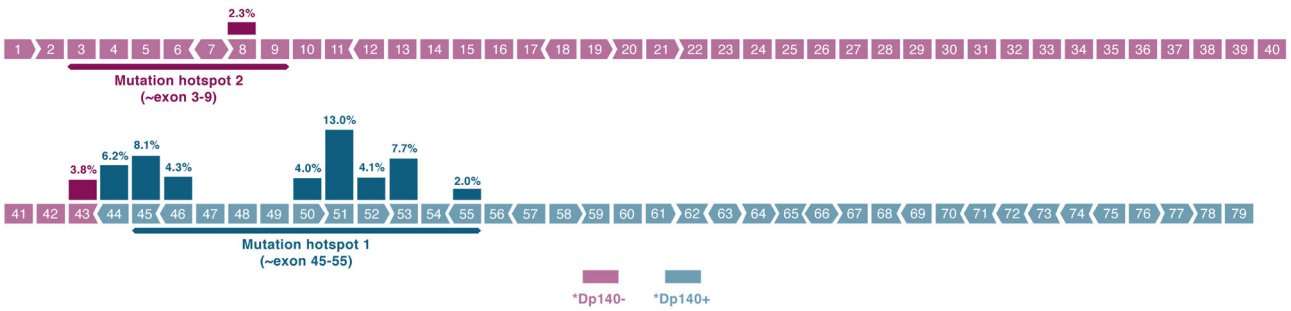

FIGURE 1 Schematic of the *DMD* gene, noting the two 'hotspots' and the estimated proportion of individuals with DMD whose reading frames will be restored, hypothetically, by skipping the indicated exon within each hotspot, with the Dp140^{-} and Dp140^{+} regions indicated by color. DMD patients may be amenable to skipping more than one exon, thus percentage groups are not mutually exclusive. *Pathogenic variants within the Dp140^{-} region are hypothesized to be predictive of cognitive involvement, while those in the Dp140^{+} region are not. Exon-skipping amenability data from reference 7, Dp140 and cognitive function data from reference 19, and hotspot data from reference 31

ungrouped data were available. For all outcomes, the range of estimated scores by genotype was presented. Although too few data were available to synthesize estimates for mortality, the results are nevertheless summarized.

Age categories were selected to represent the key age ranges for the various clinical outcomes of interest across the range of progression outcomes considered. All data were presented grouped by age category (≤7 years, 8-13 years, 14-16 years, 17-19 years, and 20^{+} years) and genotype, except for IQ, which was not age-stratified[19] and was presented according to whether Dp140 was likely affected.[30] As an IQ of less than 70 is indicative of intellectual disability,[33] the proportion among each Dp140 subtype with values within that range is also reported. For measures of cardiac and pulmonary function, as function is relatively preserved until at least adolescence,[2] results for patients less than 13 years of age are included for reference only.

3 | RESULTS

Implementing the search strategy yielded 8582 hits; 1067 records underwent full-text review. Seventy-one potentially relevant articles were identified, 57 of which reported outcomes of interest by age and genotype (Figure 2). Of those 57 studies, 54 described outcomes related to ambulatory, upper limb, pulmonary, or cognitive function in at least one study or with at least 50 patients (Figure 3). We considered numerous outcome measures of interest a priori for understanding DMD progression (eg, measures of forced expiratory volume [FEV], Brooke upper limb score, left ventricular fractional shortening [LVFS], or North Star Ambulatory Assessment [NSAA], Muscle Function Measure [MFM], or Bayley III scores). However, because outcomes data by genotype and age were too few, further synthesis was not undertaken (Figure 3).

The evidence base included 14 cross-sectional studies, 25 prospective or retrospective cohort studies, 7 randomized clinical trials, and 8 nonrandomized clinical studies (Table S4). DMD registries and databases provided data for 10 studies, including 2 publications from CINRG[9,34] and 1 publication each from the United Dystrophinopathy Project (UDP),[35] Duchenne Registry,[12] Translational Research in Europe—Assessment & Treatment of Neuromuscular Diseases (TREAT-NMD) DMD database,[13] UMD-DMD Cochin database,[36] French Registry for DMD,[37] Dutch Dystrophinopathy Database,[10] Japanese Registry of Muscular Disorders,[38] and one publication from

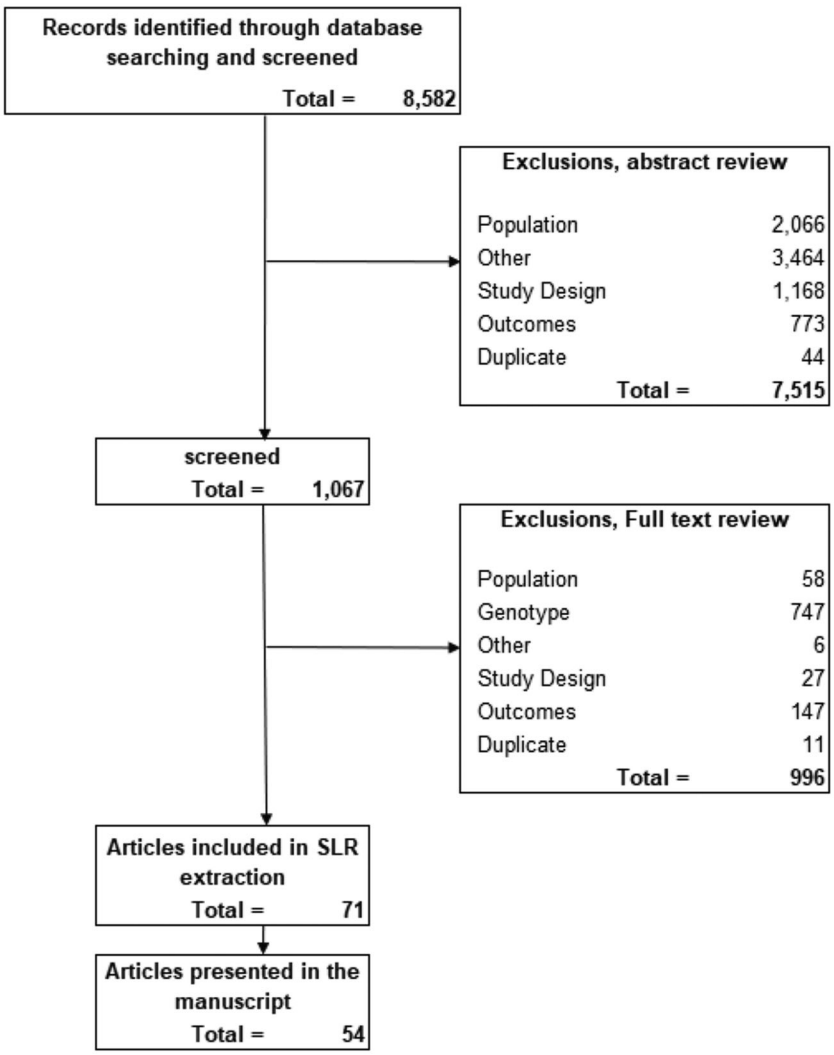

FIGURE 2 PRISMA diagram outlining study inclusion and exclusion

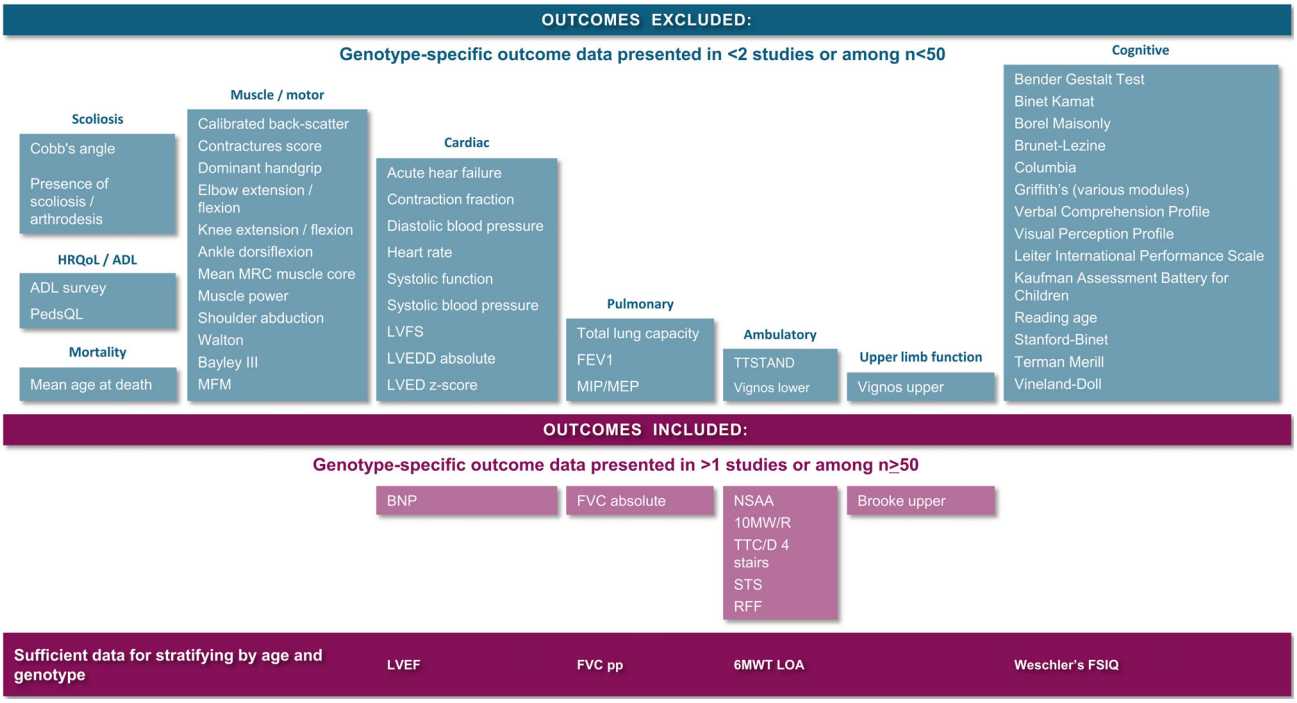

FIGURE 3 Availability of data on outcome measures by genotype

both the Strategic Targeting of Registries and International Database of Excellence—Neuromuscular Disorders (STRIDE-NMD) and CINRG databases.[39] Nine studies (17%) presented data on patients where individual corticosteroid treatment status was known, 22 (41%) presented data grouped by corticosteroid use, and 23 (43%) did not describe corticosteroid use. The findings of the quality assessment for the 54 studies are presented in Table S5.

3.1 | Ambulatory function

Twenty-four studies reported age at LOA.[9,10,12,13,36-55] Data estimating the mean age at LOA were presented in 20 studies (Figure 4A),[10,36-38,40-55] and median age in 18 studies (Figure S1).[10,36,38,40-49,51-55] These parameters were calculated from patients who had all experienced LOA. Estimates of mean (95% confidence interval) age at LOA ranged from 9.1 (8.7-9.6) years among 90 patients amenable to skipping exon 53,[10,36,37,40,42,49,50,53-55] to 11.5 (9.5-13.5) years among three patients amenable to skipping exon 8.[41,53] Among the subset treated with corticosteroids, ages at LOA were generally later, ranging from 9.1 (5.0-13.3) years in two patients with pathogenic variants amenable to stop-codon readthrough and 10.0 (9.2-10.8) years in 18 patients with skip 53–amenable variants[10,36,42,55] to 12.7 (11.2-14.2) years in 15 patients with skip 44–amenable variants.[10,41,50] Estimates of the median (minimum-maximum) age at LOA ranged from 9.0 (6.0-12.0) years in 32 patients with skip 53–amenable pathogenic variants[36,40,42,49,50,53-55] to 12.0 (7.0-13.0) years in 8 patients with skip 55–amenable variants (Figure S1).[45,49,53] Among the subset treated with corticosteroids, estimates ranged from 8.3 (8.0-8.5) years in two patients with pathogenic variants amenable to stop-codon readthrough[41,43] to 12 years in a patient with a skip 55–amenable variant.[53]

Estimates of median age at LOA were presented from three large non–treatment-specific registries,[9,12,13] and one long-term study of ataluren treatment for patients with pathogenic variants amenable to stop-codon readthrough therapy (Figure 4B).[39] Corticosteroid use was categorized differently between the studies: one study presented estimates among corticosteroid-treated patients[12]; a second study presented an overall cohort with a corticosteroid-treated subgroup[9]; a third study presented estimates among those "never" and "ever" treated with corticosteroids[13]; and a fourth study presented overall estimates for the group, for which 68% were treated with corticosteroids.[39] Among patients treated with corticosteroids, estimates of the median time to LOA tended to range from 12 (in patients amenable to skip 45 or 51) to 20 years (in del 44 [amenable to skipping 43 or 45] or skip 44–amenable patients).[9,12,13]

Cross-sectional and longitudinal data for the 6MWT were available by age and genotype from 16 studies.[11,25-27,48,56-66] Cross-sectional data for mean (SD) 6MWT distance (Figure 5A), among those 3 to ≤7 years old, ranged from 335.3 (85.5) meters in 7 patients amenable to skipping exon 46[11] to 400.4 (58.9) meters in 110 patients amenable to skipping exon 51.[11,48,58,60,63,64] Among those 8 to 13 years old, the 6MWT distance ranged from 330.4 (89.6) meters in 7 patients amenable to skipping exon 45[11] to 452 meters in a patient with a skip 46–amenable pathogenic variant.[63] Most patients for whom 6MWT data were available were corticosteroid-treated (eg, 99% of 309 skip 51–amenable patients, 63% of 507 stop-codon

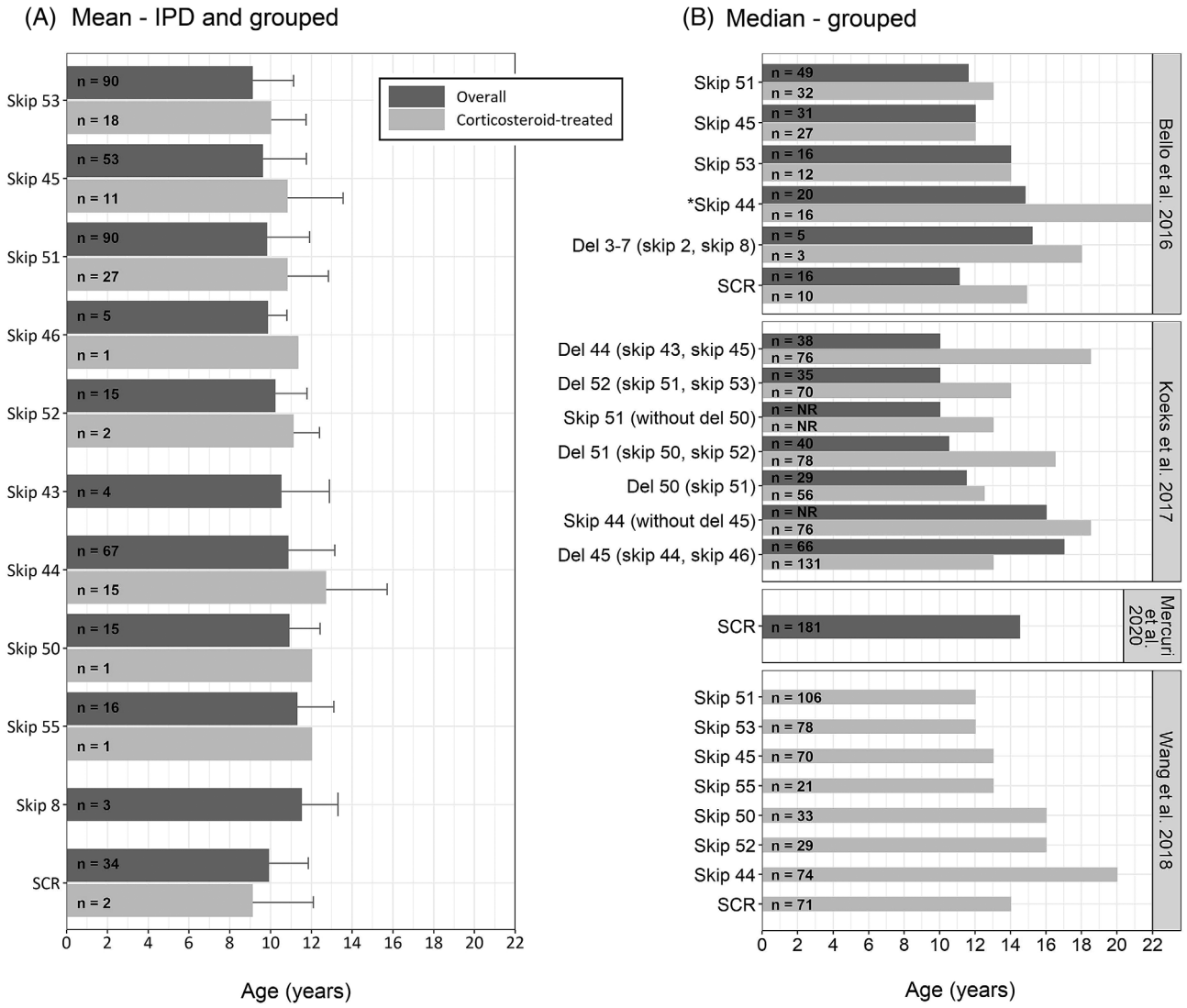

FIGURE 4 Mean (SD) age at LOA by genotype from IPD and grouped estimates from DMD patients who had lost ambulation—overall and among those corticosteroid-treated (A); and median age at LOA by genotype, with grouped estimates from DMD patients who had and had not lost ambulation—overall and among those with corticosteroid treatment (B). Abbreviations: Del, deletion; DMD, Duchenne muscular dystrophy; IPD, individual patient data; LOA, loss of ambulation; SCR, stop-codon readthrough; SD, standard deviation. *50% LOA had not occurred at the time of analysis for the 16 skip 44-amenable, corticosteroid-treated patients.[9] A, Patients from the Goemans et al (2017) study had been treated previously with drisapersen (n = 3)[48]; and one patient from the Kulshreshtha et al (2019) study had been treated previously with ataluren (n = 1).[44] B, Patients from the Mercuri et al (2020) study had been treated previously with ataluren (n = 181)[39]

readthrough–amenable patients, and all patients from other genotype groups). Therefore, results for the corticosteroid-treated subset are not shown. Cross-sectional data on percent predicted 6MWT showed similar trends by genotype, but data were sparse (data not shown). Longitudinal data on 6MWT by age, genotype, and other disease-modifying treatments are presented in Figure S2.

3.2 | Pulmonary function

Six studies reported cross-sectional measures of percent predicted forced vital capacity (FVC) (n = 146; Figure 5B).[34,36,37,46,53,61] Among those 8 to 13 years of age, FVC percent predicted ranged from 26% (in a patient with a skip 55–amenable pathogenic variant)[53] to 90.0% (in a patient with a skip 52–amenable variant).[36] Pulmonary function generally declined with increasing age across genotypes, and among those over 19 years of age, ranged from 12% (in a patient amenable to skipping exons 44 and 55)[53] to 33% (in a patient amenable to skipping exon 51). Seventy-eight of the 146 patients were corticosteroid-treated, and most (n = 119) were 8 to 13 years of age at time of assessment. Among these boys, FVC percent predicted ranged from 73% (in a patient with a skip 53–amenable pathogenic variant)[36] to 90.0% (in a patient with a skip 52–amenable variant).[53] One 17-year-old patient, who was amenable to stop-codon readthrough therapy,

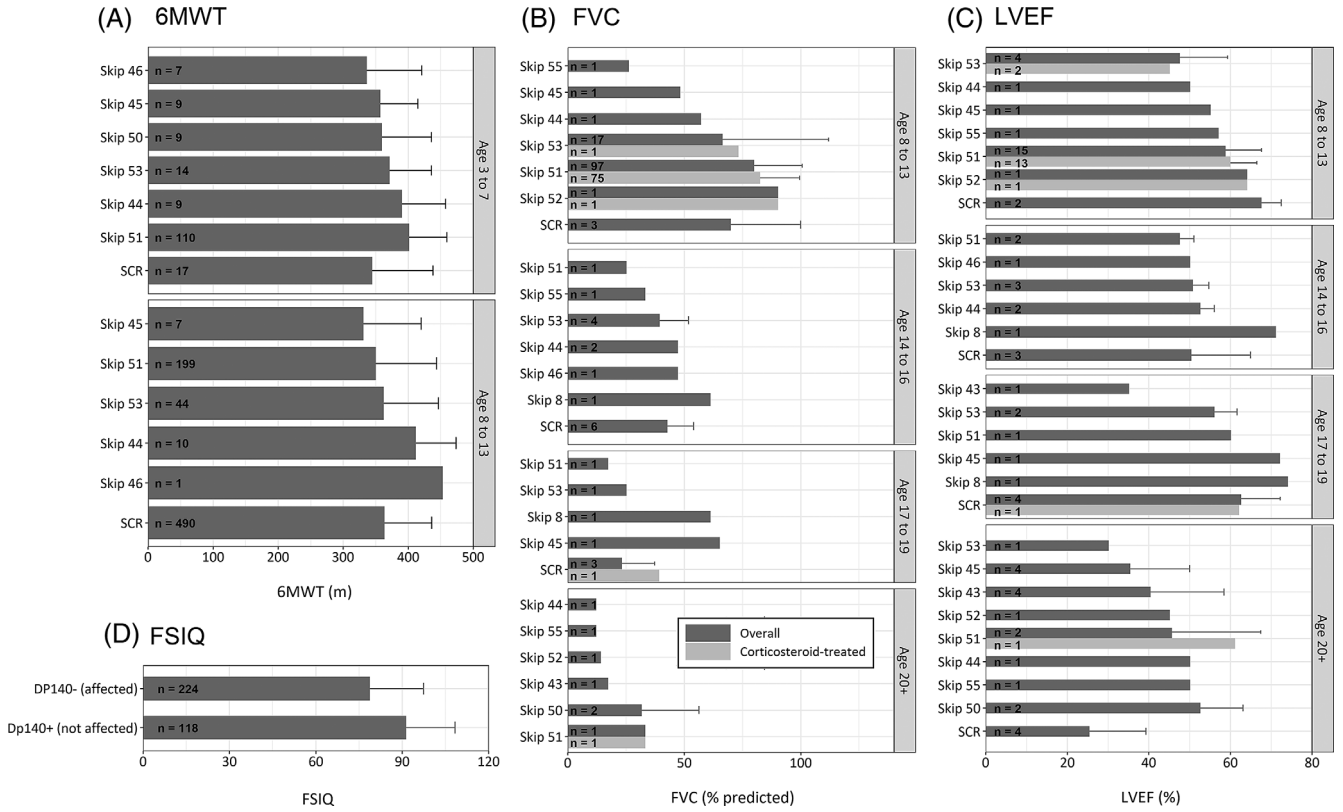

FIGURE 5 Mean (SD) 6MWT among those with corticosteroid treatment (unless otherwise noted) (A); percent predicted FVC (B); LVEF (C); by genotype and age, overall, and among corticosteroid-treated patients; and Weschler's FSIQ by genotype (predicted Dp140 isoform status) (D). Abbreviations: 6MWT, 6-minute walk test; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; Dp, dystrophin protein; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; m, meter; SCR, stop-codon readthrough; SD, standard deviation; FSIQ, full-scale intelligence quotient. A, For 6MWT, patients from the Goemans et al (2017) study had been treated previously with drisapersen (n = 12)[48]; patients from the Mercuri et al study (2016) had been treated previously with ataluren (n = 49)[26]. B, For FVC, in the Seferian et al (2015) study, 19 of 25 patients received ACE inhibitors[53]; C, for LVEF, in the Fayssoil et al (2017) study, all patients received ACE inhibitors[67]; in the Alfano et al (2019) study, 2 of 12 patients received losartan (ARB) and carvedilol (beta blocker), whereas 7 of 12 received unspecified preventive cardiovascular medications[70]; and, in the Sato et al (2019) study, 1 patient received carvedilol (beta blocker) and the ACE inhibitor enalapril[69]

had an FVC percent predicted of 39%, and a 20.5-year-old patient with a skip 51–amenable variant had an FVC of 33%.[53]

3.3 | Cardiac function

Seven studies reported LVEF data (n = 58; Figure 5C).[36,44,53,67-70] Among those 8 to 13 years of age, estimates ranged from 47.5% (among 4 patients with skip 53–amenable pathogenic variants),[36] to 67.5% (among 2 patients with pathogenic variants amenable to stop-codon readthrough).[36,53] As with pulmonary function, cardiac function declined with increasing age across genotypes, and, among those older than 19 years of age, ranged from 25.3% (among 4 patients with pathogenic variants amenable to stop-codon readthrough)[44,67] to 52.5% (in 2 patients with skip 50–amenable pathogenic variants).[53] Seventeen of the 58 patients had confirmed corticosteroid treatment, and most were 8 to 13 years of age. Estimates ranged from 45% (in 2 patients—1 with a variant amenable to skip 51 or 53 and 1 to skip 53)[36] to 64% (among a patient with a skip 52–amenable variant).[36] One 17.8-year-old patient amenable to stop-codon readthrough had an LVEF of 62%, and a 20.5-year-old adult amenable to skipping exon 51 had an LVEF of 61%.[53]

3.4 | Cognitive function

Ten studies reported cognitive function by cross-sectional scores on the Weschler IQ test, according to pathogenic variants classifiable by dystrophin protein domain affected (Figure 5D).[19,29,30,45,71-76] The mean (SD) IQ among the 118 patients with $Dp140^{+}$ variants was 91.3 (17.1); 8% had an IQ of less than 70.[19,29,30,71-74,76] The mean (SD) IQ among the 224 patients with $Dp140^{-}$ variants was 78.8 (18.6), and 29% had an IQ of less than 70 (Figure 5D).[19,29,30,45,71-76] No trend was identified when Weschler IQ data were classified according to exon-skip amenability (data not shown).

3.5 | Mortality

Few mortality data were identified and no study specifically estimated mortality by genotype. As a result, a synthesis was not possible. One 1991 study reported four DMD patients were deceased at the time of the (retrospective) study in their molecular analysis of 67 DMD patients; two of these patients had exon-skip–amenable classifiable pathogenic variants and those were skip 43 and skip 51 amenable, but no cause of death was provided.[40] Another study from 2016 reported age and cause of death in 8 of 91 (8.8%) patients over a 24-month period; 4 had exon-skip–amenable variants (1 each with variants amenable to skip 51, 51 and/or 53, and 50 and/or 52, and 1 with a nonsense mutation).[77] The cause of death among seven patients was cardiomyopathy and/or respiratory failure, one of which was reported in a 12.3-year-old boy with a pathogenic variant in exon 56. The eighth subject in that noninterventional study had a variant amenable to skipping exon 51 and died at 14.8 years of age after a fall.[77]

4 | DISCUSSION

Understanding the impact of pathogenic variants in DMD is important for prognosis,[7] and research suggests major differences in the natural history. In this review we have identified three large studies with good capture of ambulatory function and, as a result, the impact of genotype on LOA is well-described. Individuals with pathogenic variants amenable to skipping exon 44 may have a milder phenotype than individuals with other variants.[9,12,13] However, for most other outcomes, particularly those occurring later in life, such as mortality, few comparable data were available to infer trends by age and genotype.[36,37,46,47,53,63,78,79] Only a few studies aimed to compare outcomes among patients of different genotypes, and genotype-specific samples tended to be small.[11,36,78] Some outcomes of interest, including the impact of genotype on mortality in DMD, were not described at all. Clearly, many gaps remain in our understanding of genotype and phenotype. As more outcome studies with capture of careful DMD genotyping and other key clinical factors (such as corticosteroid regimen) are published, meta-analysis may further elucidate the effects of DMD genotype on the clinical course.

This review has highlighted the major reasons why relationships between genotype and the occurrence of key natural history milestones are not easily synthesized, such as variability in outcome measures and description of pathogenic variants across studies, between-patient heterogeneity, and genetic variation in other contributing genes.[15] These gaps could in part be reconciled by increasing the reporting of outcomes by genotype in prospective studies that could potentially allow for future meta-analysis across studies. Challenges remain in interpretation due to study design and inclusion criteria.[35,61,64] Observed differences in the age at key clinical milestones between this synthesis, and registry estimates,[9,12,13] highlight variability across data sources. As an example, data from treatment trials are derived from populations with at least some function remaining, and data on patients unable to perform functional assessments, or who have died, are not represented. This type of survival bias likely resulted in a sample phenotypically milder than would be observed from a natural history study where more severely affected individuals would not have been artificially removed from analysis. In addition, corticosteroid use is associated with delayed muscular, ambulatory, pulmonary, and cardiac function decline and should be captured in every study, along with age started, type and dose given, and duration.[13] The use of any other disease-modifying therapies should be similarly reported.

Genotypic influence on the clinical course of patients with DMD is now beginning to be understood. Some pathogenic variants allow expression of small amounts of dystrophin, perhaps due to re-initiation of translation downstream of N-terminal domain mutations resulting in "revertant" DMD fibers,[80,81] or low levels of spontaneous exon skipping,[7,10] which would result in a relatively more positive DMD trajectory.[9] Indeed, spontaneous skipping is suggested to contribute to the milder phenotype observed among patients with pathogenic variants amenable to exon 44 skipping.[10,15] Similarly, the observed variation in phenotype among those with nonsense mutations may be due to occasional readthrough, the frequency of which depends on the location and sequences flanking the variant.[15] However, disease severity varies even for individuals with the same pathogenic variant within the same family; thus, genetic modifiers also influence the clinical course of DMD.[82] For example, variants of the *LTBP4* gene modify ambulatory function, variants of the *ACTN3* gene modify cardiac decline, and variants of the *SPP1* gene affect response to long-term corticosteroid treatment through inflammatory pathways in DMD patients.[16,83-85]

Another potentially important contributor to heterogeneity in DMD is variation in dystrophin isoform expression. The *DMD* gene encodes a number of different protein isoforms named after their length and splicing patterns. These include full-length dystrophin (Dp427), expressed in skeletal and cardiac muscle and the brain; Dp260, expressed in the retina; Dp140, expressed in the brain, retina, and kidney; and Dp116, expressed in peripheral nerves.[86] Pathogenic variants in both the coding and regulatory regions associated with each isoform are predicted to affect tissue-specific function.[30,72] Within the studies included in this review, the presence of cardiac dysfunction was reported to vary by dystrophin isoform affected.[87,88] The relationships are emerging for other outcomes. Dystrophin plays a role in brain development and neurodevelopmental disorders, including autism spectrum disorder, attention-deficit hyperactive disorder, obsessive-compulsive disorder, and epilepsy, and other language and learning developmental delays are associated with DMD.[28,89] Cognitive dysfunction, which affects approximately 30% of patients, appears to be present from birth and stable over time in DMD.[19,90] In the studies included in this review, pathogenic variants affecting the Dp140 isoform, hypothesized to underlie intellectual impairment in DMD,[28-30] were inconsistently found to be predictive of cognitive dysfunction.[19,29,30,45,49,72-76,91-96] Although some studies of cognitive function in DMD focused on variants affecting the entire sequence of Dp140 (downstream of exon 45),[19] others focused on the noncoding regulatory region around exons 44 and 45.[28-30] Investigators classified variants in the Dp140 isoform differently.[29,30] In this

synthesis, we classified pathogenic variants lying downstream of exon 45 as "affecting Dp140" (Dp140^{-}),[28] unless otherwise indicated by the original investigators. Although a trend toward lower IQ was observed among patients classified as Dp140^{-}, more sophisticated classification of underlying variants may better elucidate their relationship with IQ. Unfortunately, in this review sufficient data to categorize pathogenic variants were not presented in all studies reporting IQ data.

Although assessment of outcomes according to mutation location was investigated, limited data availability ruled-out these analyses. It was not the focus of our review, but we did identify studies that reported clinical heterogeneity by variant type (rather than location). In one study of 436 DMD patients, point mutations were associated with a significantly younger age at cardiac dysfunction as well as deletions with a significantly younger age at LOA.[97] Pane et al also found a trend toward better 6MWT scores among those with duplications compared to those with other variant types.[11,37] In other studies, however, evidence did not support differences by pathogenic variant type, specifically for Brooke or Vignos scores,[79] or for motor involvement, cardiac, and respiratory function.[93] At present, variability in outcome measures and variant types included across these studies makes understanding the potential impact of mutation location on DMD patient prognosis a challenge.

5 | CONCLUSIONS

DMD is a degenerative neuromuscular disease resulting in progressive loss of muscle function and premature death,[2,3] regardless of genotype. A systematic synthesis of existing literature reporting the relationship between genotype and phenotype in DMD consistently shows, on average, that patients with pathogenic variants amenable to skipping exon 44 may have a milder phenotype with respect to age at LOA. However, likely due to limited data, outcomes occurring later in life did not show clear trends by genotype, and individual clinical courses are heterogeneous.

CONFLICT OF INTEREST

S.M.S. and A.T.M. are employees of Broadstreet HEOR, which received funds from Sarepta for this work. K.L.G. is currently employed by Sarepta. R.M.S. was employed by Sarepta at the time of this work. A.M.C. has served on advisory boards for Sarepta, Avexis, Genentech-Roche, and NS-Pharma, and serves on the data management safety board for Catabasis.

ETHICAL PUBLICATION STATEMENT

The authors confirm that they have read the Journal's position on issues involved in ethical publication and confirm that this report is consistent with those guidelines.

AUTHOR CONTRIBUTIONS

All authors participated in the design of this systematic review. S.M.S. and A.T.M. were responsible for the conduct of the systematic review, data extraction, and synthesis. All authors contributed to interpretation of the findings. S.M.S., A.T.M., and A.C. developed the first manuscript draft. All authors edited the draft of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were generated during the conduct of this literature review.

REFERENCES

1. Wein N, Alfano L, Flanigan KM. Genetics and emerging treatments for Duchenne and Becker muscular dystrophy. *Pediatr Clin North Am*. 2015;62:723-742.
2. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurol*. 2018;17:347-361.
3. Yiu EM, Kornberg AJ. Duchenne muscular dystrophy. *J Paediatr Child Health*. 2015;51:759-764.
4. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol*. 2018;17:251-267.
5. Gao QQ, McNally EM. The dystrophin complex: structure, function, and implications for therapy. *Compr Physiol*. 2015;5:1223-1239.
6. Mah JK. Current and emerging treatment strategies for Duchenne muscular dystrophy. *Neuropsychiatr Dis Treat*. 2016;12:1795-1807.
7. Aartsma-Rus A, Fokkema I, Verschuuren J, et al. Theoretic applicability of antisense-mediated exon skipping for Duchenne muscular dystrophy mutations. *Hum Mutat*. 2009;30:293-299.
8. Bladen CL, Salgado D, Monges S, et al. The TREAT-NMD DMD global database: analysis of more than 7,000 Duchenne muscular dystrophy mutations. *Hum Mutat*. 2015;36:395-402.
9. Bello L, Morgenroth LP, Gordish-Dressman H, Hoffman EP, McDonald CM, Cirak S. DMD genotypes and loss of ambulation in the CINRG Duchenne natural history study. *Neurology*. 2016;87:401-409.
10. van den Bergen JC, Ginjaar HB, Niks EH, Aartsma-Rus A, Verschuuren JJ. Prolonged ambulation in Duchenne patients with a mutation amenable to exon 44 skipping. *J Neuromuscul Dis*. 2014;1:91-94.
11. Pane M, Mazzone ES, Sormani MP, et al. 6 minute walk test in Duchenne MD patients with different mutations: 12 month changes. *PLoS One*. 2014;9:e83400.
12. Wang RT, Barthelemy F, Martin AS, et al. DMD genotype correlations from the Duchenne registry: endogenous exon skipping is a factor in prolonged ambulation for individuals with a defined mutation subtype. *Hum Mutat*. 2018;39:1193-1202.
13. Koeks Z, Bladen CL, Salgado D, et al. Clinical outcomes in Duchenne muscular dystrophy: a study of 5345 patients from the TREAT-NMD DMD global database. *J Neuromuscul Dis*. 2017;4:293-306.
14. The Cooperative International Neuromuscular Research Group. The Cooperative International Neuromuscular Research Group (CINRG): Ongoing studies. 2019. https://cinrgresearch.org. Accessed 29 November 2021.
15. Aartsma-Rus A, Ginjaar IB, Bushby K. The importance of genetic diagnosis for Duchenne muscular dystrophy. *J Med Genet*. 2016;53:145-151.
16. Bello L, Kesari A, Gordish-Dressman H, et al. Genetic modifiers of ambulation in the cooperative international neuromuscular research group Duchenne natural history study. *Ann Neurol*. 2015;77:684-696.
17. Barp A, Bello L, Politano L, et al. Genetic modifiers of Duchenne muscular dystrophy and dilated cardiomyopathy. *PLoS One*. 2015;10:e0141240.
18. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62:1006-1012.

19. Chieffo D, Brogna C, Berardinelli A, et al. Early neurodevelopmental findings predict school age cognitive abilities in Duchenne muscular dystrophy: a longitudinal study. *PLoS One*. 2015;10:e0133214.
20. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Epidemiology*. 2007;18:800-804.
21. Riley DS, Barber MS, Kienle GS, et al. CARE guidelines for case reports: explanation and elaboration document. *J Clin Epidemiol*. 2017;89:218-235.
22. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ (Clin Res Ed)*. 2019;366:l4898.
23. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg*. 2003;73:712-716.
24. Fletcher S, Adams AM, Johnsen RD, Greer K, Moulton HM, Wilton SD. Dystrophin isoform induction in vivo by antisense-mediated alternative splicing. *Mol Ther*. 2010;18:1218-1223.
25. McDonald CM, Campbell C, Torricelli RE, et al. Ataluren in patients with nonsense mutation Duchenne muscular dystrophy (ACT DMD): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;390:1489-1498.
26. Mercuri E, McIntosh J, Fengbin J, et al. Ambulatory outcome measures after the initial 48-week period of a long-term, open-label treatment with Ataluren in patients previously enrolled in Ataluren clinical trials for nonsense mutation Duchenne muscular dystrophy (nmDMD). *Ann Neurol*. 2016;80(suppl):S367-S369.
27. McDonald CM, Henricson EK, Abresch RT, et al. The 6-minute walk test and other endpoints in Duchenne muscular dystrophy: longitudinal natural history observations over 48 weeks from a multicenter study. *Muscle Nerve*. 2013;48:343-356.
28. Thangarajh M, Hendriksen J, McDermott MP, Martens W, Hart KA, Griggs RC. Relationships between DMD mutations and neurodevelopment in dystrophinopathy. *Neurology*. 2019;93:e1597-e1604.
29. Bardoni A, Felisari G, Sironi M, et al. Loss of Dp140 regulatory sequences is associated with cognitive impairment in dystrophinopathies. *Neuromuscul Disord*. 2000;10:194-199.
30. Chamova T, Guergueltcheva V, Raycheva M, et al. Association between loss of dp140 and cognitive impairment in duchenne and Becker dystrophies. *Balkan J Med Genet*. 2013;16:21-30.
31. Echigoya Y, Lim KRQ, Nakamura A, Yokota T. Multiple exon skipping in the Duchenne muscular dystrophy hot spots: prospects and challenges. *J Pers Med*. 2018;8(4):41.
32. Matthews E, Brassington R, Kuntzer T, Jichi F, Manzur AY. Corticosteroids for the treatment of Duchenne muscular dystrophy. *Cochrane Database of Syst Rev*., 2016;(5):CD003725. doi: 10.1002/14651858.CD003725.pub4
33. School Psychological Files. Understanding test scores. https://schoolpsychologistfiles.com/testscores. Accessed 29 November 2021.
34. Khan N, Eliopoulos H, Han L, et al. Eteplirsen treatment attenuates respiratory decline in ambulatory and non-ambulatory patients with Duchenne muscular dystrophy. *J Neuromuscul Dis*. 2019;6:213-225.
35. Kinane TB, Mayer OH, Duda PW, Lowes LP, Moody SL, Mendell JR. Long-term pulmonary function in Duchenne muscular dystrophy: comparison of Eteplirsen-treated patients to natural history. *J Neuromuscul Dis*. 2018;5:47-58.
36. Servais L, Montus M, Guiner CL, et al. Non-ambulant Duchenne patients theoretically treatable by exon 53 skipping have severe phenotype. *J Neuromuscul Dis*. 2015;2:269-279.
37. Hogrel JY, Wary C, Moraux A, et al. Longitudinal functional and NMR assessment of upper limbs in Duchenne muscular dystrophy. *Neurology*. 2016;86:1022-1030.
38. Okubo M, Noguchi S, Hayashi S, et al. Exon skipping induced by nonsense/frameshift mutations in DMD gene results in Becker muscular dystrophy. *Hum Genet*. 2020;139:247-255.
39. Mercuri E, Muntoni F, Osorio AN, et al. Safety and effectiveness of ataluren: comparison of results from the STRIDE registry and CINRG DMD natural history study. *J Comp Eff Res*. 2020;9:341-360.
40. Covone AE, Lerone M, Romeo G. Genotype-phenotype correlation and germline mosaicism in DMD/BMD patients with deletions of the dystrophin gene. *Hum Genet*. 1991;87:353-360.
41. Spitali P, Zaharieva I, Bohringer S, et al. TCTEX1D1 is a genetic modifier of disease progression in Duchenne muscular dystrophy. *Eur J Hum Genet*. 2020;28:815-825.
42. Brogna C, Coratti G, Pane M, et al. Long-term natural history data in Duchenne muscular dystrophy ambulant patients with mutations amenable to skip exons 44, 45, 51 and 53. *PLoS One*. 2019;14:e0218683.
43. Fujii T, Takeshita E, Iwata Y, et al. Cumulative jerk as an outcome measure in nonambulatory Duchenne muscular dystrophy. *Brain Dev*. 2019;41:796-802.
44. Kulshrestha R, Sewry C, Emery N, Willis T. Additional benefi ts of Ataluren: 2 case reports. *J Neuromuscul Dis*. 2019;6(suppl 1):S30 (abstract D26).
45. Daoud F, Angeard N, Demerre B, et al. Analysis of Dp71 contribution in the severity of mental retardation through comparison of Duchenne and Becker patients differing by mutation consequences on Dp71 expression. *Hum Mol Genet*. 2009;18:3779-3794.
46. Ebrahimi-Fakhari D, Dillmann U, Flotats-Bastardas M, et al. Off-label use of Ataluren in four non-ambulatory patients with nonsense mutation Duchenne muscular dystrophy: effects on cardiac and pulmonary function and muscle strength. *Front Pediatr*. 2018;6:316.
47. Gayraud J, Ramonatxo M, Rivier F, Humberclaude V, Petrof B, Matecki S. Ventilatory parameters and maximal respiratory pressure changes with age in Duchenne muscular dystrophy patients. *Pediatr Pulmonol*. 2010;45:552-559.
48. Goemans N, Tulinius M, Kroksmark AK, Wilson R, van den Hauwe M, Campion G. Comparison of ambulatory capacity and disease progression of Duchenne muscular dystrophy subjects enrolled in the drisapersen DMD114673 study with a matched natural history cohort of subjects on daily corticosteroids. *Neuromuscul Disord*. 2017;27:203-213.
49. Hodgson SV, Abbs S, Clark S, et al. Correlation of clinical and deletion data in Duchenne and Becker muscular dystrophy, with special reference to mental ability. *Neuromuscul Disord*. 1992;2:269-276.
50. Kleopa KA, Drousiotou A, Mavrikiou E, Ormiston A, Kyriakides T. Naturally occurring utrophin correlates with disease severity in Duchenne muscular dystrophy. *Hum Mol Genet*. 2006;15:1623-1628.
51. Magri F, Del Bo R, D'Angelo MG, et al. Clinical and molecular characterization of a cohort of patients with novel nucleotide alterations of the dystrophin gene detected by direct sequencing. *BMC Med Genet*. 2011;12:37.
52. Nigro V, Nigro G, Esposito MG, et al. Novel small mutations along the DMD/BMD gene associated with different phenotypes. *Hum Mol Genet*. 1994;3:1907-1908.
53. Seferian AM, Moraux A, Annoussamy M, et al. Upper limb strength and function changes during a one-year follow-up in non-ambulant patients with Duchenne muscular dystrophy: an observational multicenter trial. *PLoS One*. 2015;10:e0113999.
54. Talkop UA, Klaassen T, Piirsoo A, et al. Duchenne and Becker muscular dystrophies: an Estonian experience. *Brain Dev*. 1999;21:244-247.
55. van Deutekom JC, Janson AA, Ginjaar IB, et al. Local dystrophin restoration with antisense oligonucleotide PRO051. *N Engl J Med*. 2007;357:2677-2686.
56. Bushby K, Finkel R, Wong B, et al. Ataluren treatment of patients with nonsense mutation dystrophinopathy. *Muscle Nerve*. 2014;50:477-487.

57. Goemans N, Mercuri E, Belousova E, et al. A randomized placebo-controlled phase 3 trial of an antisense oligonucleotide, drisapersen, Duchenne muscular dystrophy. *Neuromuscul Disord*. 2018;28:4-15.
58. Goemans NM, Tulinius M, van den Akker JT, et al. Systemic administration of PRO051 in Duchenne's muscular dystrophy. *N Engl J Med*. 2011;364:1513-1522.
59. Lowes LP, Alfano L, Dracker R, Duda P, Mendell J. Long-term treatment with eteplirsen in nonambulatory patients: a case study in identical twins. *Acta Myol*. 2017;36:73.
60. McDonald CM, Wong B, Flanigan KM, et al. Placebo-controlled phase 2 trial of drisapersen for Duchenne muscular dystrophy. *Ann Clin Transl Neurol*. 2018;5:913-926.
61. Mendell JR, Goemans N, Lowes LP, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. *Ann Neurol*. 2016;79:257-271.
62. Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol*. 2013;74:637-647.
63. Vill K, Ille L, Schroeder SA, Blaschek A, Müller-Felber W. Six-minute walk test versus two-minute walk test in children with Duchenne muscular dystrophy: is more time more information? *Eur J Paediatr Neurol*. 2015;19:640-646.
64. Voit T, Topaloglu H, Straub V, et al. Safety and efficacy of drisapersen for the treatment of Duchenne muscular dystrophy (DEMAND II): an exploratory, randomised, placebo-controlled phase 2 study. *Lancet Neurol*. 2014;13:987-996.
65. Ruggiero L, Iodice R, Esposito M, et al. One-year follow up of three Italian patients with Duchenne muscular dystrophy treated with ataluren: is earlier better? *Ther Adv Neurol Disord*. 2018;11:1756286418809588.
66. Frank DE, Schnell FJ, Akana C, et al. Increased dystrophin production with golodirsen in patients with Duchenne muscular dystrophy. *Neurology*. 2020;94:e2270-e2282.
67. Fayssoil A, Yaou RB, Ogna A, et al. Clinical profiles and prognosis of acute heart failure in adult patients with dystrophinopathies on home mechanical ventilation. *ESC Heart Fail*. 2017;4:527-534.
68. Jin JB, Carter JC, Sheehan DW, Birnkrant DJ. Cardiopulmonary phenotypic discordance is common in Duchenne muscular dystrophy. *Pediatr Pulmonol*. 2019;54:186-193.
69. Sato M, Shiba N, Miyazaki D, et al. Amelioration of intracellular Ca(2+) regulation by exon-45 skipping in Duchenne muscular dystrophy-induced pluripotent stem cell-derived cardiomyocytes. *Biochem Biophys Res Commun*. 2019;520:179-185.
70. Alfano LN, Charleston JS, Connolly AM, et al. Long-term treatment with eteplirsen in nonambulatory patients with Duchenne muscular dystrophy. *Medicine (Baltimore)*. 2019;98:e15858.
71. Bushby KM, Appleton R, Anderson LV, Welch JL, Kelly P, Gardner-Medwin D. Deletion status and intellectual impairment in Duchenne muscular dystrophy. *Dev Med Child Neurol*. 1995;37:260-269.
72. Milic Rasic V, Vojinovic D, Pesovic J, et al. Intellectual ability in the Duchenne muscular dystrophy and dystrophin gene mutation location. *Balkan J Med Genet*. 2014;17:25-35.
73. Taylor PJ, Betts GA, Maroulis S, et al. Dystrophin gene mutation location and the risk of cognitive impairment in Duchenne muscular dystrophy. *PLoS One*. 2010;5:e8803.
74. Wingeier K, Giger E, Strozzi S, et al. Neuropsychological impairments and the impact of dystrophin mutations on general cognitive functioning of patients with Duchenne muscular dystrophy. *J Clin Neurosci*. 2011;18:90-95.
75. Giliberto F, Ferreiro V, Dalamon V, Szijan I. Dystrophin deletions and cognitive impairment in Duchenne/Becker muscular dystrophy. *Neurol Res*. 2004;26:83-87.
76. D'Angelo MG, Lorusso ML, Civati F, et al. Neurocognitive profiles in Duchenne muscular dystrophy and gene mutation site. *Pediatr Neurol*. 2011;45:292-299.
77. Connolly AM, Florence JM, Zaidman CM, et al. Clinical trial readiness in non-ambulatory boys and men with Duchenne muscular dystrophy: MDA-DMD network follow-up. *Muscle Nerve*. 2016;54:681-689.
78. Wang M, Birnkrant DJ, Super DM, Jacobs IB, Bahler RC. Progressive left ventricular dysfunction and long-term outcomes in patients with Duchenne muscular dystrophy receiving cardiopulmonary therapies. *Open Heart*. 2018;5:e000783.
79. Jung IY, Chae JH, Park SK, et al. The correlation analysis of functional factors and age with Duchenne muscular dystrophy. *Ann Rehabil Med*. 2012;36:22-32.
80. Winnard AV, Mendell JR, Prior TW, Florence J, Burghes AH. Frameshift deletions of exons 3-7 and revertant fibers in Duchenne muscular dystrophy: mechanisms of dystrophin production. *Am J Hum Genet*. 1995;56:158-166.
81. Gualandi F, Rimessi P, Trabanelli C, et al. Intronic breakpoint definition and transcription analysis in DMD/BMD patients with deletion/duplication at the 5′ mutation hot spot of the dystrophin gene. *Gene*. 2006;370:26-33.
82. Vo AH, McNally EM. Modifier genes and their effect on Duchenne muscular dystrophy. *Curr Opin Neurol*. 2015;28:528-534.
83. Nagai M, Awano H, Yamamoto T, Bo R, Matsuo M, Iijima K. The ACTN3 577XX null genotype is associated with low left ventricular dilation-free survival rate in patients with Duchenne muscular dystrophy. *J Card Fail*. 2020;26:841-848.
84. Bello L, Piva L, Barp A, et al. Importance of SPP1 genotype as a covariate in clinical trials in Duchenne muscular dystrophy. *Neurology*. 2012;79:159-162.
85. Flanigan KM, Ceco E, Lamar KM, et al. LTBP4 genotype predicts age of ambulatory loss in Duchenne muscular dystrophy. *Ann Neurol*. 2013;73:481-488.
86. Waite AB, Blake DJ. The dystrophin-glycoprotein complex in brain development and disease. *Trends Neurosci*. 2012;35:487-496.
87. Yamamoto T, Awano H, Zhang Z, et al. Cardiac dysfunction in Duchenne muscular dystrophy is less frequent in patients with mutations in the Dystrophin Dp116 coding region than in other regions. *Circ Genom Precis Med*. 2018;11:e001782.
88. Yamamoto T, Hiroyuki A, Imanishi T, et al. Expression of DP116 is a predisposing factor for cardiac dysfunction in duchenne muscular dystrophy. *J Neuromuscul Dis*. 2018;5(suppl 1):S103-S104.
89. Doorenweerd N, Mahfouz A, Van Putten M, et al. Timing and localization of human dystrophin isoform expression provide insights into the cognitive phenotype of Duchenne muscular dystrophy. *Neuromuscul Disord*. 2018;28(suppl 1):S10.
90. Cotton S, Voudouris NJ, Greenwood KM. Intelligence and Duchenne muscular dystrophy: full-scale, verbal, and performance intelligence quotients. *Dev Med Child Neurol*. 2001;43:497-501.
91. Banihani R, Smile S, Yoon G, et al. Cognitive and neurobehavioral profile in boys with Duchenne muscular dystrophy. *J Child Neurol*. 2015;30:1472-1482.
92. Lenk U, Hanke R, Thiele H, Speer A. Point mutations at the carboxy terminus of the human dystrophin gene: implications for an association with mental retardation in DMD patients. *Hum Mol Genet*. 1993;2:1877-1881.
93. Magri F, Govoni A, D'Angelo MG, et al. Genotype and phenotype characterization in a large dystrophinopathic cohort with extended follow-up. *J Neurol*. 2011;258:1610-1623.
94. Moizard MP, Toutain A, Fournier D, et al. Severe cognitive impairment in DMD: obvious clinical indication for Dp71 isoform point mutation screening. *Eur J Hum Genet*. 2000;8:552-556.
95. Mukherjee S, Roy M, Guha G, Saha SP. Mutation location and cognitive impairment in Duchenne muscular dystrophy. *J Neurosci Rural Pract*. 2018;9:410-413.
96. Pane M, Mazzone E, Sormani MP, et al. P.2.7 6 min walk test 12 month changes in DMD: correlation with genotype. *Neuromuscul Disord*. 2013;23:750-751.

97. Pane M, Mazzone E, Sormani MP, et al. Impact of genotype on boys with Duchenne muscular dystrophy. *J Heart Lung Transplant*. 2018; 37(suppl 1):S122.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Szabo SM, Gooch KL, Mickle AT, Salhany RM, Connolly AM. The impact of genotype on outcomes in individuals with Duchenne muscular dystrophy: A systematic review. *Muscle & Nerve*. 2022;65(3):266-277. doi:10.1002/mus.27463