RESEARCH ARTICLE

Prognostic indicators of disease progression in Duchenne muscular dystrophy: A literature review and evidence synthesis

Nermina Ferizovic1,2,* , Jessica Summers1, Igor Beitia Ortiz de Zárate3, Christian Werner4, Joel Jiang5, Erik Landfeldt6☯, Katharina Buesch7☯

1 MAP BioPharma Ltd, Cambridge, England, United Kingdom, 2 BresMed Health Solutions, Sheffield, England, United Kingdom, 3 PTC Therapeutics France SAS, Paris, France, 4 PTC Therapeutics Germany GmbH, Frankfurt/Main, Germany, 5 PTC Therapeutics, South Plainfield, New Jersey, United States of America, 6 ICON plc, Stockholm, Sweden, 7 PTC Therapeutics Switzerland GmbH, Zug, Switzerland

* These authors contributed equally to this work.
* nermina.ferizovic@hotmail.co.uk

Abstract

Background

Duchenne muscular dystrophy (DMD) is a rare, severely debilitating, and fatal neuromuscular disease characterized by progressive muscle degeneration. Like in many orphan diseases, randomized controlled trials are uncommon in DMD, resulting in the need to indirectly compare treatment effects, for example by pooling individual patient-level data from multiple sources. However, to derive reliable estimates, it is necessary to ensure that the samples considered are comparable with respect to factors significantly affecting the clinical progression of the disease. To help inform such analyses, the objective of this study was to review and synthesise published evidence of prognostic indicators of disease progression in DMD. We searched MEDLINE (via Ovid), Embase (via Ovid) and the Cochrane Library (via Wiley) for records published from inception up until April 23 2021, reporting evidence of prognostic indicators of disease progression in DMD. Risk of bias was established with the grading system of the Centre for Evidence-Based Medicine (CEBM).

Results

Our search included 135 studies involving 25,610 patients from 18 countries across six continents (Africa, Asia, Australia, Europe, North America and South America). We identified a total of 23 prognostic indicators of disease progression in DMD, namely age at diagnosis, age at onset of symptoms, ataluren treatment, ATL1102, BMI, cardiac medication, DMD genetic modifiers, DMD mutation type, drisapersen, edasalonexent, eteplirsen, glucocorticoid exposure, height, idebenone, lower limb surgery, orthoses, oxandrolone, spinal surgery, TAS-205, vamorolone, vitlolarsen, ventilation support, and weight. Of these, cardiac medication, DMD genetic modifiers, DMD mutation type, and glucocorticoid exposure were designated core prognostic indicators, each supported by a high level of evidence and significantly affecting a wide range of clinical outcomes.
This study provides a current summary of prognostic indicators of disease progression in DMD, which will help inform the design of comparative analyses and future data collection initiatives in this patient population.

1. Introduction

Duchenne muscular dystrophy (DMD) is a rare, neuromuscular disease characterised by progressive muscle degeneration caused by mutations in the X-linked DMD gene [1, 2]. The DMD gene encodes dystrophin, a structural protein which forms part of complexes predominantly found in muscle cells where it plays a significant role in the stabilisation of cell membranes [3]. To date, over 1,100 mutations have been identified, including 891 responsible for DMD phenotypes [4]. The incidence of DMD has been estimated at between 1 in 3,500 and 5,000 live male births [5, 6].

Patients with DMD are diagnosed around the age of four years, but many boys show symptoms earlier due to proximal muscle weakness resulting in delayed physical milestones (e.g., walking, running, and climbing stairs). As the disease progresses, patients become non-ambulatory usually in their early teens, followed by increasing loss of upper limb strength and function [7–11]. Respiratory and cardiac decline ensue, with patients eventually requiring mechanical ventilation support for survival [9, 10]. The median life expectancy at birth is around 30 years [12]. At present, there is no cure for DMD, and standard of care is mainly aimed at managing disease symptoms and promoting patient quality of life [13].

In medical research, it is occasionally necessary to pool patient-level data from different studies to indirectly assess the efficacy of a treatment due to low statistical power because of small patient samples and/or the absence of direct comparators in randomised controlled trials (RCTs). To minimize bias in such analyses, it is important to ensure that the populations to be compared are sufficiently homogeneous with respect to factors that would be expected to directly or indirectly affect outcomes of interest [14]. For example, in the context of DMD, it would be relevant to adjust any indirect comparison for the current age of the patient, among other factors, given the progressive, age-related nature of the disease. However, to date, no study has systematically reviewed the body of evidence for factors affecting disease progression outcomes in DMD. To bridge this evidence gap, the objective of this study was to review and synthesise the published evidence on prognostic indicators of disease progression in DMD.

2. Methods

This literature review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15]. The study protocol is not publicly available due to intellectual property restrictions.

2.1. Search strategy

We searched MEDLINE (via Ovid), Embase (via Ovid) and the Cochrane Library (via the Wiley online platform) for records of studies published from inception up until April 23 2021, reporting evidence of prognostic indicators of disease progression in DMD. The search string contained “Duchenne muscular dystrophy” as a Medical Subject Heading term or free text term in combination with variations of the free text term “prognostic indicator”. For example,
the MEDLINE population terms were: 1. “exp Muscular Dystrophy, Duchenne/”, 2. “(Duchenne and dystro”的.mp.” and 3. “1 or 2”. These were combined with the prognostic indicator terms; 4. “(prognos“ or (disease adj3 course) or (disease adj3 impact) or natural history or (disease adj3 predict“) or (disease adj3 outcome) or (disease adj3 progres“)).mp.” and 5. “3 and 4”. Then the searches filtered out irrelevant study designs with the following; 6. “(comment or letter or editorial or notes or review).pt.”, 7. “(exp animals/ or exp invertebrate/ or animal experiment/ or animal model/) and (human/)” and 8. “(exp animals/ or exp invertebrate/ or animal experiment/ or animal model/) not 7”, 9. “6 or 8” and 10. “5 not 9”. Full search strings are provided in S1 Appendix.

2.2. Selection criteria
Eligibility criteria based on the Population, Intervention, Comparison, Outcomes and Study design (PICOS) framework for study inclusion are presented in Table 1. Only English language texts were included. For the purposes of this review, a prognostic indicator was defined as any factor, either endogenous or exogenous, affecting the clinical progression of disease.

2.3. Screening and data extraction
One investigator (NF) initially screened article titles and abstracts for eligibility, and subsequently reviewed full-text versions of selected records. The reason for exclusion was recorded and confirmed by a second investigator (JS). For all articles that met the inclusion criteria upon full-text review, the following information was extracted into a pre-designed data extraction form: Author, year, geographical setting, study design, interventions, patient sample population characteristics, disease progression outcome measures, prognostic indicators, and the impact of the prognostic indicators on disease progression. For the purpose of this review, we only considered statistically significant prognostic indicators (as reported in the included studies).

We synthesised extracted evidence of the impact of identified prognostic indicators of disease progression in DMD into eight outcome categories: cardiac health and function, loss of independent ambulation, lower extremity and motor function, muscle strength, respiratory health and function, scoliosis, survival, and upper extremity function. Although loss of ambulation is a clinical milestone within the lower extremity and motor function domain, we decided to report evidence separately for this factor given its central role in DMD research (e.g., as a primary endpoint in RCTs). Due to the monotonic progression of DMD, we did not

| Table 1. PICOS eligibility criteria for study inclusion. |
|------------------------------------------------------|
| **Population**                                      |
| Patients diagnosed with DMD                         |
| Patients without a diagnosis of DMD                  |
| **Intervention**                                    |
| Any                                                  |
| None                                                 |
| **Comparators**                                     |
| Any                                                  |
| None                                                 |
| **Outcome**                                         |
| Prognostic indicator of disease progression          |
| None                                                 |
| **Study design**                                    |
| Any                                                  |
| Systematic literature reviews and meta-analyses were not formally included, but screened for relevant references |

Note: Population, Intervention, Comparison, Outcomes and Study design (PICOS). Duchenne muscular dystrophy (DMD).

https://doi.org/10.1371/journal.pone.0265879.t001
consider current age a prognostic factor of interest, nor bisphosphonate therapy because of the negative impact from both glucocorticoids and DMD on bone health [13].

2.4. Level of evidence
The level of evidence of included studies was established using a modified version of the grading system of the Centre for Evidence-Based Medicine (CEBM) [16]. Specifically, five levels of evidence were designated based on study design: (1) systematic review of randomised trials or n-of-1 trials, (2) randomised trial or observational study with dramatic effect, (3) non-randomised controlled cohort/follow-up study, (4) case-series, case-control studies, or historically controlled studies, and (5) mechanism-based reasoning. For reporting purposes, we categorised evidence levels 1 and 2 as “high level of evidence”, level 3 as “moderate level of evidence”, and levels 4 and 5 as “low level of evidence”.

3. Results
The search was performed on April 26 2021, and resulted in the identification of 3,018 publications (including journal articles and congress/conference abstracts) reporting evidence of prognostic indicators of disease progression in DMD (Fig 1). Of these, 740 records were duplicates, 1,966 excluded following title and abstract screening, and 312 selected for full-text review. An additional 54 articles were included from the reference searches of identified systematic literature reviews (SLRs) and meta-analyses (MAs). Finally, 294 publications were considered for data extraction, with 135 studies reporting statistically significant prognostic indicators of disease progression that were subsequently included for evidence synthesis and grading. Summary details of the included studies are presented in Table 2. Identified studies encompassed 25,610 patients with DMD from 18 countries (Argentina, Australia, Belgium, Canada, China, Denmark, Egypt, France, Germany, Holland, India, Italy, Japan, Korea, Sweden, Turkey, the United Kingdom and the United States).

We identified a total of 23 prognostic indicators of disease progression in DMD. Endogenous indicators included age at diagnosis, age at onset of symptoms, DMD genetic modifiers, DMD mutation type, height, weight and body mass index (BMI). Exogenous indicators included ataluren treatment, ATL1102, cardiac medication, drisapersen, edasalonexent, eteplirsen, glucocorticoid exposure (including age at glucocorticoid treatment initiation, dose, duration of exposure, pharmacological agent, and regimen), idebenone, lower limb surgery, orthoses, oxandrolone, spinal surgery, TAS-205, vamorolone, vitlolarsen, and ventilation support. The evidence for these prognostic indicators across the pre-defined outcome categories is summarised below and illustrated in Fig 2.

3.1. Cardiac health and function
We identified 29 studies presenting evidence of prognostic indicators of disease progression in DMD measured in terms of cardiac health and function [17–45, 91, 111, 199]. In total, seven prognostic indicators were identified: BMI, cardiac medication, DMD genetic modifiers, DMD mutation type, glucocorticoid exposure, idebenone and ventilation support (Table 2). Angiotensin-converting enzyme (ACE) inhibitors, including timing of treatment initiation, have been shown to be significantly associated with improved left ventricular ejection fraction (LVEF) [CEBM Evidence Level 2] [29, 32–34, 42–44], and left ventricular end diastolic and systolic dimension (LVEDd/LVESd) [Level 2]; [30, 31, 45] and left ventricular myocardial velocity [Level 2] [30], beta blockers, when administered in combination with ACE inhibitors, with improved LVEF [Level 4] [32–35], left ventricular fractional shortening (LVFS) [Level 2] [31], LVEDd and LVESd [Level 2] [35], left ventricular myocardial
performance index (LVMPI) [Level 4] [35], and left ventricular sphericity index [Level 4];[35] beta blockers with reduced heart failure and arrhythmia [Level 3] [37], and improved LVMPI [Level 2]; [30] timing of unspecified cardiac medication with later onset of cardiomyopathy [Level 4]; [38] eplerenone (EPL) with improved left ventricular systolic strain, LVEF, and end systolic volume (ESV) [Level 2]; [36] and ventilation support in combination with cardiac medication with decreased LVEF and left atrium diameter [Level 4] [39]. Glucocorticoid exposure has been shown to be significantly associated with improved LVEF [Level 4] [17–19, 21, 22, 25], LVFS [Level 3] [17–19, 25–27], LVEDd [Level 4] [19, 25, 26], meridional wall stress (mWS) [Level 4] [26], stabilisation of velocity of circumferential fibre shortening (VCFc) [Level 4] [26], reduction in cardiomyopathy [Level 4] [18, 20, 25, 199], and increases in summed rest score [Level 3] [24], as well as increased risk of cardiomyopathy [Level 4] [28], and decline in LVEF [Level 4] [23] linked to duration of glucocorticoid exposure. Idebenone
| Author, year (country) | Study design (level of evidence)† | Interventions, DMD genetic modifiers, and/or DMD mutation types | Patient population | Disease progression outcome category | Disease progression outcome results | Identified prognostic indicator‡ |
|------------------------|----------------------------------|---------------------------------------------------------------|-------------------|-------------------------------------|---------------------------------|-------------------------------|
| Biggar et al., 2006 (CA) [17] | Non-randomised controlled cohort (Level 3) | DFZ | 74 patients with DMD (mean age: NR, range: 10–18 years) | Cardiac Health and Function | Improved fractional shortening and ejection fraction | Glucocorticoid exposure |
| Houde et al., 2008 (CA) [18] | Case-control study (Level 4) | DFZ | 79 patients with DMD treated with DFZ (mean age: 13 years, range: NR) or no treatment (mean age: 18 and 10 years, range: NR) | Cardiac Health and Function | Improved fractional shortening, ejection fraction, and reduced risk of cardiomyopathy | Glucocorticoid exposure |
| Silversides et al., 2003 (CA) [19] | Case-control study (Level 4) | DFZ | 33 patients with DMD treated with DFZ (mean age: 14 years, range: 10–18 years) or no treatment (mean age: 16 years, range: 11–18 years) | Cardiac Health and Function | Improved fractional shortening, ejection fraction, and LVEDd | Glucocorticoid exposure |
| Barber et al., 2013 (US) [20] | Case-control study (Level 4) | DFZ and PDN/PRED | 462 patients with DMD (mean age: NR, range: NR) | Cardiac Health and Function | Reduced risk of cardiomyopathy onset versus untreated and linked to duration of use | Glucocorticoid exposure |
| Bello et al., 2019 (IT) [21] Bello et al., 2019 (IT) [22] | Case series (Level 4) | DFZ and PDN/PRED LTBP4, minor alleles at SPP1, and CD40 SNPs Dp140 and Exon 8 skipping | 374 patients with DMD (mean age: NR, range: NR) | Cardiac Health and Function | DFZ and PDN/PRED Improved ejection fraction LTBP4 Preserved ejection fraction | Glucocorticoid exposure; DMD genetic modifiers; and DMD mutation type |
| Tandon et al., 2015 (US) [23] | Case series (Level 4) | DFZ and PDN/PRED | 98 patients with DMD (mean age: NR, range: NR) | Cardiac Health and Function | Decline in LVEF linked to duration of use | Glucocorticoid exposure |
| Zhang et al., 2015 (CN) [24] | Non-randomised controlled cohort study (Level 3) | DFZ and PDN/PRED | 77 patients with DMD (mean age: NR, range: 2–13 years) | Cardiac Health and Function | Increased summed rest score | Glucocorticoid exposure |

(Continued)
Table 2. (Continued)

| Author, year (country) | Study design (level of evidence)† | Interventions, DMD genetic modifiers, and/or DMD mutation types | Patient population | Disease progression outcome category | Disease progression outcome results | Identified prognostic indicator‡ |
|------------------------|----------------------------------|---------------------------------------------------------------|--------------------|-------------------------------------|----------------------------------|---------------------------------|
| Schram et al., 2013 (CA) [25] | Case series (Level 4) | DFZ and PDN/PRED All patients were receiving cardiac medication (ACE inhibitors/ARBs) | 86 patients with DMD (mean age: NR, range: NR) | Cardiac Health and Function | Reduced risk of cardiomyopathy, improved fractional shortening, ejection fraction, and LVEDd | Glucocorticoid exposure |
| Markham et al., 2008 (US) [26] | Case-control study (Level 4) | DFZ and PDN/PRED | 37 patients with DMD (mean age: NR, range: NR) | Cardiac Health and Function | Improved LVEDd, shortening fraction, mWS, and VCFc | Glucocorticoid exposure |
| Markham et al., 2005 (US) [27] | Case-control study (Level 4) | DFZ and PDN/PRED | 111 patients with DMD treated with DFZ and PDN/PRED (mean age: 11 years, range: 3–21 years) or no treatment (mean age: 12 years, range: 3–21 years) | Cardiac Health and Function | Improved fractional shortening | Glucocorticoid exposure |
| Kim et al., 2017 (US) [28] | Case series (Level 4) | DFZ and PDN/PRED | 255–660 patients with DMD (mean age: NR, range: NR) | Cardiac Health and Function | Increased risk of cardiomyopathy linked to duration of use | Glucocorticoid exposure |
| Aikawa et al., 2019 (JP) [29] | Case series (Level 4) | ACE inhibitor (cilazapril or enalapril) | 21 patients with DMD (median age: 12 years, IQR: 6–16 years) | Cardiac Health and Function | Improved LVEF | Cardiac medication |
| Kwon et al., 2012 (KR) [30] | Randomised trial (Level 2) | ACE inhibitor (enalapril) or BB (carvedilol) | 23 patients with DMD (mean age: 13 years, range: NR) | Cardiac Health and Function | BB Improved LVMI ACE Improved LVESd and left ventricular free wall systolic myocardial velocity | Cardiac medication |
| Kajimoto et al., 2006 (JP) [31] | Non-randomised controlled cohort (Level 3) | ACE inhibitor (enalapril), or ACE inhibitor (enalapril) and BB (carvedilol) | 25 patients with DMD treated with ACE inhibitors/BBs (mean age: 18 years, range: 7–27 years) or ACE inhibitors (mean age: 15 years, range 8–29 years) | Cardiac Health and Function | ACE Improved LVEDd ACE/BB Improved LVFS | Cardiac medication |
| Thrush et al., 2012 (US) [32] Thrush et al., 2012 (US) [33] | Case-control study (Level 4) | ACE inhibitor (drug NR), or ACE inhibitor (drug NR) and BB (drug NR) | 25 patients with DMD treated with ACE inhibitors/BBs (mean age: 16 years, range: NR) or ACE inhibitors (mean age: 14 years, range: NR) | Cardiac Health and Function | Both ACE inhibitor and ACE inhibitor/BB improved ejection fraction compared to natural history | Cardiac medication |
| Viollet et al., 2012 (US) [34] | Case-control study (Level 4) | ACE inhibitor (lisinopril), or ACE inhibitor (lisinopril) and BB (metoprolol) | 54 patients with DMD treated with ACE inhibitors/BBs (mean age: 16 years, range: 10–24 years) or ACE inhibitors (mean age: 14 years, range: 7–27 years) | Cardiac Health and Function | Improved ejection fraction versus natural history control | Cardiac medication |
| Author, year (country) | Study design (level of evidence)† | Interventions, DMD genetic modifiers, and/or DMD mutation types | Patient population | Disease progression outcome category | Disease progression outcome results | Identified prognostic indicator‡ |
|------------------------|-----------------------------------|---------------------------------------------------------------|-------------------|-------------------------------------|----------------------------------|---------------------------------|
| Jefferies et al., 2005 (US) [35] | Case series (Level 4) | ACE inhibitor (drug NR) and BB (drug NR) | 62 patients with DMD (mean age: NR, range: NR) | Cardiac Health and Function | Improved LVEDd, LVEF, LVMI, and left ventricular sphericity index | Cardiac medication; and DMD mutation type |
|                         |                                   | Exon 51 and 52                                                 |                   |                                     | Cardioprotective                  |                                  |
|                         |                                   | Exon 12, 14, 15, 16, and 17                                  |                   |                                     | Onset of cardiomyopathy           |                                  |
| Raman et al., 2015 (US) [36] | Randomised trial (Level 2) | EPL and PLC                                                   | 42 patients with DMD (mean age: 15 years, range: 11–19 years) or PLC (mean age: 15 years, range: 11–19 years) | Cardiac Health and Function | Improved left ventricular systolic strain, LVEF, and ESV | Cardiac medication |
| Matsumura et al., 2010 (JP) [37] | Non-randomised controlled cohort study (Level 3) | BB                                                        | 54 patients with DMD treated with BBs (mean age: 19 years, range: 11–29 years) or BSC (mean age: 23 years, range: 15–35 years) | Cardiac Health and Function | Reduction in heart failure and arrhythmias | Cardiac medication |
| Van Ruiten et al., 2017 (UK) [38] | Case control (Level 4) | Cardiac medication (drug NR)                                  | 108 patients with DMD (mean age: NR, range: NR) | Cardiac Health and Function | Timing of cardiac medication impacts on cardiomyopathy | Cardiac medication |
|                         |                                   | DFZ and PDN/PRED                                               |                   |                                     | Loss of Ambulation                | Glucocorticoid exposure          |
|                         |                                   |                                                             |                   |                                     | Ventilation support               |                                 |
| Fayssoil et al., 2018 (FR) [39] | Case series (Level 4) | Ventilation support in combination with cardiac medication (drug NR) | 101 patients with DMD (median age: 21 years, IQR: 18–26 years) | Cardiac Health and Function | Decreased left atrium diameter and LVEF | Ventilation support |
| Nagai et al., 2020 (JP) [40] | Case-control study (Level 4) | ACTN3 null genotype                                          | 77 patients with DMD (median age: NR; IQR: 7.9–11.5 years) | Cardiac Health and Function | Earlier onset of cardiac dysfunction; early onset of LV dilation; lower LV dilation-free rate | DMD genetic modifier |
| Cheeran et al., 2017 (US) [41] | Case-control study (Level 4) | BMI                                                            | 43 patients with DMD (median age: 21 years; IQR: 21–24 years) | Cardiac Health and Function | Higher BMI is associated with reduced cardiomyopathy | BMI |
| Duboc et al., 2005 (FR) [42] | Randomised trial (Level 2) | Perindopril and PLC                                           | 57 patients with DMD (mean age: NR; range: 9.5–13 years) | Cardiac Health and Function | Maintains LVEF                     | Cardiac medication |
|                       |                                   |                                                             |                   |                                     | Survival                         | Improvement in survival          |
| Ishikawa et al., 1999 (NR) [44] | Follow-up study (Level 3) | ACE (enalapril and lisinopril) and BB                        | 11 patients with DMD (mean age: 17; range: 12.6–22.8) | Cardiac Health and Function | Increased LVEF                     | Cardiac medication |
| Ramaciotti et al., 2006 (USA) [45] | Case-series (Level 4) | ACE (enalapril)                                              | 50 patients with DMD (mean age: NR; range: 10–20 years) | Cardiac Health and Function | Improved left ventricular function | Cardiac medication |
| King et al., 2007 (US) [46] | Case-control study (Level 4) | DFZ and PDN/PRED                                              | 143 patients with DMD treated with DFZ and PDN/PRED (mean age: 17 years, range: 6–31 years) or no treatment (mean age: 14 years, range: 2–40 years) | Cardiac Health and Function | Scoliosis                           | Glucocorticoid exposure |
|                         |                                   |                                                             |                   |                                     | Loss of Ambulation                | Delay in loss of ambulation       |

(Continued)
| Author, year (country) | Study design (level of evidence)† | Interventions, DMD genetic modifiers, and/or DMD mutation types | Patient population | Disease progression outcome category | Disease progression outcome results | Identified prognostic indicator‡ |
|------------------------|-----------------------------------|---------------------------------------------------------------|-------------------|--------------------------------------|-----------------------------------|-------------------------------|
| Balaban et al., 2005 (NR) [47] | Case-control study (Level 4) | DFZ and PDN/PRED | 49 patients with DMD treated with DFZ (mean age: 14 years, range: NR) or PDN/PRED (mean age: 15 years, range: NR) or no treatment (mean age: 14 years, range: NR) | Scoliosis | Reduced number of spinal surgeries versus untreated | Glucocorticoid exposure |
| Alman et al., 2004 (CA) [48] | Non-randomised controlled cohort study (Level 3) | DFZ | 54 patients with DMD treated with DFZ (mean age: 9 years, range: NR) or no treatment (mean age: 9 years, range: NR) | Scoliosis | Decrease in rate of scoliosis > 20 degrees and need for spinal surgery | Glucocorticoid exposure |
| Lebel et al., 2013 (CA) [49] | Non-randomised controlled cohort study (Level 3) | DFZ | 54 patients with DMD treated with DFZ (mean age: 9 years, range: NR) or no treatment (mean age: 9 years, range: NR) | Scoliosis | Decrease in rate of scoliosis > 20 degrees and need for spinal surgery | Glucocorticoid exposure |
| Kinali et al., 2007 (UK) [50] | Case series (Level 4) | KAFOS; PDN/PRED | 123 patients with DMD (mean age: NR, range: NR) | Scoliosis | KAFOS Longer duration of use reduces scoliosis severity PDN/PRED Later age at scoliosis onset linked to duration of use | Orthoses; and Glucocorticoid exposure |
| McDonald et al., 2018 (*) [51] | Observational study with dramatic effect (Level 2) | DFZ and PDN/PRED | 440 patients with DMD (mean age: NR, range: 2–28 years) | Survival | Reduction in mortality (>1 year of exposure) | Glucocorticoid exposure |
| Ogata et al., 2009 (JP) [52] | Case series (Level 4) | ACE inhibitor (enalapril/losinopril) and BB (bisoprolol/carvedilol/metoprolol) | 52 patients with DMD receiving symptomatic treatment (mean age: 18 years, range: NR) or asymptomatic treatment (mean age: 20 years, range: NR) | Survival | Overall survival improved in the early treatment (asymptomatic) group | Cardiac medication |
| Rall and Grim, 2012 (DE) [53] | Case-control study (Level 4) | Ventilation support | 94 patients with DMD (mean age: NR, range: NR) | Survival | Improved overall survival | Ventilation support |

(Continued)
Table 2. (Continued)

| Author, year (country) | Study design (level of evidence)† | Interventions, DMD genetic modifiers, and/or DMD mutation types | Patient population | Disease progression outcome category | Disease progression outcome results | Disease progression outcome indicators‡ |
|-----------------------|----------------------------------|---------------------------------------------------------------|-------------------|--------------------------------------|-------------------------------------|--------------------------------------|
| Jeppesen et al., 2003 (DK) [54] | Case-control study (Level 4) | Ventilation support | 159 patients with DMD (mean age: NR, range: NR) | Survival | Reduction in all-cause mortality | Ventilation support |
| Eagle et al., 2007 (UK) [55] | Case-control study (Level 4) | Spinal surgery and ventilation; ventilation no spinal surgery; no spinal surgery or ventilation | 100 patients with DMD (mean age: NR, range: NR) | Survival | Spinal surgery/ ventilation and ventilation no spinal surgery improved survival with spinal surgery/ventilation having a larger impact | Ventilation support; and spinal surgery |
| Eagle et al., 2002 (UK) [56] | Case-control study (Level 4) | Nocturnal ventilation support | 183 patients with DMD (mean age: NR, range: NR) | Survival | Reduction in mortality | Ventilation support |
| Gomez-Merino et al., 2002 (NR) [57] | Case-control study (Level 4) | Non-invasive respiratory aids | 91 patients with DMD (mean age: NR, range: NR) | Survival | Prolongation of survival | Ventilation support |
| Kieny et al., 2013 (FR) [58] | Case-control study (Level 4) | Ventilation support | 119 patients with DMD (mean age: NR, range: NR) | Survival | Prolongation of survival | Ventilation support |
| Ishikawa et al., 2011 (JP) [59] | Case-control study (Level 4) | Non-invasive respiratory aids (including mechanically assisted coughing) | 187 patients with DMD (mean age: NR, range: NR) | Survival | Prolongation of survival compared to invasive treatment | Ventilation support |
| Adorissio et al., 2019 (NR) [60] | Case-control study (Level 4) | Left ventricular assist device with cardiac medication and OMT | 12 patients with DMD (mean age: NR, range: NR) | Survival | Improved survival | Left ventricular assist device |
| Davidson et al., 2012 (AU) [61] | Case series (Level 4) | DFZ and PDN/PRED dystrophin gene deletions | 144 patients with DMD (mean age: NR, range: NR) | Loss of Ambulation | Reduction in risk of loss of ambulation | Glucocorticoid exposure; and DMD mutation type |
| Bonifati et al., 2006 (IT) [62] | Non-randomised controlled cohort study (Level 3) | DFZ and PDN/PRED deletions | 48 patients with DMD (mean age: NR, range: NR) | Loss of Ambulation | Early treatment initiation and increased treatment duration delay loss of ambulation | Glucocorticoid exposure |
| Bello et al., 2015 (*) [63] Bello et al., 2015 (*) [64] Bello et al., 2015 (*) (IT) [65] | Observational study with dramatic effect (Level 2) | DFZ and PDN/PRED TG/GG genotype at SPP1 rs28357094 LTBP4 haplotype | 340 patients with DMD (283 for the genotype sub-population) (mean age: 16 years, range: 5–33 years) | Loss of Ambulation | Delay in loss of ambulation; DFZ more favourable | Glucocorticoid exposure; and DMD genetic modifiers |
| Bello et al., 2014 (*) [66] | Observational study with dramatic effect (Level 2) | DFZ and PDN/PRED G allele at SPP1rs28357094 | 332 patients with DMD (mean age: NR, range: NR) | Loss of Ambulation | Delay in loss of ambulation, DFZ more favourable | Glucocorticoid exposure; and DMD genetic modifiers |
| Bello et al., 2016 (*) [11] | Observational study with dramatic effect (Level 2) | DFZ and PDN/PRED Deletion of exon 3–7 and exon 44 skipping | 212 patients with DMD (mean age: NR, range: NR) | Loss of Ambulation | Delay in loss of ambulation | Glucocorticoid exposure; and DMD mutation type |
| Bello et al., 2016 (*) [67] | Observational study with dramatic effect (Level 2) | Exon 44 skipping | | | | |
| Goemans et al., 2019 (*) [68] Goemans et al., 2019 (*) [69] | Case series (Level 4) | DFZ and PDN/PRED | 85 patients with DMD (mean age: 9 years, range: NR) | Loss of Ambulation | Predictive of loss of ambulation | Glucocorticoid exposure; greater weight; lower height; and lower BMI (in combination) |

(Continued)
Table 2. (Continued)

| Author, year (country) | Study design (level of evidence)† | Interventions, DMD genetic modifiers, and/or DMD mutation types | Patient population | Disease progression outcome category | Disease progression outcome results | Identified prognostic indicator‡ |
|------------------------|----------------------------------|---------------------------------------------------------------|-------------------|--------------------------------------|----------------------------------|---------------------------------|
| Kim et al., 2015 (US) [70] | Observational study with dramatic effect (Level 2) | DFZ and PDN/PRED | 477 patients with DMD (mean age: NR, range: NR) | Loss of Ambulation | Delay in loss of ambulation with larger effect for those treated longer in the <11 year olds | Glucocorticoid exposure |
| Schara et al., 2001 (DE) [71] | Case-control study (Level 4) | DFZ | 13 patients with DMD (mean: NR, range: 9–18 years) | Loss of Ambulation | Delay in loss of ambulation | Glucocorticoid exposure |
| Van den Bergen et al., 2014 (NL) [72] | Retrospective observational study (Level 2) | Glucocorticoids (drug NR) | 336 patients with DMD (mean age: NR, range: NR) | Loss of Ambulation | Delay in loss of ambulation | Glucocorticoid exposure |
| Van den Bergen et al., 2014 (NL) [73] | Case control study (Level 4) | Glucocorticoids (drug NR) Exon 44 (vs. 45, 51, and 53) | 114 patients with DMD (mean age: NR, range: NR) | Loss of Ambulation | Delay in loss of ambulation | Glucocorticoid exposure; and DMD mutation type |
| Wang et al., 2014 (US) [74] | Online survey (Level 5) | DFZ and PDN/PRED | 1,057 patients with DMD (mean age: NR, range: NR) | Loss of Ambulation | Delay in loss of ambulation with DFZ favourable over PDN/PRED | Glucocorticoid exposure |
| Ricotti et al., 2012 (UK) [75] Ricotti et al., 2011 (UK) [76] Ricotti et al., 2011 (UK) [77] | Case series (Level 4) | PDN/PRED | 334–400 patients with DMD (mean age: NR, range: 3–15 years) | Loss of Ambulation | Delay in loss of ambulation in daily PDN-treated compared to intermittent PDN | Glucocorticoid exposure |
| DeSilva et al., 1987 (US) [78] | Non-randomised controlled cohort study (Level 3) | PDN/PRED | 54 patients with DMD (mean age: NR, range: NR) | Loss of Ambulation | Delay in loss of ambulation | Glucocorticoid exposure |
| Yilmaz et al., 2004 (TR) [79] Yilmaz et al., 2004 (TR) [80] Tunca et al., 2001 (TR) [81] | Historically controlled cohort study (Level 4) | PDN/PRED | 88 patients with DMD treated with PDN/PRED (mean age: 7 years, range: 3–11 years) or no treatment (mean age: 7 years, range: 5–9 years) | Loss of Ambulation | Delay in loss of ambulation | Glucocorticoid exposure |
| Yilmaz et al., 2004 (TR) [79] Yilmaz et al., 2004 (TR) [80] | Case control (Level 4) | DFZ | 54 patients with DMD (mean age: NR, range: NR) | Loss of Ambulation | Delay in loss of ambulation | Glucocorticoid exposure |

(Continued)
Table 2. (Continued)

| Author, year (country) | Study design (level of evidence)† | Interventions, DMD genetic modifiers, and/or DMD mutation types | Patient population | Disease progression outcome category | Disease progression outcome results | Identified prognostic indicator‡ |
|------------------------|---------------------------------|---------------------------------------------------------------|--------------------|-------------------------------------|----------------------------------|--------------------------------|
| Ciafaloni et al., 2013 (US) [83] | Observational study with dramatic effect (Level 2) | Age at onset of symptoms | 825 patients with DMD (mean age: NR, range: NR) | Loss of Ambulation | Earlier loss of ambulation for earlier symptom development | Age at onset of symptoms |
| Ciafaloni et al., 2016 (US) [84] | | Minor allele at rs1883832 | 109 patients with DMD (mean age: NR; range: NR) | Loss of Ambulation | Delay in loss of ambulation | DMD genetic modifiers |
| Bello et al., 2016 (GER) [85] | Genome-wide association study (Level 4) | Exon 8 and Exon 44 skip deletions | 358 patients with DMD (mean age: NR; range: NR) | Loss of Ambulation | Delay in loss of ambulation | DMD mutation type |
| Haber et al., 2021 (US) [86] | Case control study (Level 4) | ATA compared to external controls | 181 patients with DMD (mean age: NR, range: 2–28 years) | Loss of Ambulation | Delay in loss of ambulation | Improved STS and 4SC |
| Mercuri et al., 2020 (NR) [87] | Non-randomised controlled study (Level 3) | Glucocorticoids; DMD mutation type | 765 patients with DMD (mean age: NR; range: NR) | Loss of Ambulation | Delay in loss of ambulation: Glucocorticoids, exon 44, exon 3–7, exon 45, exon 8 | Glucocorticoid exposure; DMD mutation type |
| Wang et al., 2018 (GER) [88] | Case series (Level 4) | PDN/PRED (daily dose with PLC at weekend; weekend dose with PLC during weekdays) | 64 patients with DMD (mean age: 7 years; range: NR) | Respiratory Health and Function | Weekend dosing equivalent to daily dosing as given by MVV; MIP | Glucocorticoid exposure |
| Forst et al., 1995 (GER) | Observational study with dramatic effect (Level 2) | Lower limb surgery | 213 patients with DMD (mean age: 6.36 years; range: 4.02–8.26) | Loss of Ambulation | Delay in loss of ambulation | Lower limb surgery |
| Servais et al., 2015 (FR) [91] | Case-control study (Level 4) | Exon 53 | 53 patients with DMD (DMD 53: mean age: 13.9, range: NR or DMD-all-non-53: mean age: 14 years, range: NR or DMD-del-non-53: mean age: 14.1, range: NR) | Loss of Ambulation | Delay in loss of ambulation compared to DMD-all-non-53 and DMD del-non-53 | DMD mutation type |
| Escolar et al., 2011 (US) [92] | Randomised controlled trial (Level 2) | Respiratory Health and Function | Weekend dosing equivalent to daily dosing as given by MVV; MIP | Cardiac Health and Function | Lower LVEF and higher contracture score compared to DMD-del-non-53 | Glucocorticoid exposure |

(Continued)
| Author, year (country) | Study design (level of evidence) † | Interventions, DMD genetic modifiers, and/or DMD mutation types | Patient population | Disease progression outcome category | Disease progression outcome results | Identified prognostic indicator ‡ |
|------------------------|--------------------------------------|---------------------------------------------------------------|-------------------|--------------------------------------|-----------------------------------|----------------------------------|
| Tachas et al., 2020 (NR) [93] | Randomised trial (Level 2) | ATL1102 compared to external natural history control | 29 patients with DMD (mean age: 14.9 years, range: 12–18 years) or external control (mean age: 15.61, range: NR) | Upper Extremity Function | Improved upper limb function as given by PUL | ATL1102 treatment |
| Daftary et al., 2007 (US) [94] | Case-control study (Level 4) | DFZ and PDN/PRED | 35 patients with DMD (mean age: NR, range: 7–21 years) | Respiratory Health and Function | Long-term glucocorticoid therapy improves PCF and MEP | Glucocorticoid exposure |
| Abresch et al., 2013 ( ) [95] | Case-control study (Level 4) | DFZ and PDN/PRED | 341 patients with DMD (mean age: NR, range: 6–28 years) | Respiratory Health and Function | Improved MIP, MEP and PCF | Glucocorticoid exposure |
| Henricson et al., 2013 ( ) [96] | Case series (Level 4) | DFZ and PDN/PRED (current users vs. naïve users) | 340 patients with DMD (mean age: NR, range: 2–28 years) | Respiratory Health and Function | Improved FVC, MIP; PEFR; FEV<sub>1</sub> | Glucocorticoid exposure |
| McDonald et al., 2018 ( ) [97] | Case control study (Level 4) | DFZ and PDN/PRED | 397 patients with DMD (median: 9 years, IQR: 2–28 years) | Respiratory Health and Function | Improved FVC | Glucocorticoid exposure |
| Henricson et al., 2017 (US) [98] | Case control (Level 4) | DFZ and PDN/PRED | 233 patients with DMD (mean age: 13 years, range: 6–28 years) | Respiratory Health and Function | Sustained FVC and PEFR | Glucocorticoid exposure |
| McDonald et al., 2017 (US) [99] | Case series (Level 4) | DFZ and PDN/PRED | 334–400 patients with DMD (mean age: NR, range: 3–15 years) | Respiratory Health and Function | Sustained FVC in daily PDN | Glucocorticoid exposure |
| Ricotti et al., 2011 (UK) [77] | Case series (Level 4) | PDN/PRED | 334–400 patients with DMD (mean age: NR, range: 3–15 years) | Respiratory Health and Function | Sustained FVC in daily PDN | Glucocorticoid exposure |
| Pradhan 2006 (IN) [100] | Non-randomised controlled cohort study (Level 3) | PDN/PRED | 34 patients with DMD (mean age: NR, range: NR) | Respiratory Health and Function | Improved short-term PEFR | Glucocorticoid exposure |
| Fenichel et al., 1991 (US) [101] | RCT (Level 2) | PDN/PRED | 103 patients with DMD (mean age: NR, range: 5–15 years) | Respiratory Health and Function | Daily and alternate day PDN/PRED improved FVC and MVV at 12 months | Glucocorticoid exposure |
| | | | | | Muscle Strength | Improved MRC | |
| | | | | | Lower Extremity and Motor Function | Daily and alternate day PDN/PRED improved STS and 4SC | |

(Continued)
Table 2. (Continued)

| Author, year (country) | Study design (level of evidence)† | Interventions, DMD genetic modifiers, and/or DMD mutation types | Patient population | Disease progression outcome category | Disease progression outcome results | Identified prognostic indicator‡ |
|------------------------|-----------------------------------|---------------------------------------------------------------|--------------------|--------------------------------------|----------------------------------|---------------------------------|
| Dubow et al., 2016 (NR) [102] | RCT (Level 2) | DFZ and PDN/PRED | 45 patients with DMD (mean age: NR, range: NR) | Respiratory Health and Function | 1.2 mg/kg/day dose of DFZ versus PLC improves MVV | Glucocorticoid exposure |
| Comi et al., 2017 (†) [103]; McDonald et al., 2016 (†) [104] | Historically-controlled study (Level 4) | ATA | 167 patients with DMD (mean age: 16 years, range: NR) | Respiratory Health and Function | Improved FVC | ATA treatment |
| Kelley et al., 2019 (†) [105] | Case series (Level 4) | Gly16 ADRB2 polymorphism | 175 patients with DMD (mean age: NR, range: 3–25 years) | Respiratory Health and Function | Gly16 genotype 6.52X likelier of receiving nocturnal ventilation compared to Arg16 Patient weight | DMD genetic modifier; weight |
| Angliss et al., 2020 (AU) [106] | Case control (Level 4) | Ventilation | 29 patients with DMD (median: 14.66; IQR: NR) | Respiratory Health and Function | FVC improved in steroid naïve but accelerated decline in steroid users | Ventilation support |
| Bello et al., 2020 (IT) [107] | Case control (Level 4) | DMD mutation type and DMD genetic modifiers; Glucocorticoids | 327 patients with DMD (mean age: 11.7, range: NR) | Respiratory Health and Function | Exon 44 3’ mutation: Lower FVC, lower FEV1 and lower PEF Glucocorticoid Increased FVC, FEV1 and PEF Skip 51, Skip 53 Decreased FVC, decreased FEV1, decreased PEF Splice site, Skip 8, Skip 44 Increased FVC Skip 8, splice site Increased FEV1, increased PEF Nonsense mutation Decreased FVC and FEV1 Dominant G genotype at rs28357094 in the SPP1 promoter Reduced FVC and PEF Additive T genotype at rs1883832 in the CD40 5’ untranslated region Reduced FVC, FEV1 and PEF | Glucocorticoid exposure; DMD mutation type; DMD genetic modifiers |
| Iff et al., 2020 (US) [108] | Case control (Level 4) | ETEP versus untreated controls | 283 patients with DMD (mean age: 14.1 years, range: NR) | Respiratory Health and Function | Attenuates respiratory function (indirectly measured) | ETEP exposure |
| McDonald et al., 2020 (†) [109]; McDonald et al., 2020 (†) [110] | Randomised trial (Level 2) | ATA versus external natural history control | 95 patients with DMD (mean age: NR, range: NR) | Respiratory Health and Function | Delay in respiratory decline as given by FVC | ATA treatment |
| Buyse et al., 2011 (BE) [111] | Randomised trial (Level 2) | IDE and PLC | 21 patients with DMD (mean age: NR, range: 8–16 years) | Respiratory Health and Function | Improved PEF | IDE treatment |

(Continued)
| Author, year (country) | Study design (level of evidence)† | Interventions, DMD genetic modifiers, and/or DMD mutation types | Patient population | Disease progression outcome category | Disease progression outcome results | Identified prognostic indicator‡ |
|------------------------|----------------------------------|---------------------------------------------------------------|--------------------|--------------------------------------|----------------------------------|---------------------------------|
| Karafilidis et al., 2018 (NR) [112] | Randomised trial (Level 2) | IDE and PLC | 64 patients with DMD (mean age: NR, range: 10–18 years) | Respiratory Health and Function | Improved PEF and FEV1 | IDE treatment |
| Khan et al., 2019 (NR) [113] | Randomised trial (Level 2) | ETEP and natural history control | 414 patients with DMD (mean age: NR, range: 7–16 years) or natural history control (mean age: NR, range: 2–28 years) | Respiratory Health and Function | Reduced decline in respiratory decline as given by percent predicted FVC | ETEP treatment |
| Mendell et al., 2014 (NR) [116] | Randomised trial (Level 2) | ETEP and PLC | 12 patients with DMD (median age: 9.7 years, IQR: NR; range: 7–13 years) | Respiratory Health and Function | Improved MEP and FVC | ETEP treatment |
| Mendell et al., 2021 (NR) [126] | Randomised controlled trial (Level 2) | ETEP compared to external controls | 12 patients with DMD (mean age: 9.4 years, range: 7–13 years) or no treatment (mean age: 9.6 years, range: 7–13 years) | Loss of Ambulation | Delay in loss of ambulation | ETEP treatment |

(Continued)
| Author, year (country) | Study design (level of evidence)† | Interventions, DMD genetic modifiers, and/or DMD mutation types | Patient population | Disease progression outcome category | Disease progression outcome results | Identified prognostic indicator‡ |
|-------------------------|----------------------------------|---------------------------------------------------------------|-------------------|--------------------------------------|---------------------------------|--------------------------------|
| McDonald et al., 2020 (‘) [131] | Randomised trial (Level 2) | Analysis of PLC arm data; DFZ and PDN/PRED | 115 patients with DMD (mean age: NR, range: 7–14 years) | Lower Extremity and Motor Function | Improved 4SC, 6MWT, STS and NSAA | Glucocorticoid exposure |
| Lawrence et al., 2018 (NR) [132] | Randomised trial (Level 2) | IDE and PLC | 23 patients with DMD (mean age: NR, range: 10–18 years) | Respiratory Health and Function | Improvement in respiratory function as given by reduced bronchopulmonary adverse events | IDE treatment |
| Rummey et al., 2018 (NR) | Follow-up study (Level 3) | IDE and PLC | 64 patients with DMD (mean age: 14.3 years, range: 10–18 years) | Respiratory Health and Function | Improved PEF | IDE treatment |
| Kanazawa et al., 1991 (JP) [134] | Follow-up study (Level 3) | cDMD deficit | 24 patients with DMD (mean age: 14.2 years, range: NR) or non-deficit group: mean age: 14.7 years, range: NR | Respiratory Health and Function | Worse pulmonary function | DMD mutation type |
| Hussein et al., 2006 (EG) [135] | Case-control (Level 4) | PDN/PRED | 18 patients with DMD (mean age: 5 years, range: NR) | Muscle Strength | Improvement in muscle strength as given by MRC scale | Glucocorticoid exposure |
| Angelini et al., 1994 (IT) [136] | RCT (Level 2) | DFZ | 28 patients with DMD treated with DFZ (mean age: 8 years, range: NR) or PLC (mean age: 8 years, range: NR) | Muscle Strength | Improvement in muscle strength as given by MRC scale (>1 year of treatment) | Glucocorticoid exposure |
| Fenichel et al., 1991 (US) [137] | Historically-controlled study (Level 4) | PDN/PRED | 92 patients with DMD (mean age: NR, range: 5–15 years) | Muscle Strength | Improved muscle strength using an unspecified measure versus controls Improved more for >0.65mg/kg dose compared to <0.65mg/kg | Glucocorticoid exposure |
| Hu et al., 2015 (CN) [138] | RCT (Level 2) | PDN/PRED | 66 patients with DMD (mean age: NR, range: 4–12 years) | Muscle Strength | Stabilised MRC | Glucocorticoid exposure |
| Rifai et al., 1995 (US) [139] | Case-control (Level 4) | PDN/PRED | 6 patients with DMD (mean age: NR, range: 5–8 years) | Muscle Strength | Improved muscle strength and mass as given by MMT, QMT, and creatinine excretion | Glucocorticoid exposure |
| Backman and Henriksson, 1995 (SE) [140] | RCT (Level 2) | PDN/PRED | 37 ambulatory (mean age: 8 years, range: 4–11 years) or non-ambulatory (mean age: 13 years, range: 8.0–19 years) patients with DMD | Muscle Strength | Improved muscle strength as given by grip strength (strain gauge) and myometric evaluation | Glucocorticoid exposure |
| Author, year (country) | Study design (level of evidence)† | Interventions, DMD genetic modifiers, and/or DMD mutation types | Patient population | Disease progression outcome category | Disease progression outcome results | Identified prognostic indicator‡ |
|------------------------|----------------------------------|---------------------------------------------------------------|-------------------|----------------------------------|----------------------------------|---------------------------------|
| Connolly et al., 2002 (US) [141] | Historically controlled cohort study (Level 4) | PDN/PRED | 42 patients with DMD (mean age: NR, range: NR) | Muscle Strength | Improvement in grip (Jamar grip meter) and upper extremity strength using a myometry | Glucocorticoid exposure |
| Griggs et al., 1993 (CA/US) [142] | RCT (Level 2) | PDN/PRED | 107 patients with DMD (mean age: NR, range: 5–15 years) | Muscle Strength | Improved muscle strength as given by muscle mass increases (creatinine excretion), myometric evaluation and MMT. Larger improvement in 0.75mg/kg versus 0.30mg/kg | Glucocorticoid exposure |
| Mesa et al., 1991 (AR) [143] | Non-randomised controlled study (Level 3) | DFZ | 28 patients with DMD (mean age: NR, range: 5–11 years) | Muscle Strength | Improvement in muscle strength as given by myometric evaluation | Glucocorticoid exposure |
| Beenakker et al., 2005 (NL) [144] | RCT (Level 2) | PDN/PRED | 17 patients with DMD (mean age: 6 years, range: NR) | Muscle Strength | Intermittent PDN/PRED improves total muscle force as given by myometric evaluation | Glucocorticoid exposure |
| Griggs et al., 1991 (CA/US) [145] | RCT (Level 2) | PDN/PRED | 99 patients with DMD (mean age: NR, range: NR) | Muscle Strength | Improved muscle strength as given by myometric evaluation and MMT. Improvements larger in 0.75mg/kg versus 0.30mg/kg | Glucocorticoid exposure |
| Merlini et al., 2003 (IT) [146] | Case-control study (Level 4) | PDN/PRED | 8 patients with DMD treated with PDN/PRED (mean age: 4 years, range: NR) or no treatment (mean age: 4 years, range: NR) | Muscle Strength | Improved muscle strength as given by myometric evaluation but only in the leg megascoring | Glucocorticoid exposure |
| Pegoraro et al., 2011 (IT) [147] | Historically controlled cohort study (Level 4) | SPP1 genotype | 262 patients with DMD (mean age: NR, range: NR) | Muscle Strength | G allele leads to weaker MRC scores and lower grip strength | DMD genetic modifiers |
| Fenichel et al., 2001 (NR) [148] | Randomised trial (Level 2) | OXAN vs PLC | 51 patients with DMD (mean age: NR, range: 5–10 years) | Muscle Strength | Improved muscle strength score using an unspecified measure | OXAN treatment |

(Continued)
| Author, year (country) | Study design (level of evidence)† | Interventions, DMD genetic modifiers, and/or DMD mutation types | Patient population | Disease progression outcome category | Disease progression outcome results | Identified prognostic indicator‡ |
|-----------------------|----------------------------------|---------------------------------------------------------------|-------------------|-------------------------------------|----------------------------------|-----------------------------|
| Fenichel et al., 1997 (US) [149] | Case-series (Level 4) | OXAN | 10 patients with DMD (mean age: NR, range: 6–9 years) | Muscle Strength | Improved muscle strength as given by manual muscle testing | OXAN treatment |
| Campbell et al., 2020 (*) [150] | Meta-analysis (Level 1) | ATA and PLC | 342 patients with DMD (mean age: NR; range: 8.3–9.0) | Lower Extremity and Motor Function | Improved 6MWD, 4SC and 10WRT | ATA treatment |
| Chesshyre et al., 2020 (ENG) [151] | Case series (Level 4) | Dp140 deletion | 320 patients with DMD (mean age: MR; range: NR) | Lower Extremity and Motor Function | Lower NSAA | DMD genetic modifiers |
| Clemens et al., 2020 (US and CAN) [152] | Randomised trial (Level 2) | Vitilolarsen (low dose and high dose) | 16 patients with DMD (mean age: 7.4; range: NR) | Lower Extremity and Motor Function | Improved 10WRT, 6MWT, STS and NSAA | VIT treatment |
| Finkel et al., 2021 (NR) [153] | Randomised trial (Level 2) | EDASA and PLC | 31 patients with DMD (mean age: 6.1; range: 4–7) | Muscle Strength | Improved lower leg muscle health as given by MRI transverse relaxation time constant | EDASA treatment |
| Finkel et al., 2018 (NR) [154] | | | | | | |
| Finkel et al., 2019 (NR) [155] | | | | | | |
| Finkel et al., 2019 (NR) [156] | | | | | | |
| Sweeney et al., 2019 (US) [157] | | | | | | |
| Parreira et al., 2010 (NR) [158] | Case series (Level 4) | DFZ and PDN/PRED | 90 patients with DMD (mean age: NR, range: 5–12 years) | Muscle Strength | Delay in decline in muscle strength as given by MRC index | Glucocorticoid exposure |
| Willcocks et al., 2013 (NR) [159] | Follow-up study (Level 3) | DFZ and PDN/PRED | 145 patients with DMD (mean age: NR, range: 5–14 years) | Muscle Strength | Delays decline in muscle as given by MRI and MRS transverse relaxation time constant | Glucocorticoid exposure |
| Goemans et al., 2020 (NR) [160] | Case series (Level 4) | DFZ | 316 patients with DMD (median age: 7.9 years, range 4.4–19.4 years) | Lower Extremity and Motor Function | Delay loss of STS | Glucocorticoid exposure |
| Goemans et al., 2020 (NR) [161] | Historically controlled study (Level 4) | Glucocorticoid, height, weight, BMI | 371 patients with DMD (mean age: NR; range: 8.81 and 9.36) | Lower Extremity and Motor Function | Glucocorticoid, including duration, height, weight and BMI predictive of 4SC | Glucocorticoid exposure, height, weight, BMI |
| Wilton et al., 2013 (US) [162] | Randomised trial (Level 2) | ETEP and PLC | NR patients with DMD (mean age: NR, range: NR) | Lower Extremity and Motor Function | Improvements in 6MWT | ETEP treatment |

(Continued)
Table 2. (Continued)

| Author, year (country) | Study design (level of evidence)† | Interventions, DMD genetic modifiers, and/or DMD mutation types | Patient population | Disease progression outcome category | Disease progression outcome results | Identified prognostic indicator‡ |
|------------------------|----------------------------------|---------------------------------------------------------------|-------------------|-------------------------------------|----------------------------------|-------------------------------|
| Signorovitch et al., 2017 (†) [163] | MA (Level 1) | DFZ and PDN/PRED | 231 patients with DMD (mean age: NR, range: NR) | Lower Extremity and Motor Function | DFZ improved NSAA, 6MWT, STS, and 4SC compared to PDN/PRED | Glucocorticoid exposure |
| Signorovitch et al., 2019 (†) [164] | | | | | | |
| Signorovitch et al., 2019 (†) [165] | | | | | | |
| Signorovitch et al., 2019 (†) [166] | | | | | | |
| Gupta et al., 2020 (UK) [167] | Case series Level 4 | Glucocorticoids (drug NR) | 465 patients with DMD (mean age: NR, range: NR) | Lower Extremity and Motor Function | Improved NSAA compared to steroid-naïve | Glucocorticoid exposure |
| Goemans et al., 2016 (NR) [168] | Open-label study (Level 2) | DRIS and natural history control | 12 patients with DMD (mean age: 9.9 years, range: NR) or natural history control (mean age: 9.4 years, range: NR) | Lower Extremity and Motor Function | Improvement in 6MWT | DRIS treatment |
| Goemans et al., 2016 (NR) [169] | | | | | | |
| Ricotti et al., 2013 (UK) [170] | Case series (Level 4) | PDN/PRED | 334–400 patients with DMD (mean age: NR, range: 3–15 years) | Lower Extremity and Motor Function | Improved NSAA in daily PDN-treated compared to intermittent PDN | Glucocorticoid exposure |
| Ricotti et al., 2012 (UK) [75] | | | | | | |
| Ricotti et al., 2011 (UK) [76] | | | | | | |
| Ricotti et al., 2011 (UK) [77] | | | | | | |
| Schreiber et al., 2018 (FR) [171] | Case-control study (Level 4) | DFZ and PDN/PRED | 74–76 patients with DMD treated with DFZ and PDN/PRED (mean age: 8 years, range: 6–11 years) or no treatment (mean age: 8 years, range: 6–12 years) | Lower Extremity and Motor Function | Improved muscle function measure | Glucocorticoid exposure |
| Schreiber et al., 2015 (FR) [172] | | | | | | |
| Schreiber et al., 2016 (FR) [173] | | | | | | |
| Alfano et al., 2019 (US) [174] | Non-randomised controlled study (Level 3) | DFZ and PDN/PRED | 148 patients with DMD (mean age: NR, range: 3–16 years) | Lower Extremity and Motor Function | Improved 10WRT and 100m walking ability | Glucocorticoid exposure |
| Goemans et al., 2016 (BE) [175] | Case series (Level 4) | DFZ and PDN/PRED | 39 patients with DMD (mean age: 9 years, range: 4–16 years) | Lower Extremity and Motor Function | Improved 6MWD including duration of use; those with lower 6MWD showed larger declines | Glucocorticoid exposure |
| Goemans et al., 2018 (BE) [176] | Case series (Level 4) | DFZ and PDN/PRED | 81 patients with DMD (mean age: 10 years, range: NR) | Lower Extremity and Motor Function | Improved 4SC including duration of use | Glucocorticoid exposure |
| Mazzone et al., 2014 (NR) [177] | Non-randomised controlled study (Level 3) | DFZ and PDN/PRED | 96 patients with DMD (mean age: NR, range: NR) | Lower Extremity and Motor Function | Improved 6MWT; baseline 6MWT >350m showed larger improvements | Glucocorticoid exposure |

(Continued)
| Author, year (country) | Study design (level of evidence)† | Interventions, DMD genetic modifiers, and/or DMD mutation types | Patient population | Disease progression outcome category | Disease progression outcome results | Identified prognostic indicator‡ |
|------------------------|----------------------------------|---------------------------------------------------------------|-------------------|-------------------------------------|-----------------------------------|-------------------------------|
| Shieh et al., 2018 (NR) [178] | Meta-analysis (Level 1) | DFZ and PDN/PRED | 147 patients with DMD (mean age: NR, range: NR) | Lower Extremity and Motor Function | Improved 6MWT favouring DFZ | Glucocorticoid exposure |
| Shieh et al., 2018 (NR) [178] | | | | | | |
| Darras et al., 2018 (NR) [179] [NR] | | | | | | |
| Bushby et al., 2014 (ᵪ) [180] Mah et al., 2011 (ᵪ) [181] McDonald et al., 2013 (ᵪ) [182] McDonald et al., 2014 (ᵪ) [183] McDonald et al., 2014 (ᵪ) [184] | Randomised trial (Level 2) | ATA | 174 patients with DMD (median age: 8 years, IQR: 5–20 years) | Lower Extremity and Motor Function | Low dose ATA improved 6MWT including larger improvements in baseline 6MWT <350m | ATA treatment |
| McDonald et al., 2017 (ᵪ) [185] | Randomised trial (Level 2) | ATA | 230 patients with DMD treated with ATA (mean age: 9 years, range: 7–10 years) or PLC (mean age: 9 years, range: 8–10 years) | Lower Extremity and Motor Function | Improved 6MWT in 300-400m baseline 6MWT subgroup | ATA treatment |
| McDonald et al., 2019 (ᵪ) [186] McDonald et al., 2019 (ᵪ) [187] Bushby et al., 2016 (NR) [188] | Randomised trial (Level 2) | ATA | 228 patients with DMD (mean age: NR, range: NR) | Lower Extremity and Motor Function | Preserved NSAA | ATA treatment |
| McDonald et al., 2017 (ᵪ) [189] McDonald et al., 2018 (ᵪ) [190] McDonald et al., 2018 (ᵪ) [191] | Randomised trial (Level 2) | ATA | 168 patients with DMD (mean age: NR, range: NR) | Lower Extremity and Motor Function | Improved 6MWT, 4SC, and 10WRT | ATA treatment |
| Mercuri et al., 2019 (NR) [192] Muntoni et al., 2019 (NR) [193] | Non-randomised controlled study (Level 3) | ATA versus external natural history control | 187 patients with DMD (mean age: NR, range: NR) | Lower Extremity and Motor Function | Improved STS and 4SC | ATA treatment |
| Brogna et al., 2019 (ᵪ) [194] Brogna et al., 2019 (ᵪ) [195] | Case series (Level 4) | Skip exons 44, 45, 51, and 53 | 92 patients with DMD (mean age: 8 years, range: NR) | Lower Extremity and Motor Function | Exon skipping impacts 6MWT | DMD mutation type |

(Continued)
| Author, year (country) | Study design (level of evidence)† | Interventions, DMD genetic modifiers, and/or DMD mutation types | Patient population | Disease progression outcome category | Disease progression outcome results | Identified prognostic indicator‡ |
|-----------------------|----------------------------------|---------------------------------------------------------------|-------------------|-------------------------------------|----------------------------------|-------------------------------|
| Komaki et al., 2020 (JP) [196] | Randomised trial (Level 2) | TAS-205 and PLC | 36 patients with DMD (mean age: 8.3, range: NR) | Lower Extremity and Motor Function | High dose improves muscle volume index | TAS-205 treatment |
| Hoffman et al., 2019 (NR) [197] | Randomised non-controlled trial (Level 3) | VAM | 48 patients with DMD (mean age: NR; range: 4–7 years) | Lower Extremity and Motor Function | Improved 10WRT, STS, 6MWT | VAM treatment |
| Smith et al., 2020 (†) [198] | Historically controlled study (Level 4) | VAM and external natural history control | 122 patients with DMD (mean age: NR; range: 4–7 years) | Lower Extremity and Motor Function | Improved STS, 4SC, NSAA, 10WRT | VAM treatment |
| Koeks et al., 2017 (†) [199] | Case series (Level 4) | Glucocorticoid exposure | 5345 patients with DMD (mean age: NR; range: NR) | Loss of Ambulation | Delay in loss of ambulation | Glucocorticoid exposure; DMD mutation type |
| Exon 45 deletion | | | | Reduced scoliosis | | |
| | | | | Respiratory Health and Function | Reduced need for ventilation | |
| | | | | Cardiac Health and Function | Reduced cardiomyopathy | |
| | | | | | | |
| Voit et al., 2014 (†) [200] | Randomised trial (Level 2) | DRIS and PLC | 53 patients with DMD (DRIS continuous: mean age: 7.2 years, range: NR and DRIS intermittent: mean age: 7.7 years) or PLC (mean age: 6.9 years, range: NR) | Lower Extremity and Motor Function | Improved STS versus PLC for both continuous and intermittent DRIS. 6MWD was improved in the continuous regimen versus PLC at week 25 | DRIS treatment |
| | | | | | | |
| McDonald et al., 2015 (NR) [201] | Randomised trial (Level 2) | DRIS | 535 patients with DMD (mean age: NR; range: NR) | Lower Extremity and Motor Function | Improvement in 6MWT | DRIS treatment |
| McDonald et al., 2014 (NR) [202] | Randomised trial (Level 2) | DRIS | 535 patients with DMD (mean age: NR; range: NR) | Lower Extremity and Motor Function | Improvement in 6MWT | DRIS treatment |
| Mayer et al., 2017 (†) [203] | Randomised trial (Level 2) | IDE and PLC | 64 patients with DMD (mean age: NR; range: 10–19 years) | Respiratory Health and Function | Reduced decline in pulmonary function as given by FVC | IDE treatment |

Note: Argentina (AR). Australia (AU). Belgium (BE). Canada (CA). China (CN). Denmark (DK). Egypt (EG). France (FR). Germany (DE). Holland (NL). India (IN). Italy (IT). Japan (JP). Korea (KR). Not reported (NR). Sweden (SE). Turkey (TR). United Kingdom (UK). United States of America (US). Angiotensin-converting enzyme (ACE). Angiotensin receptor blocker (ARB). Ataluren (ATA). Best standard of care (BSC). Beta2-adrenergic receptor (ADRB2). Beta blocker (BB). Body mass index (BMI). Cluster of differentiation 40 (CD40). Delilacort (DFZ). Driapersen (DRIS). Duchenne muscular dystrophy (DMD). Dystrophin protein 140 (Dp140). Edasalone xent (EDASA). End systolic volume (ESV). Eplerenone (EPL). Eteplirsen (ETEP). Forced expiratory volume in 1 second (FEV1). Four Stair Climb (4SC). Idebenone (IDE). Interquartile range (IQR). Knee-ankle-foot-orthoses (KAFOS). Latent transforming growth factor-beta-binding protein 4 (LTBP4). Left ventricular ejection fraction (LVEF). Left ventricular end diastolic dimension (LVEDD). Left ventricular end systolic dimension (LVEFs). Left ventricular fractional shortening (LVFS). Left ventricular myocardial performance index (LVMPI). Manual muscle testing (MMT). Maximum expiratory pressure (PEFR). Peak cough flow (PCF). Peak expiratory flow rate (PEFR). Peak expiratory flow (PEF). Performance of Upper Limb (PUL). Placebo (PLC). Prednisone (PDN). Prednisolone (PRED). Quantitative muscle testing (QMT). Randomised controlled trial (RCT). Secreted phosphoprotein 1 (SPP1). Single nuclear polymorphisms (SNPs). Six-Minute Walk Test (6MWT). Supine-to-Stand (STS). Ten Metre Walk/Run Test (10WRT). Velocity of circumferential fibre shortening (VCFc). Vamolorone (VAM). Vitilolarsen (VIT). † OCEBM Level of Evidence. ‡ Indicators with a significant impact on listed disease progression outcome measures. * Multi-national.
improves peak systolic radial strain in the LV inferolateral wall [Level 2] [111]. BMI is prognostic of cardiomyopathy [Level 4] [41]. Finally, mutations in exons 51 and 52, as well as latent transforming growth factor beta-binding protein 4 (LTBP4), have been shown to be significantly associated with improved or sustained cardiac health and function [Level 4]; [21, 22, 35]; mutations in exons 12, 14, 15, 16, and 17 with increased risk of cardiomyopathy [Level 4] [35]. and deletions in exon 53 with lower LVEF and higher contracture score compared with deletions not treatable by exon 53 skipping [Level 4] [91]. The ACTN3 null genotype is associated with earlier onset of cardiac dysfunction specifically, lower LV dilation-free rate [Level 4] [40].

3.2. Loss of independent ambulation

We identified 35 studies presenting evidence of prognostic indicators of disease progression in DMD measured in terms of loss of independent ambulation [11, 18–20, 38, 46, 51, 61–66, 68–91, 109, 126–130, 192, 193, 199]. In total, nine prognostic indicators were identified: age at diagnosis, age at onset of symptoms, ataluren treatment, DMD genetic modifiers, DMD mutation type, glucocorticoid exposure, eteplirsen treatment, height, and weight (Table 2). Prolonged independent ambulation was found in patients with later onset of symptoms [Level 2]; [83, 84] patients treated with glucocorticoids, including age at treatment initiation, duration of exposure, and pharmacological agent [Level 2]; [11, 18–20, 38, 46, 51, 61–64, 66, 70–82, 88, 199]; ataluren treatment [Level 2] [87, 109, 110, 192, 193]; eteplirsen treatment [Level 2] [126–130]; LTBP4 genotype [Level 2]; [65] lower limb surgery [Level 2] [89, 90] and mutations in exons 44 [Level 2] [11, 67, 73, 86, 88] and exons 3–7 [Level 2]; [11, 88] exon 8 [Level 4] [86, 88]; exon 45 [Level 4] [88, 199]; exon 53 [Level 4] [91] and the minor allele at rs1883832 [Level 4] [85]. Earlier loss of ambulation was found in patients with TG/GG genotype at the rs28357094 secreted phosphoprotein 1 (SPP1) promoter [Level 2]; [63–66] exon 51 skipping and exon 49–50 deletions [Level 4] [88]; and deletions in the dystrophin gene [Level 4] [61]. Older age at diagnosis (>4 years) has been shown to be a predictor of later loss of ambulation [Level 5] [74]. Finally, greater weight and lower height have been shown to predict delayed time to loss of ambulation in patients treated with glucocorticoids [Level 4] [68, 69].

3.3. Lower extremity and motor function

We found 47 studies presenting evidence of prognostic indicators of disease progression in DMD measured in terms of lower extremity and motor function [47, 51, 71, 75–77, 79–82, 87, 92, 96, 101, 119–131, 136, 138, 140, 141, 143–146, 150–152, 160–186, 188–198, 200–202]. In total, twelve prognostic indicators were identified: ataluren treatment, BMI, DMD genetic modifiers, DMD mutation type, drisapersen treatment, eteplirsen treatment, glucocorticoid exposure, height, TAS-205 treatment, vamorolone treatment, vitlolarsen treatment, and weight (Table 2). Glucocorticoid treatment, including dose, duration of exposure, and regimen, have been shown to be significantly associated with improvement in motor function as measured using the Scott functional score [Level 2] [140, 143], the Vignos scale [Level 4] [71, 96], muscle function measure [Level 4] [171, 172], improvements in the NorthStar Ambulatory Assessment (NSAA) scale [Level 1] [75–77, 131, 163–167, 170], the 6-minute walk test (6MWT) including duration of glucocorticoid exposure [Level 1] [131, 163–166, 175, 177–179], 10 Meter Walk/Run Test (10WRT) [Level 2] [79–81, 92, 96, 138, 174], 100 metre walk/run test [Level 3] [174], 9 metre walk/run test [Level 2] [47, 141, 144, 145], unspecified walking test [Level 4] [71], Supine-to-Stand (STS) test [Level 1] [47, 51, 71, 82, 92, 96, 101, 131, 136, 138, 141, 143, 145, 146, 160, 163–166], and 4-Stairs Climb Test (4SCT) including duration of exposure [Level 1] [47, 71, 82, 92, 96, 101, 131, 138, 141, 144, 145, 151, 163–166, 176]. Ataluren treatment has been shown to be significantly associated with better performance in timed
function tests, including the 4SCT [Level 2] [87, 150, 189–193], the STS test [Level 3] [87, 192, 193], the 10WRT [Level 2] [150, 189–191], the NSAA [Level 2] [186–188], and the 6MWT [Level 2]; [150, 180–185, 189–191] treatment with TAS-205 has been shown to increase muscle volume index [Level 2] [196]; treatment with vitlolarsen associated with improved 10WRT, 6MWT, STS and NSAA [Level 2] [152]; treatment with vamorolone improves 6MWT [Level 3] [197] STS [197, 198], 10WRT [197, 198], 4SCT and NSAA [Level 4] [198]; treatment with drisapersen improves STS and 6MWT [Level 2] [168, 169, 200–202]. Eteplirsen treatment improves 6MWT [Level 2] [119–130, 162]. Greater height and weight have been shown to be significantly associated with decline in the 6MWT [Level 4]; [175] similarly, height, weight BMI and glucocorticoid exposure including duration are predictive of 4SC [Level 4] [161]. Finally, skip exon mutations has been shown to be significantly associated with 6MWT performance [Level 4] and [194, 195] Dp140 deletions associated with lower NSAA scores [Level 4] [151].
3.4. Muscle strength

We found 26 studies presenting evidence of prognostic indicators of disease progression in DMD measured in terms of muscle strength [18, 47, 71, 79, 80, 91, 92, 100, 101, 135–149, 153–159]. In total, five prognostic indicators were identified: DMD genetic modifiers, DMD mutation type, edasalonexent, glucocorticoid exposure and oxandrolone (Table 2). Specifically, glucocorticoid treatment, including dose, duration of exposure, and regimen, have been shown to be associated with muscle strength as quantified by the Medical Research Council (MRC) muscle power assessment scale [Level 2] [18, 71, 100, 135, 136, 138, 158], quantitative muscle testing (QMT) [Level 2] [92, 139], muscle mass as given by creatine excretion [Level 2] [137, 139, 142], manual muscle testing (MMT) [Level 2] [92, 139, 142, 145], myometric evaluation [Level 2] [140–146], unspecified muscle strength testing [Level 2] [101, 137], grip and pinch strength [Level 2] [47, 140, 141], Lovett’s test [Level 4]; [79, 80] and transverse relaxation time constant [Level 2] [159]. Edasalonexent improves the transverse relaxation time constant [Level 2] [153–157]. Oxandrolone improves muscle strength as given by MMT [Level 4] [149] and an unspecified measure [Level 2] [148]. Finally, GT/GG genotypes at the rs28357094 SPP1 promoter have been shown to be significantly associated with lower composite MRC scores and grip strength compared with the TT genotype [Level 4] [147]. and exon 53 deletions with lower pinch strength compared to all mutations not treatable by exon 53 skipping [Level 4] [91].

3.5. Respiratory health and function

We identified 35 studies presenting evidence of prognostic indicators of disease progression in DMD measured in terms of respiratory health and function [17–19, 21, 22, 28, 38, 47, 71, 77, 82, 92, 94–118, 132–134, 145, 199, 203]. In total, eight prognostic indicators were identified: ataluren treatment, DMD genetic modifiers, DMD mutation type, eteplirsen treatment, glucocorticoid exposure, idebenone treatment, ventilation support and weight (Table 2). Specifically, ataluren treatment has been shown to be significantly associated with improved forced vital capacity (FVC) [Level 2]; [103, 104, 109, 110] glucocorticoid treatment, including dose, duration of exposure, and regimen, with improved maximum inspiratory pressure (MIP) [Level 2] [92, 95, 96], maximum expiratory pressure (MEP) [Level 4] [94, 95], peak cough flow (PCF) [Level 4]; [94, 95] FVC [Level 2]; [17, 18, 21, 22, 38, 47, 71, 77, 82, 96–99, 101, 145] forced expiratory volume in 1 second (FEV₁) [Level 2] [96, 107], maximum voluntary ventilation (MVV) [Level 2], [92, 101, 102], FVC [Level 4] [107], reduced need for ventilation [Level 4] [199] and peak expiratory flow rate (PEFR) [Level 3] [96, 98–100, 107] and pulmonary function preservation [Level 4] [19]. Duration of glucocorticoid exposure has also been linked to declining FVC levels [Level 4] [28]. Eteplirsen has been shown to be associated with an attenuation in respiratory function [Level 4] [108, 118] and reduced decline in FVC [Level 2] [113–117] and MEP [Level 2] [116, 117]; and idebenone reduces the decline in respiratory function as given by FVC [Level 2] [203], FEV1 [Level 2] [112] and PEF [Level 2] [111, 112, 133] as well as reducing bronchopulmonary adverse events [Level 2] [132]. Weight has been shown to be a significant predictor of need for full-time ventilation support [Level 4] [105]. Ventilation support has been shown to reduce the rate of decline of FVC [Level 4] [106]. Finally, Gly16 beta2--adrenergic receptor (ADRB2) polymorphism has been shown to be significantly associated with increased risk of requiring nocturnal ventilation support (compared with the Arg16 polymorphism) [Level 4] [105]; dystrophin protein 140 (Dp140)–related mutations with lower FVC [Level 4] [21, 22]; mutations in exon 44 with lower FVC, FEV1 and PEF [Level 4] [107]; skip 51 and 53 mutations with decreased FEV1, PEF and FVC [Level 4] [107]; splice site, skip 8 and skip 44 with increased FVC [Level 4] [107]; skip 8 and splice site mutations with increased FEV1 and increased PEF [Level 4] [107]; nonsense mutation with decreased FEV1
and FVC [Level 4] [107]; dominant G genotype at rs28357094 in the SPP1 promoter with reduced FVC and PEF [Level 4] [107]; additive T genotype at rs1883832 in the CD40 5’ untranslated region with reduced FVC, FEV1 and PEF [Level 4] [107]; mutations in exon 8 with improved PEF [Level 4]; [21, 22]; cDMD deficit with worsened respiratory function [Level 3] [134]; and SPP1 and cluster of differentiation 40 (CD40) polymorphisms with reduced FVC and PEF, respectively [Level 4] [21, 22] with both mutations associated with NIV initiation [Level 4] [107].

3.6. Scoliosis

We identified 7 studies presenting evidence of prognostic indicators of disease progression in DMD measured in terms of risk of scoliosis [18, 46–50, 199]. In total, two prognostic indicators were identified: glucocorticoid exposure, and orthoses (Table 2). Specifically, glucocorticoid treatment, including duration of exposure, have been shown to significantly reduce the risk of developing scoliosis, including the degree of scoliosis and the need for spinal surgery [Level 3] [18, 46–50, 199]. Time in orthoses has been shown to be significantly related to scoliosis severity [Level 4] [50].

3.7. Survival

We identified 13 studies presenting evidence of prognostic indicators of disease progression in DMD measured in terms of survival [25, 42, 43, 49, 51–60]. In total, five prognostic indicators were identified: cardiac medication, glucocorticoid exposure, left ventricular assist devices, spinal surgery, and ventilation support (Table 2). Specifically, prolonged survival was found in patients treated with ACE inhibitors [Level 2] [42, 43] ACE inhibitors in combination with beta blockers, including timing of treatment initiation [Level 4]; [52] in patients treated with glucocorticoids (including duration of exposure) [Level 2]; [25, 49, 51] in patients receiving ventilation support [Level 4]; [53–59] and in those undergoing spinal surgery in combination with ventilation support [Level 4] [55]; and in those implanted with left ventricular assist devices in combination with cardiac medication [Level 4] [60].

3.8. Upper extremity function

We identified 5 studies presenting evidence of prognostic indicators of disease progression in DMD measured in terms of upper extremity function [51, 92, 93, 96, 140]. In total, two prognostic indicators were identified: glucocorticoid exposure (including pharmacological agent) and ATL1102 treatment (Table 2). Glucocorticoid treatment has been shown to significantly retain hand-to-mouth function as measured using the Brooke score [Level 2]; [51, 92, 96, 140] and deflazacort (DFZ) exposure significantly delays loss of hand-to-mouth function compared to prednisone (PDN) [Level 2] [51]. Treatment with ATL1102 improves upper limb function in non-ambulant boys as given by performance of upper limb (PUL) scores [Level 2] [93].

4. Discussion

In many disease areas, including DMD, RCTs are commonly unavailable, resulting in the need to indirectly compare treatment effects, for example, by pooling individual patient-level data from multiple sources. However, to derive reliable estimates, it is necessary to ensure that the samples considered are comparable with respect to factors significantly affecting the clinical progression of the disease. To help inform such analyses, the objective of this study was to review and synthesise the published evidence of prognostic indicators of disease progression in DMD. From our literature search, we identified 23 factors significantly affecting disease
progression outcomes in DMD, namely age at diagnosis, age at onset of symptoms, ataluren treatment, ATL1102, BMI, cardiac medication, DMD genetic modifiers, DMD mutation type, drisapersen, edasalonexent, eteplirsen, glucocorticoid exposure, height, idebenone, lower limb surgery, orthoses, oxandrolone, spinal surgery, TAS-205, vamorolone, vitlolarsen, ventilation support, and weight. Of these, two endogenous and two exogenous core prognostic indicators were designated, each supported by a high level of clinical evidence.

The most commonly examined prognostic indicator identified in the literature related to treatment with glucocorticoids—the cornerstone of the current pharmacological management of DMD. This core exogenous factor was found to significantly impact a wide range of disease progression outcomes, including loss of independent ambulation, lower extremity and motor function, muscle strength, respiratory health and function, survival, and upper extremity function (high level of evidence); cardiac health and function (moderate level of evidence); and possibly risk of developing scoliosis (low level of evidence). The body of evidence, spanning a total of 73 individual studies, encompassed various commonly reported features of glucocorticoid therapy, such as age at treatment initiation, dose, duration of exposure, pharmacological agent, and regimen.

The second exogenous core prognostic indicator of disease progression in DMD was cardiac medication, supported by data from a total of 13 studies of varying levels of evidence (Fig 2). As expected, this indicator only concerned cardiac health and function (with the exception of a single study of low evidence level showing an impact on survival). Even so, bearing in mind that cardiomyopathy has emerged as one of the leading causes of death in the aging DMD population in the presence of the routine use of mechanical ventilation support [12], the significance of this indicator should not be underestimated, in particular when comparing samples encompassing patients residing in more advanced stages of the disease.

The two endogenous core prognostic indicators of disease progression in DMD identified in our review were DMD genetic modifiers and DMD mutation type. Although more research is needed to quantify the impact of specific modifiers and mutations, emerging data show that these genetic aspects may play a non-trivial role in the overall progression of the disease. These findings underscore the importance of collecting genetic data from DMD patients as part of studies and patient registries.

Our study is subject to three specific limitations. First, our review did not cover grey literature, which means that evidence for some indicators of disease progression in DMD might have not been fully identified. However, given the comprehensive scope of our search and the limited body of clinical evidence disseminated in non-indexed journals, the impact of this limitation is expected to be negligible (in particular in terms of detecting novel prognostic indicators currently not included in our synthesis). Second, for interpretation of results, it is important to keep in mind that our study did not seek to assess the efficacy or effectiveness of current disease interventions, nor the sensitivity of specific indicators, but rather identify factors that have been shown to significantly alter the clinical progression of DMD (irrespective of magnitude). Although we only considered statistically significant factors, this means that it is not possible to discern the relative clinical importance, or relevance, of included indicators. Finally, the fact that we only reported statistically significant and not also non-significant results means that we were more likely to accept false positive than false negative conclusions of specific indicators. That being said, collating and synthesizing also non-significant results, of which a non-trivial proportion ($\beta$) would be expected to be false, were outside the scope of this review.

In conclusion, we identified a total of 23 prognostic indicators of disease progression in DMD, of which cardiac medication, DMD genetic modifiers, DMD mutation type, and glucocorticoid exposure were designated core indicators significantly affecting a wide range of
clinical outcomes. Our up-to-date summary of prognostic indicators in DMD should be helpful to inform the design of comparative analyses and future data collection initiatives in this patient population.

Supporting information

S1 Checklist. PRISMA 2009 checklist.
(PDF)

S1 Appendix. Search strings.
(DOCX)

Author Contributions

Conceptualization: Nermina Ferizovic, Jessica Summers, Igor Beitia Ortiz de Zárate, Christian Werner, Erik Landfeldt, Katharina Buesch.

Data curation: Nermina Ferizovic, Jessica Summers, Erik Landfeldt, Katharina Buesch.

Formal analysis: Nermina Ferizovic, Jessica Summers, Christian Werner, Erik Landfeldt, Katharina Buesch.

Funding acquisition: Nermina Ferizovic, Erik Landfeldt, Katharina Buesch.

Investigation: Nermina Ferizovic, Erik Landfeldt, Katharina Buesch.

Methodology: Nermina Ferizovic, Jessica Summers, Igor Beitia Ortiz de Zárate, Joel Jiang, Erik Landfeldt, Katharina Buesch.

Project administration: Nermina Ferizovic, Erik Landfeldt, Katharina Buesch.

Resources: Nermina Ferizovic, Erik Landfeldt, Katharina Buesch.

Software: Nermina Ferizovic, Erik Landfeldt, Katharina Buesch.

Supervision: Nermina Ferizovic, Erik Landfeldt, Katharina Buesch.

Validation: Nermina Ferizovic, Jessica Summers, Christian Werner, Joel Jiang, Erik Landfeldt, Katharina Buesch.

Visualization: Nermina Ferizovic, Erik Landfeldt, Katharina Buesch.

Writing – original draft: Nermina Ferizovic, Erik Landfeldt, Katharina Buesch.

Writing – review & editing: Nermina Ferizovic, Jessica Summers, Igor Beitia Ortiz de Zárate, Christian Werner, Joel Jiang, Erik Landfeldt, Katharina Buesch.

References

1. Emery AE. The muscular dystrophies. Lancet. 2002; 359(9307):687–95. https://doi.org/10.1016/S0140-6736(02)07815-7 PMID: 11879882

2. Davies KE, Pearson PL, Harper PS, Murray JM, O’Brien T, Sarfarazi M, et al. Linkage analysis of two cloned DNA sequences flanking the Duchenne muscular dystrophy locus on the short arm of the human X chromosome. Nucleic Acids Res. 1983; 11(8):2303–12. https://doi.org/10.1093/nar/11.8.2303 PMID: 6304647

3. Gao QQ, McNally EM. The Dystrophin Complex: Structure, Function, and Implications for Therapy. Compr Physiol. 2015; 5(3):1223–39. https://doi.org/10.1002/cphy.c140048 PMID: 26140716

4. Flanagan KM, Dunn DM, von Niederhausen A, Soltanzadeh P, Gappmaier E, Howard MT, et al. Mutational spectrum of DMD mutations in dystrophinopathy patients: application of modern diagnostic techniques to a large cohort. Hum Mutat. 2009; 30(12):1657–66. https://doi.org/10.1002/humu.21114 PMID: 19937601
5. Moat SJ, Bradley DM, Salomon R, Clarke A, Hartley L. Newborn bloodspot screening for Duchenne muscular dystrophy: 21 years experience in Wales (UK). Eur J Hum Genet. 2013; 21(10):1049–53. https://doi.org/10.1038/ejhg.2012.301 PMID: 23340516

6. Parent Project Muscular Dystrophy. About Duchenne. Available from: https://www.parentprojectmd.org/about-duchenne/. Accessed 05/01/2022.

7. van Ruiten HJA, Straub V, Bushby K, Guglieri M. Improving recognition of Duchenne muscular dystrophy: a retrospective case note review. Archives of Disease in Childhood. 2014; 99(12):1074. https://doi.org/10.1136/archdischild-2014-306366 PMID: 25187493

8. Wong SH, McClaren BJ, Archibald AD, Weeks A, Langmaid T, Ryan MM, et al. A mixed methods study of age at diagnosis and diagnostic odyssey for Duchenne muscular dystrophy. European journal of human genetics. 2014; 99(12):1074. https://doi.org/10.1038/ejhg.2014.301 PMID: 2562706

9. Blake DJ, Weir A, Newey SE, Davies KE. Function and Genetics of Dystrophin and Dystrophin-Related Proteins in Muscle. Physiological Reviews. 2002; 82(2):291–329. https://doi.org/10.1152/physrev.00028.2001 PMID: 11917091

10. Ryder S, Leadley RM, Armstrong N, Westwood M, de Kock S, Butt T, et al. The burden, epidemiology, costs and treatment for Duchenne muscular dystrophy: an evidence review. Orphanet Journal of Rare Diseases. 2017; 12:79. https://doi.org/10.1186/s13023-017-0631-3 PMID: 28446219

11. Libarati A, Altman DG, Tetzlaff J, Mulrow C, Ioannidis J, Prisma statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009; 339:b2700. https://doi.org/10.1136/bmj.b2700 PMID: 19622552

12. Bello L, Morgenroth LP, Gordish-Dressman H, Hoffman EP, McDonald CM, Cirak S, et al. DMD genotypes and loss of ambulation in the CINRG Duchenne Natural History Study. Neurology. 2016; 87(4):401–9. https://doi.org/10.1212/WNL.000000000002891 PMID: 27343068

13. Landfeldt E, Thompson R, Sejersen T, McMillan HJ, Kirschner J, Lochmüller H. Life expectancy at birth in Duchenne muscular dystrophy: a systematic review and meta-analysis. Eur J Epidemiol. 2020; 35(7):643–53. https://doi.org/10.1007/s10654-020-00613-8 PMID: 32107739

14. Birnkrant DJ, Bushby K, Bann CM, Alman BA, Apkon SD, Blackwell A, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. Lancet. 2018; 17(4):347–61. https://doi.org/10.1016/S1474-4422(18)30025-5 PMID: 29395990

15. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Stürmer T. Variable selection for propensity score models. Am J Epidemiol. 2006; 163(12):1149–56. https://doi.org/10.1093/aje/kwj149 PMID: 16624967

16. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Ioannidis J, Prisma statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009; 339:b2700. https://doi.org/10.1136/bmj.b2700 PMID: 19622552

17. OCEBM Levels of Evidence Working Group. The Oxford Levels of Evidence 2. 2021. https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocemb-levels-of-evidence. Accessed 31 Jan 2021. 2011

18. Biggar WD, Harris VA, Eliasoph L, Alman BA. Long-term benefits of deflazacort treatment for boys with Duchenne muscular dystrophy in their second decade. Neuromuscul Disord. 2006; 16(4):249–55. https://doi.org/10.1016/j.nmd.2006.01.010 PMID: 16545568

19. Houde S, Filatriault M, Fournier A, Dubé J, D’Arcy S, Bérubé D, et al. Deflazacort use in Duchenne muscular dystrophy: an 8-year follow-up. Pediatr Neurol. 2008; 38(3):200–6. https://doi.org/10.1016/j.pediatrneurol.2007.11.001 PMID: 18279756

20. Silversides CK, Webb GD, Harris VA, Biggar DW. Effects of deflazacort on left ventricular function in patients with Duchenne muscular dystrophy. Am J Cardiol. 2003; 91(6):769–72. https://doi.org/10.1016/s0002-9149(02)03429-x PMID: 12633823

21. Barber BJ, Andrews JG, Lu Z, West NA, Meaney FJ, Price ET, et al. Oral Corticosteroids and Onset of Cardiomyopathy in Duchenne Muscular Dystrophy. The Journal of Pediatrics. 2013; 163(4):1080–4. e1. https://doi.org/10.1016/j.jpeds.2013.05.060 PMID: 23866715

22. Bello L, D’Angelo G, Bruno C, Berardinielli A, Cori G, D’Amico A, et al. P.267 Modifiers of respiratory and cardiac function in the Italian Duchenne muscular dystrophy network and CINRG Duchenne natural history study. Neuromuscular Disorders. 2019; 29(Suppl 1):S145.

23. Bello L, D’Angelo G, Villa M, Fusto A, Vianello S, Merlo B, et al. Modifiers of respiratory and cardiac function in the Italian Duchenne muscular dystrophy network and CINRG Duchenne Natural History Study. Acta myologica Proceedings Of The XIX Congress Of The Italian Society of Myology: Bergamo, Italy. 2019; 38(2):103–4.

24. Tandon A, Villa CR, Hor KN, Jefferys J, Gao Z, Towbin JA, et al. Myocardial fibrosis burden predicts left ventricular ejection fraction and is associated with age and steroid treatment duration in duchenne muscular dystrophy. J Am Heart Assoc. 2015; 4(4):e001338. https://doi.org/10.1161/JAHA.114.001338 PMID: 25814625
24. Zhang L, Liu Z, Hu K-Y, Tian Q-B, Wei L-G, Zhao Z, et al. Early myocardial damage assessment in dystrophinopathies using (99m)Tc-MIBI gated myocardial perfusion imaging. Ther Clin Risk Manag. 2015; 11:1819–27. https://doi.org/10.2147/TCRM.S89962 PMID: 26677332

25. Schram G, Fournier A, Leduc H, Dahdah N, Therien J, Vanasse M, et al. All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy. J Am Coll Cardiol. 2013; 61(9):948–54. https://doi.org/10.1016/j.jacc.2012.12.008 PMID: 23352781

26. Markham LW, Kinnett K, Wong BL, Woodrow Benson D, Cripe LH. Corticosteroid treatment retards development of ventricular dysfunction in Duchenne muscular dystrophy. Neuromuscul Disord. 2008; 18(5):365–70. https://doi.org/10.1016/j.nmd.2008.03.002 PMID: 18436445

27. Kim S, Zhu Y, Romitti PA, Fox DJ, Sheehan DW, Valdez R, et al. Associations between timing of corticosteroid treatment initiation and clinical outcomes in Duchenne muscular dystrophy. Pediatr Neurol. 2015; 50(3):202–8. https://doi.org/10.1016/j.pen.2015.04.021 PMID: 26020571

28. Schram G, Fournier A, Leduc H, Dahdah N, Therien J, Vanasse M, et al. All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy. J Am Coll Cardiol. 2013; 61(9):948–54. https://doi.org/10.1016/j.jacc.2012.12.008 PMID: 23352781

29. Markham LW, Spicer RL, Khoury PR, Wong BL, Mathews KD, Cripe LH. Steroid therapy and cardiac function in Duchenne muscular dystrophy. Pediatr Cardiol. 2005; 26(6):768–71. https://doi.org/10.1007/s00246-005-0909-4 PMID: 15990951

30. Kim S, Zhu Y, Romitti PA, Fox DJ, Sheehan DW, Valdez R, et al. Associations between timing of corticosteroid treatment initiation and clinical outcomes in Duchenne muscular dystrophy. Neuromuscul Disord. 2017; 27(8):730–7. https://doi.org/10.1016/j.nmd.2017.05.019 PMID: 28645460

31. Akaiwa T, Takeda A, Oyama-Manabe N, Naya M, Yamazaw a H, Koyanagawa K, et al. Progressive left ventricular dysfunction and myocardial fibrosis in Duchenne and Becker muscular dystrophy: a longitudinal cardiovascular magnetic resonance study. Pediatr Cardiol. 2019; 40(2):384–92. https://doi.org/10.1007/s00246-018-2046-x PMID: 30564867

32. Thrush P, Viollet L, Flanigan K, Mendell J, Allen H. Natural history of cardiomyopathy in Duchenne muscular dystrophy and the effects of angiotensin-converting enzyme inhibitor with or without beta-blocker. Journal of the American College of Cardiology. Journal of the American College of Cardiology. 2012; 58(Suppl 13):E820.

33. Thrush P, Viollet L, Flanigan K, Mendell J, Allen H. Natural history of cardiomyopathy in Duchenne muscular dystrophy and the effects of angiotensin-converting enzyme inhibitor with or without β-blocker (S15.003). Neurology. 2012; 78(Suppl 1):S15 003.

34. Viollet L, Thrush PT, Flanigan KM, Mendell JR, Allen HD. Effects of angiotensin-converting enzyme inhibitors and/or beta blockers on the cardiomyopathy in Duchenne muscular dystrophy. Am J Cardiol. 2012; 110(1):98–102. https://doi.org/10.1016/j.amjcard.2012.02.064 PMID: 22438399

35. Jefferies JL, Eidem BW, Belmont JW, Craigen WJ, Ware SM, Fernbach SD, et al. Genetic Predictors and Remodeling of Dilated Cardiomyopathy in Muscular Dystrophy. Circulation. 2005; 112(18):2799–804. https://doi.org/10.1161/CIRCULATIONAHA.104.528281 PMID: 16246949

36. Raman SV, Hor KN, Mazur W, Halnon NJ, Kissel JT, He X, et al. Eplerenone for early cardiomyopathy in Duchenne muscular dystrophy: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2015; 14(2):153–61. https://doi.org/10.1016/S1474-4422(14)70318-7 PMID: 25554404

37. Matsumura T, Tamura T, Kuru S, Kikuchi Y, Kawai M. Carvedilol can prevent cardiac events in Duchenne muscular dystrophy. Intern Med. 2010; 49(14):153–61. https://doi.org/10.1016/j.amjcard.2012.02.064 PMID: 22438399

38. van Ruiten HJA, Jimenez-Moronen AC, Elliott E, Mayhew A, James M, Mariní-Bettolo C, et al. Impact of three decades of improvements in standards of care on clinical outcomes in Duchenne muscular dystrophy. European Journal of Paediatric Neurology. 2017; 21(Suppl 1):e235–e6.

39. Fayssoil A, Ogna A, Chaffaut C, Lamothe L, Ambrosi X, Nardi O, et al. Natural history of cardiac function in Duchenne and Becker muscular dystrophies on home mechanical ventilation. Medicine (Baltimore). 2018; 97(27):e11381. https://doi.org/10.1097/MD.00000000000011381 PMID: 29979426

40. 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. Journal of Cardiac Failure. 2020; 26(10):841–8. https://doi.org/10.1016/j.cardfail.2020.08.002 PMID: 32791185

41. Cheeran D, Khan S, Khera R, Bhatt A, Garg S, Grodin JL, et al. Predictors of death in adults with Duchenne muscular dystrophy—associated cardiomyopathy. Journal of the American Heart Association. 2017; 6(10):e006340. https://doi.org/10.1161/JAHA.117.006340 PMID: 29042427

42. Duboc D, Meune C, Lebours G, Devaux JY, Vaksman G, Bécane HM. Effect of perindopril on the onset and progression of left ventricular dysfunction in Duchenne muscular dystrophy. J Am Coll Cardiol. 2005; 45(6):855–7. https://doi.org/10.1016/j.jacc.2004.09.078 PMID: 15766818
43. Duboc D, Meune C, Pierre B, Wahbi K, Eymard B, Toutain A, et al. Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years’ follow-up. Am Heart J. 2007; 154(3):596–602. https://doi.org/10.1016/j.ahj.2007.05.014 PMID: 17719312

44. Ishikawa Y, Bach JR, Minami R. Cardioprotection for Duchenne’s muscular dystrophy. American Heart Journal. 1999; 137(5):895–902. https://doi.org/10.1016/s0002-8703(99)70414-x PMID: 10220638

45. Ramaciotti C, Heistein LC, Coursey M, Lemler MS, Eapen RS, Iannaccone ST, et al. Left ventricular function and response to enalapril in patients with duchenne muscular dystrophy during the second decade of life. Am J Cardiol. 2006; 98(6):825–7. https://doi.org/10.1016/j.amjcard.2006.04.020 PMID: 16950195

46. King WM, Rutten cutter R, Nagaraja HN, Matkovic V, Landoll J, Hoyle C, et al. Orthopedic outcomes of long-term daily corticosteroid treatment in Duchenne muscular dystrophy. Neurology. 2007; 68 (19):1607–13. https://doi.org/10.1212/01.wnl.0000260974.41514.83 PMID: 17485648

47. Balaban B, Matthews DJ, Clayton GH, Carry T. Corticosteroid treatment and functional improvement in Duchenne muscular dystrophy: long-term effect. Am J Phys Med Rehabil. 2005; 84(11):843–50. https://doi.org/10.1097/01.phm.0000184156.98671.d0 PMID: 16244521

48. Alman BA, Raza SN, Biggar WD. Steroid Treatment and the Development of Scoliosis in Males with Duchenne Muscular Dystrophy. J Bone Joint Surg Am. 2004; 86(3):519–24. https://doi.org/10.2106/00004623-20040300-00009 PMID: 14996877

49. Lebel DE, Corston JA, McAdam LC, Biggar WD, Alman BA. Glucocorticoid treatment for the prevention of scoliosis in children with Duchenne muscular dystrophy: long-term follow-up. J Bone Joint Surg Am. 2013; 95(12):1057–61. https://doi.org/10.2106/JBJS.L.01577 PMID: 23783200

50. Kinai M, Main M, Eliaho J, Messina S, Knight RK, Lehovsky J, et al. Predictive factors for the development of scoliosis in Duchenne muscular dystrophy. Eur J Paediatr Neurol. 2007; 11(3):160–6. https://doi.org/10.1016/j.ejpn.2006.12.002 PMID: 17257866

51. McDonald CM, Henrichson EK, Abresch RT, Duong T, Joyce NC, Hu F, et al. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. The Lancet. 2018; 391(10119):451–61.

52. Ogata H, Ishikawa Y, Ishikawa Y, Minami R. Beneficial effects of beta-blockers and angiotensin-converting enzyme inhibitors in Duchenne muscular dystrophy. Journal of Cardiology. 2009; 53(1):72–8. https://doi.org/10.1016/j.jcc.2008.08.013 PMID: 19167641

53. Rall S, Grimm T. Survival in Duchenne muscular dystrophy. Acta Myol. 2012; 31(2):117–20. PMID: 23097602

54. Jeppesen J, Green A, Steffensen BF, Rahbek J. The Duchenne muscular dystrophy population in Denmark, 1977–2001: prevalence, incidence and survival in relation to the introduction of ventilator use. Neuromuscular Disorders. 2003; 13(10):804–12. https://doi.org/10.1016/s0960-8966(03)00162-7 PMID: 14678803

55. Eagle M, Bourke J, Bullock R, Gibson M, Mehta J, Giddings D, et al. Managing Duchenne muscular dystrophy—The additive effect of spinal surgery and home nocturnal ventilation in improving survival. Neuromuscular Disorders. 2007; 17(6):470–5. https://doi.org/10.1016/j.nmd.2007.03.002 PMID: 17490881

56. Eagle M, Baudouin SV, Chandler C, Giddings DR, Bullock R, Bushby K. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. Neuromuscular Disorder. 2002; 12(10):926–9. https://doi.org/10.1016/s0960-8966(02)00140-2 PMID: 12467747

57. Gomez-Merino E, Bach JR, Duchenne muscular dystrophy: prolongation of life by noninvasive ventilation and mechanically assisted coughing. Am J Phys Med Rehabil. 2002; 81(6):411–5. https://doi.org/10.1097/00002060-200206000-00003 PMID: 12023596

58. Kiery P, Chollet S, Delalande P, Le Fort M, Magot A, Pereon Y, et al. Evolution of life expectancy of patients with Duchenne muscular dystrophy at AFM Yolaine de Kepper centre between 1981 and 2011. Annals of physical and rehabilitation medicine. 2013; 56(6):443–54. https://doi.org/10.1016/j.aphysci.2013.06.002 PMID: 23876223

59. Ishikawa Y, Miura T, Ishikawa Y, Aoyagi T, Ogata H, Hamada S, et al. Duchenne muscular dystrophy: survival by cardio-respiratory interventions. Neuromuscular Disorders. 2011; 21(1):47–51. https://doi. org/10.1016/j.nmd.2010.08.006 PMID: 21144751

60. Adorision R, D’Amario D, Cantarutti N, Cicenia M, D’Amico A, Baban A, et al. P3446Left-ventricular assist device as a destination therapy in Duchenne cardiomypathy: are we ready to change the natural history? European Heart Journal. 2019; 40(Supplement_1).
61. Davidson ZE, Kornberg AJ, Ryan MM, Sinclair K, Cairns A, Walker KZ, et al. G.P.7 7 Deletions in the dystrophin gene predict loss of ambulation before 10 years of age in boys with Duchenne muscular dystrophy. Neuromuscular Disorders. 2012; 22(9):835.

62. Bonifati DM, Witchel SF, Ermani M, Hoffman EP, Angelini C, Pegoraro E. The glucocorticoid receptor N363S polymorphism and steroid response in Duchenne dystrophy. Journal of neurology, neurosurgery, and psychiatry. 2006; 77(10):1177–9. https://doi.org/10.1136/jnnp.2005.078345 PMID: 16980656

63. Bello L, Gordish-Dressman H, Morgenroth L, Henricson E, Duong T, Hoffman E, et al. Prednisone/prednisolone and deflazacort differ in long term outcomes on ambulation and side effects in the CINRG Duchenne Natural History Study (S50.001). Neurology. 2015; 84(Suppl 14):S50001.

64. Bello L, Gordish-Dressman H, Morgenroth LP, Henricson EK, Duong T, Hoffman EP, et al. Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study. Neurology. 2015; 85(12):1048–55. https://doi.org/10.1212/WNL.00000000000001950 PMID: 26311750

65. Bello L, Kesari A, Gordish-Dressman H, Cnaan A, Morgenroth LP, Punetha J, et al. Genetic modifiers of ambulation in the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Muscular Dystrophy (DMD) cohort is synergistically influenced by glucocorticoid corticosteroid treatment and candidate genetic polymorphisms. Journal of Neuromuscular Diseases 13th International congress on Neuromuscular Diseases. 2014; 1(Suppl 1):S124.

66. Bello L, Morgenroth L, Gordish-Dressman H, Hoffman E, McDonald C, Cirak S. DMD genotypes and loss of ambulation in the CINRG Duchenne natural history study. Neuromuscular Disorders. 2016; 26:S119. https://doi.org/10.1212/WNL.00000000000002891 PMID: 27343068

67. Goemans N, Signorovitch J, Sajeev G, Fillbrunn M, Wong H, Ward S, et al. P.202 A composite prognostic score for time to loss of walking ability in Duchenne muscular dystrophy (DMD). Neuromuscular Disorders. 2015; 29(Suppl 1):S108.

68. Goemans N, Signorovitch J, Sajeev G, Fillbrunn M, Wong H, Ward SJ, et al. PRO126 A composite prognostic score for time to loss of walking ability in Duchenne muscular dystrophy (DMD). Value in Health. 2019; 22(Suppl 3):S864.

69. van den Bergen JC, van Essen AJ, Pangalila R, de Groot IJ, Wijkstra PJ, et al. Forty-Five Years of Duchenne Muscular Dystrophy in The Netherlands. J Neuromuscul Dis. 2014; 1(1):99–109. PMID: 27858664

70. van den Bergen JC, van Essen AJ, Niks EH, Aartsma-Rus A, Verschuren JJGM. Prolonged Ambulation in Duchenne Patients with a Mutation Amenable to Exon 44 Skipping. J Neuromuscul Dis. 2014; 1:91–4. PMID: 27858662

71. Wang RT, Silverstein Fadlon CA, Ulm JW, Jankovic I, Eskin A, Lu A, et al. Online self-report data for Duchenne muscular dystrophy confirms natural history and can be used to assess for therapeutic benefits. PLoS Curr. 2014;6. https://doi.org/10.1371/currents.md.e1e8f2be7c949f9fe81ec6fca1ce6a PMID: 25635234

72. Ricotti V, Manzur A, Scott E, Muntoni F. Benefits and adverse effects of glucocorticoids in males with Duchenne muscular dystrophy: A UK perspective. Developmental Medicine & Child Neurology. 2012; 54(Suppl 1):14–5.

73. Ricotti V, Manzur A, Scott E, Muntoni F. 2FC2.6 Benefits and adverse effects of glucocorticoids in boys with Duchenne Muscular Dystrophy: A UK perspective. European Journal of Paediatric Neurology. 2011; 15(Suppl 1):S21.

74. DeSilva S, Drachman DB, Mellitte D, Kunc RW. Prednisone treatment in Duchenne muscular dystrophy. Long-term benefit. Arch Neurol. 1987; 44(8):818–22. https://doi.org/10.1001/archneur.1987.00520000202012 PMID: 3632394

75. Yilmaz O, Karaduman A, Topaloglu H. Prednisolone therapy in Duchenne muscular dystrophy prolongs ambulation and prevents scoliosis. Eur J Neurol. 2004; 11(8):541–4. https://doi.org/10.1111/j.1468-1331.2004.00866.x PMID: 15272899
80. Yilmaz O, Karaduman A, Aras O, Basoglu B, Topaloglu H. Prednisolone therapy in Duchenne muscular dystrophy prolongs ambulation and prevents scoliosis. Neuromuscul Disorders. 2004; 14(8–9):581. https://doi.org/10.1111/j.1468-1331.2004.00866.x PMID: 15272899

81. Tunca O, Kabakus O, Herguner A, Karaduman A, T H.. Alternate day prednisone therapy in Duchenne muscular dystrophy. 2001; 11:630.

82. Biggar WD, Gingras M, Fehlings DL, Harris VA, Steele CA. Deflazacort treatment of Duchenne muscular dystrophy. J Pediatr. 2001; 138(1):45–50. https://doi.org/10.1067/mpd.2001.109601 PMID: 11148511

83. Ciafaloni E, McDermott M, Kumar A, Liu K, Pandya S, Westfield C, et al. Age at First Symptoms/Signs and Loss of Ambulation in Duchenne-Becker Muscular Dystrophy: Data from the MD STARNet (IN1-2.002). Neurology. 2013; 80(Suppl 7):IN1-2.002.

84. Ciafaloni E, Kumar A, Liu K, Pandya S, Westfield C, Fox DJ, et al. Age at onset of first signs or symptoms predicts age at loss of ambulation in Duchenne and Becker Muscular Dystrophy: Data from the MD STARNet. J Pediatr Rehabil Med. 2016; 9(1):5–11. https://doi.org/10.3233/PRM-160361 PMID: 26966795

85. Bello L, Flanigan KM, Weiss RB, Dunn DM, Swoboda KJ, Gappmaier E, et al. Association study of exon variants in the NF-κB and TGFβ pathways identifies CD40 as a modifier of Duchenne muscular dystrophy. The American Journal of Human Genetics. 2016; 99(5):1163–71. https://doi.org/10.1016/j.ajhg.2016.08.023 PMID: 27745838

86. Haber G, Conway KM, Paramsothy P, Roy A, Rogers H, Ling X, et al. Association of genetic mutations and loss of ambulation in childhood-onset dystrophinopathy. Muscle & Nerve. 2021; 63(2):181–91. https://doi.org/10.1002/mus.27113 PMID: 33150975

87. Mercuri E, Muntoni F, Osorio AN, Tulinius M, Buccella F, Morgenroth LP, et al. Safety and effectiveness of ataluren: comparison of results from the STRIDE Registry and CINRG DMD Natural History Study. Journal of comparative effectiveness research. 2020; 9(5):341–60. https://doi.org/10.2217/cer-2019-0171 PMID: 31997646

88. Wang RT, Barthelemy F, Martin AS, Douine ED, Eskin A, Lucas A, 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(9):1193–202. https://doi.org/10.1002/humu.23561 PMID: 29907980

89. Forst J, Forst R. Lower limb surgery in Duchenne muscular dystrophy. Neuromuscul Disord. 1999; 9 (3):176–81. https://doi.org/10.1016/s0960-8966(98)00113-8 PMID: 10382913

90. Forst R, Forst J. Importance of lower limb surgery in Duchenne muscular dystrophy. Arch Orthop Trauma Surg. 1995; 114(2):106–11. https://doi.org/10.1007/BF00422837 PMID: 7734231

91. Servais L, Montus M, Guiner CL, Ben Yaou R, Annousamy M, Moraux A, et al. Non-ambulant Duchenne patients theoretically treatable by exon 53 skipping have severe phenotype. J Neuromuscular Dis. 2015; 2(3):269–79. https://doi.org/10.3233/JND-150100 PMID: 25907980

92. Escolar DM, Hache LP, Clemons PR, Cnaan A, McDonald CM, Viswanathan V, et al. Randomized, blinded trial of weekend vs daily prednisone in Duchenne muscular dystrophy: the STRIDE Registry. Neurology. 2011; 77 (5):444–52. https://doi.org/10.1212/WNL.0b013e318227b164 PMID: 21753160

93. Tachas G, Desem N, Button P, Coratti G, Pane M, Mercuri E, et al. DMD-TH ERAPY: P. 284 ATL1102 treatment improves PUL2.0 in non-ambulant boys with Duchenne muscular dystrophy compared to a natural history control. Neuromuscular Disorders. 2020; 30:S129–S30.

94. Daftary AS, Crisanti M, Kaira M, Wong B, Amin R. Effect of long-term steroids on cough efficiency and respiratory muscle strength in patients with Duchenne muscular dystrophy. Pediatrics. 2007; 119(2):e320–4. https://doi.org/10.1542/peds.2006-1400 PMID: 17272595

95. Abresch RT, McDonald CM, Henricson EK, Gustavo N, Hu F, Duong T, et al. P.11.11 Pulmonary function characteristics of boys with Duchenne Muscular Dystrophy by age groups, ambulatory status and steroid use. Neuromuscular Disorders. 2013; 23(9):801–2.

96. Henricson EK, Abresch RT, Cnaan A, Hu F, Duong T, Arrieta A, et al. The cooperative international neuromuscular research group Duchenne natural history study: glucocorticoid treatment preserves clinically meaningful functional milestones and reduces rate of disease progression as measured by manual muscle testing and other commonly used clinical trial outcome measures. Muscle Nerve. 2013; 48(1):55–67. https://doi.org/10.1002/mus.23808 PMID: 23649481

97. McDonald CM, Gordish-Dressman H, Henricson EK, Duong T, Joyce NC, Jhawar S, et al. Longitudinal pulmonary function testing outcome measures in Duchenne muscular dystrophy: Long-term natural history with and without glucocorticoids. Neuromuscul Disord. 2018; 28(11):897–909. https://doi.org/10.1016/j.nmd.2018.07.004 PMID: 30336970
98. Henricson E, McDonald C, Gordish-Dressman H, Abresch T, Cnaan A. Steroid use delays but does not prevent loss of pulmonary function in patients with Duchene muscular dystrophy (DMD). Developmental Medicine & Child Neurology. 2017; 59(Suppl 4):30.

99. McDonald C, Gordish-Dressman H, Henricson E, Abresch T, Cnaan A. Steroid Use Delays but Does Not Prevent Loss of Pulmonary Function in Patients with Duchenne Muscular Dystrophy (DMD). C105 Disorders of respiratory physiology and sleep in children. 2017; 195:A6883.

100. Pradhan S, Ghosh D, Srivastava NK, Kumar A, Mittal B, Pandey CM, et al. Prednisolone in Duchenne muscular dystrophy with imminent loss of ambulation. J Neurol. 2006; 253(10):1309–16. https://doi.org/10.1007/s00415-006-0212-1 PMID: 16786214

101. Fenichel GM, Mendell JR, Moxley RT, III, Griggs RC, Brooke MH, Miller JP, et al. A Comparison of Daily and Alternate-Day Prednisone Therapy in the Treatment of Duchenne Muscular Dystrophy. Archives of Neurology. 1991; 48(6):575–9. https://doi.org/10.1001/archneur.1991.00530180027012 PMID: 2039377

102. Dubow J, Cunniff T, Wanaski S, Meyer J. Effect of Deflazacort and Prednisone Versus Placebo on Pulmonary Function in Boys with Duchenne Muscular Dystrophy Who Have Lost Ambulation (I4.009). Neurology. 2016; 86(Suppl 16):I4.009.

103. Comi GP, Bertini E, Magri F, Luo X, McIntosh J, Ong T, et al. Respiratory function in ataluren-treated, nonambulatory patients with nonsense mutation Duchenne (nmDMD) muscular dystrophy from a long-term extension trial versus untreated patients from a natural history study. Acta myologica: myopathies and cardiomyopathies. 2017; 36(2):69.

104. McDonald CM, Tulinius M, Selby K, Kroger H, Luo X, McIntosh J, et al. Lung function in ataluren-treated, non-ambulatory patients with nonsense mutation Duchenne muscular dystrophy from a long-term extension trial versus untreated patients from a natural history study. Sinapse. 2016; 16(2):77.

105. Kelley EF, Cross TJ, Snyder EM, McDonald CM, Hoffman EP, Bello L, et al. Influence of β2 adrenergic receptor genotype on risk of nocturnal ventilation in patients with Duchenne muscular dystrophy. Respiratory Research. 2019; 20(1):221. https://doi.org/10.1186/s12931-019-1200-1 PMID: 31619245

106. Angliss ME, Scip KD, Gauld L. Early NIV is associated with accelerated lung function decline in Duchenne muscular dystrophy treated with glucocorticosteroids. BMJ open respiratory research. 2020; 7(1):e000517. https://doi.org/10.1136/bmjresp-2019-000517 PMID: 32079608

107. Bello L, D’Angelo G, Villa M, Fusto A, Vianello S, Merlo B, et al. Genetic modifiers of respiratory function in Duchenne muscular dystrophy. Annals of clinical and translational neurology. 2020; 7(5):786–98. https://doi.org/10.1002/acn3.51046 PMID: 32343055

108. Ifi J, Tuttle E, Gerrits C, Gupta D, Zhong Y. DMD–THERAPY: P. 291 Real-world evidence of eteplirsen treatment effects on Duchenne muscular dystrophy related health outcomes using claims data in the United States. Neuromuscular Disorders. 2020; 30(S1):S131–S2.

109. McDonald C, Francesco M, Rance M, McIntosh J, Jiang J, Kristensen A, et al. Ataluren delays loss of ambulation and decline in pulmonary function in patients with nonsense mutation Duchenne muscular dystrophy. Neuromuscular Disorders Presented at the 25TH International Congress of the World Muscle Society (WMS), 2020 (Virtual Congress). 2020; 30(S1):S132.

110. McDonald CM F.; Rance M.; Jiang J.; Kristensen A.; Penematsa V.; Bibbiani F.; et al. Ataluren delays loss of ambulation and decline in pulmonary function in patients with nonsense mutation Duchenne muscular dystrophy. Muscle and Nerve. 2020; 62 (SUPPL 1):S53–S4.

111. Buyse GM, Goemans N, Van den Hauwe M, Thijs D, de Groot IJ, Schara U, et al. Eteplirsen as a novel, therapeutic approach for Duchenne muscular dystrophy: results from a 12 month, double-blind, randomized placebo-controlled trial. Neuromuscular Disorders. 2011; 21(6):396–405. https://doi.org/10.1016/j.nmd.2011.02.016 PMID: 21435876

112. Karafillidis J, Mayer H, Leinonen M, Buyse G. Comparison of Longitudinal Changes in Expiratory Respiratory Function Endpoints and Inspiratory Flow Reserve (IFR) in Patients with Duchenne Muscular Dystrophy (DMD). A47 NEUROMUSCULAR DISEASE AND RESPIRATION. American Thoracic Society International Conference Abstracts: American Thoracic Society; 2018. p. A1765-A.

113. Khan N, Eliopoulos H, Han L, Kinane TB, Lowes LP, Mendell JR, et al. Eteplirsen treatment attenuates respiratory decline in ambulatory and non-ambulatory patients with Duchenne muscular dystrophy. J Neuromuscul Dis. 2019; 6(2):213–25. https://doi.org/10.3233/JND-180351 PMID: 30858119

114. Khan N, Han L, Kinane B, Gordish-Dressman H, Lowes L, McDonald C. Eteplirsen-treatment attenuates respiratory decline in ambulatory and non-ambulatory patients with duchenne muscular dystrophy: Comparison with natural history cohorts. Neurology Conference: 71st Annual Meeting of the American Academy of Neurology, AAN. 2019; 92(15(S1)).

115. Khan N, Han L, Kinane B, Gordish-Dressman H, Lowes L, McDonald C. Respiratory Function Decline in Eteplirsen-treated Patients Diverges From Natural History Comparators Over Time. J Neuromuscul Dis. 6(S1):S28.
116. Mendell J, Lowes L, Alfano L, Saoud J, Duda P, Kaye E. GP 112: Pulmonary function is stable through week 120 in patients with Duchenne muscular dystrophy (DMD) treated with exon-skipping drug eteplirsen in phase 2b study. Neuromuscular Disorders. 2014; 24(9):828–9.

117. Mendell J, Lowes L, Alfano L, Saoud J, Kaye E. Pulmonary function and safety results at week 120 of exon-skipping drug eteplirsen from the phase 2b study in patients with Duchenne muscular dystrophy (DMD). J Neuromuscul Dis. 2014; 1:S136.

118. Mendell J, Lowes L, Duda P, Saoud J, Kaye E. Pulmonary function is stable in patients with Duchenne muscular dystrophy (DMD) treated with exon-skipping drug eteplirsen in phase 2b study. Annals of neurology. 2014; 76:S237.

119. Mendell J, Rodino-Klapac L, Sahenk Z, Roush K, Bird L, Lowes L, et al. Overview of Eteplirsen Clinical Outcomes in Duchenne Muscular Dystrophy (DMD). Annals of Neurology. 2014; 76:S63.

120. Mendell JR, Rodino-Klapac L, Sahenk Z, Roush K, Bird L, Lowes L, et al. Eteplirsen in Duchenne Muscular Dystrophy (DMD): 144 week update on six-minute walk test (6MWT) and safety. Annals of Neurology. 2014; 76:S237.

121. Mendell JR, Rodino-Klapac L, Sahenk Z, Roush K, Bird L, Lowes L, et al. C-2. Eteplirsen, a Phosphorodiamidate Morpholino Oligomer (PMO) for the Treatment of Duchenne Muscular Dystrophy (DMD): 168 Week Update on Six-Minute Walk Test (6MWT), Pulmonary Function Testing (PFT), and Safety. Molecular Therapy. 2015; 23:S16.

122. Kaye E, Mendell J, Rodino-Klapac L, Sahenk Z, Roush K, Bird L, et al. Results at 96 Weeks of a Phase IIb Extension Study of the Exon-Skipping Drug Eteplirsen in Patients with Duchenne Muscular Dystrophy (DMD)(S6.002). Neurology. 2014; 82(10(S1)).

123. Kaye E, Mendell J, Rodino-Klapac L, Sahenk Z, Lowes L, Alfano L, et al. Eteplirsen, a Phosphorodiamidate morpholino oligomer (PMO) for the treatment of Duchenne muscular dystrophy (DMD): Clinical update. Neuromuscular Disorders. 2015; 25:S263.

124. Kaye E, Mendell J, Rodino-Klapac L, Sahenk Z, Lowes L, Alfano L, et al. Eteplirsen, a phosphorodiamidate morpholino oligomer (PMO) for the treatment of Duchenne muscular dystrophy (DMD). Annals of Neurology. 2015; 19:S105.

125. Kaye E, Mendell J, Rodino-Klapac L, Sahenk Z, Roush K, Lowes L, et al. Eteplirsen, a phosphorodiamidate morpholino oligomer (PMO) for Duchenne muscular dystrophy (DMD): 3.2 year update on six-minute walk test (6MWT), pulmonary function testing (PFT), and safety. European journal of paediatric neurology. 2015; 19:S69.

126. Mendell JR, Khan N, Sha N, Eliopoulos H, McDonald CM, Goemans N, et al. Comparison of long-term ambulatory function in patients with Duchenne muscular dystrophy treated with eteplirsen and matched natural history controls. J Neuromuscul Dis. 2021; 8(4):469–79. https://doi.org/10.3233/JND-200548 PMID: 33523015

127. Mendell J, Goemans N, Rodino-Klapac L, Sahenk Z, Lowes L, Alfano L, et al. Eteplirsen, a phosphorodiamidate morpholino oligomer (PMO) for Duchenne muscular dystrophy (DMD): Longitudinal comparison to external controls on six-minute walk test (6MWT) and loss of ambulation (LOA). Annals of Neurology. 2016; 80(S20):S415.

128. Mendell J, Goemans N, Rodino-Klapac L, Lowes L, Alfano L, Berry K, et al. Eteplirsen, a phosphorodiamidate morpholino oligomer (PMO) for Duchenne muscular dystrophy (DMD): Longitudinal Comparison to External Controls on Six-Minute Walk Test (6MWT) and Loss of Ambulation (LOA)(S42.004). Neurology. 2017; 88(16S1).

129. Mendell J, Goemans N, Rodino-Klapac L, Sahenk Z, Lowes L, Alfano L, et al. Eteplirsen, a phosphorodiamidate morpholino oligomer (PMO) for Duchenne Muscular Dystrophy (DMD): Clinical Update and Longitudinal Comparison to External Controls on Six-Minute Walk Test (6MWT)(S28.001). Neurology. 2016; 86(16S1).

130. Mendell JR, Goemans N, Lowes LP, Alfano LN, Berry K, Shao J, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. Annals of neurology. 2016; 79(2):257–71. https://doi.org/10.1002/ana.24555 PMID: 26573217

131. McDonald CM, Sajeev G, Yao Z, McDonnell E, Elfing G, Souza M, et al. Deflazacort vs prednisone treatment for Duchenne muscular dystrophy: A meta-analysis of disease progression rates in recent multicenter clinical trials. Muscle Nerve. 2020; 61(1):26–35. https://doi.org/10.1002/mus.26736 PMID: 31599456

132. Lawrence C, Warnock A, McDonald C, Mayer O, Meier T, Leinonen M, et al. Effect of idebenone on bronchopulmonary adverse events and hospitalizations in patients with Duchenne muscular dystrophy (DMD). Neuromuscular Disorders. 2018; 28(S1):S16–S7.

133. Rummey C, Meier T, Leinonen M, Hasham S, Voit T, Mayer O. Comparison of home-based versus hospital-based spirometry measurements in Duchenne muscular dystrophy. J Neuromuscul Dis. 2018; 5:S299-S300.
134. Kanazawa H, Takashima H, Fujishita S, Shibuya N, Tamura T. Correlation between clinical features and deletions of the gene for dystrophin in Duchenne muscular dystrophy. Jpn J Med. 1991; 30(1):1–4. https://doi.org/10.2169/internalmedicine1962.30.1 PMID: 1865668

135. Hussein MR, Hamed SA, Mostafa MG, Abu-Dief EE, Kamel NF, Kandil MR. The effects of glucocorticoid therapy on the inflammatory and dendritic cells in muscular dystrophies. Int J Exp Pathol. 2006; 87(6):451–61. https://doi.org/10.1111/j.1365-2613.2006.00470.x PMID: 17222213

136. Angelini C, Pegoraro E, Turella E, Intino MT, Pini A, Costa C. Deflazacort in Duchenne dystrophy: study of long-term effect. Muscle Nerve. 1994; 17(4):386–91. https://doi.org/10.1002/mus.880170405 PMID: 8170484

137. Fenichel GM, Florence JM, Pestronk A, Mendell JR, Moxley RT, Griggs RC, et al. Long-term benefit from prednisone therapy in Duchenne muscular dystrophy. Neurology. 1991; 41(12):1874–7. https://doi.org/10.1212/wnl.41.12.1874 PMID: 1745340

138. Hu J, Ye Y, Kong M, Hong S, Cheng L, Wang Q, et al. Daily prednisone treatment in Duchenne muscular dystrophy in southwest China. Muscle Nerve. 2015; 52(6):1001–7. https://doi.org/10.1002/mus.24665 PMID: 25809413

139. Rifai Z, Welle S, Moxley R, Lorenson M, Griggs RC. Effect of prednisone on protein metabolism in Duchenne dystrophy. Am J Physiol. 1995; 268(1 Pt 1):E67–74. https://doi.org/10.1152/ajpendo.1995. 268.1.E67 PMID: 7840185

140. Bäckman E, Henriksson KG. Low-dose prednisolone treatment in Duchenne and Becker muscular dystrophy. Neuromuscul Disord. 1995; 5(3):233–41. https://doi.org/10.1016/0960-8966(94)00048-e PMID: 7633189

141. Connolly AM, Schierbecue J, Renna R, Florence J. High dose weekly oral prednisone improves strength in boys with Duchenne muscular dystrophy. Neuromuscul Disord. 2002; 12(10):917–25. https://doi.org/10.1016/s0960-8966(02)00180-3 PMID: 12467746

142. Griggs RC, Moxley RT, Mendell JR, Fenichel GM, Brooke MH, Pestronk A, et al. Duchenne dystrophy: a randomized, controlled trial defining the time course and dose response. Clinical Investigation of Duchenne Dystrophy Group. Arch Neurol. 1991; 48(4):383–8. https://doi.org/10.1001/archneur.1991.00530160047012 PMID: 2012511

143. Griggs RC, Moxley RT, Mendell JR, Pestronk A, Brooke MH, Pestronk A, et al. Prednisone in Duchenne dystrophy. A randomized, controlled trial defining the time course and dose response. Clinical Investigation of Duchenne Dystrophy Group. Arch Neurol. 1991; 48(4):383–8. https://doi.org/10.1001/archneur.1991.00530160047012 PMID: 2012511

144. Ristivel P, Vettori M, Brugières P, Moxley R, Lorenson M, Griggs RC. Early prednisone treatment in Duchenne muscular dystrophy. Muscle Nerve. 2003; 27(2):222–7. https://doi.org/10.1002/mus.10319 PMID: 12548530

145. Peggore E, Hoffman EP, Piva L, Gavassini BF, Cagnin S, Ermani M, et al. SPP1 genotype is a determinant of disease severity in Duchenne muscular dystrophy. Neurology. 2011; 76(3):219–26. https://doi.org/10.1212/wnl.0b013e318e68207 PMID: 2187899

146. Griggs RC, Moxley RT, Mendell JR, Fenichel GM, Brooke MH, Pestronk A, et al. Deflazacort in Duchenne muscular dystrophy. A randomized, controlled trial defining the time course and dose response. Clinical Investigation of Duchenne Dystrophy Group. Arch Neurol. 1991; 48(4):383–8. https://doi.org/10.1001/archneur.1991.00530160047012 PMID: 2012511

147. Merlino L, Cicognani A, Malaspina E, Gennari M, Gnudi S, Talim B, et al. Early prednisone treatment in Duchenne muscular dystrophy. Muscle Nerve. 2003; 27(2):222–7. https://doi.org/10.1002/mus.10319 PMID: 12548530

148. Pegoraro E, Hoffman EP, Piva L, Gavassini BF, Cagnin S, Ermani M, et al. SPP1 genotype is a determinant of disease severity in Duchenne muscular dystrophy. Neurology. 2011; 76(3):219–26. https://doi.org/10.1212/wnl.0b013e318e68207 PMID: 2187899

149. Pegoraro E, Hoffman EP, Piva L, Gavassini BF, Cagnin S, Ermani M, et al. SPP1 genotype is a determinant of disease severity in Duchenne muscular dystrophy. Neurology. 2011; 76(3):219–26. https://doi.org/10.1212/wnl.0b013e318e68207 PMID: 2187899

150. Campbell C, Barohn RJ, Bertini E, Chabrol B, Comi GP, Darras BT, et al. Meta-analyses of ataluren randomized controlled trials in nonsense mutation Duchenne muscular dystrophy. Journal of comparative effectiveness research. 2020; 9(14):973–84. https://doi.org/10.2217/cer-2020-0095 PMID: 32851872

151. Chesshyre M, Ridout D, Abbott L, Ayyar Gupta V, Maresh K, Manzur A, et al. The role of dystrophin brain isoforms on early motor development and motor outcomes in young children with Duchenne muscular dystrophy. Developmental Medicine and Child Neurology. 2020; 62(S1):P110.

152. Clemens PR, Rao VK, Connolly AM, Harper AD, Mah JK, Smith EC, et al. Safety, tolerability, and efficacy of viltololase in boys with Duchenne muscular dystrophy amenable to exon 53 skipping: a phase 2 randomized clinical trial. JAMA neurology. 2020; 77(8):962–91. https://doi.org/10.1001/jamaneurol.2020.1264 PMID: 32453377
153. Finkel RS, Finanger E, Vandenborne K, Sweeney HL, Tennekoon G, Shieh PB, et al. Disease-modifying effects of edasalonexent, an NF-κB inhibitor, in young boys with Duchenne muscular dystrophy: Results of the MoveDMD phase 2 and open label extension trial. Neuromuscular Disorders. 2021; 31(5):85-96. https://doi.org/10.1016/j.nmd.2021.02.001 PMID: 33678513

154. Finkel R, Vandenborne KH, Sweeney HL, Finanger E, Tennekoon G, Shieh P, et al. MoveDMD®: Positive Effects of Edasalonexent, an NF-κB Inhibitor, in 4 to 7-Year Old Patients with Duchenne Muscular Dystrophy in Phase 2 Study with an Open-Label Extension (S29. 006). Neurology. 2018; 90(15(S1)).

155. Finkel R, Vandenborne K, Sweeney HL, Finanger E, Tennekoon G, Shieh P, et al. Edasalonexent, an NF-κB Inhibitor, Slows Longer-Term Disease Progression on Multiple Functional and MRI Assessments Compared to Control Period in 4 to 7-Year Old Patients with Duchenne Muscular Dystrophy (S51. 006). Neurology. 2019; 92(15(S1)).

156. Finkel R, Vandenborne K, Sweeney H, Finanger E, Tennekoon G, Shieh P, et al. O. 42Treatment of young boys with Duchenne muscular dystrophy with the NF-κB inhibitor edasalonexent showed a slowing of disease progression as assessed by MRI and functional measures. Neuromuscular Disorders. 2019; 29:S208.

157. Sweeney H, Vandenborne K, Finkel R, Finanger E, Tennekoon G, Willcocks R, et al. MoveDMD, a Phase 2 with Open-Label Extension Study of Treatment of Young Boys with Duchenne Muscular Dystrophy with the NF-κB Inhibitor Edasalonexent Showed a Slowing of Disease Progression as Assessed by MRI and Functional Measures. J Neuromuscul Dis. 2019; 6(S2):S33–S4.

158. Parreira SL, Resende MB, Zanoteli E, Carvalho MS, Marie SK, Reed UC. Comparison of motor strength and function in patients with Duchenne muscular dystrophy with or without steroid therapy. Arq Neuropsiquiatr. 2010; 68(5):683–8. https://doi.org/10.1590/s0004-282x2010000500002 PMID: 21049175

159. Willcocks RJ, Forbes SC, Finanger EL, Russman BS, Lott DJ, Senesac CR, et al. P.13.5 Magnetic resonance imaging and spectroscopy detect changes with age, corticosteroid treatment, and functional progression in DMD. Neuromuscular Disorders. 2013; 23(9):810.

160. Goemans N, McDonald C, Signorovitch J, Sajeev G, Filibrunn M, Wong H, et al. DMD & BMD—CLINICAL: P. 55 Prognostic factors for loss of ability to rise from supine in Duchenne muscular dystrophy (DMD). Neuromuscular Disorders. 2020; 30:S63–S4.

161. Goemans N, Wong B, Van den Hauwe M, Signorovitch J, Sajeev G, Cox D, et al. Prognostic factors for changes in the timed 4-stair climb in patients with Duchenne muscular dystrophy, and implications for measuring drug efficacy: A multi-institutional collaboration. PloS one. 2020; 15(6):e0232870. https://doi.org/10.1371/journal.pone.0232870 PMID: 32556695

162. Wilton S, editor. An update on DMD exon skipping trials: Making more sense with splice switching antisense oligonucleotides. Clinical and Experimental Pharmacology and Physiology, 2013; Hangzhou, China: Cell Therapy and Stem Cell Biology.

163. Signorovitch JE, Sajeev G, McDonnell E, Yao Z. Deflazacort or Prednisone Treatment for Duchenne Muscular Dystrophy: A Meta-Analysis of Disease Progression Rates in Recent Multicenter Clinical Trials. Value in Health. 2017; 20(9):A718.

164. Signorovitch J, Schilling T, Sajeev G, Yao Z, McDonnell E, Elfring G, et al. Deflazacort or Prednisone Treatment for Duchenne Muscular Dystrophy: A Meta-Analysis of Disease Progression Rates in Recent Multicenter Clinical Trials (P1.6–066). Neurology. 2019; 92(Suppl 15):P1.6–066.

165. Signorovitch J, Sajeev G, Yao Z, McDonnell E, Elfring G, Trifillis P, et al. Deflazacort or prednisone treatment for duchenne muscular dystrophy: A meta-analysis of disease progression rates in two multicenter clinical trials. Muscle and Nerve. 2019; 59(S2):S53–S4.

166. Signorovitch J, Sajeev G, Yao Z, McDonnell E, Elfring G, Trifilis P, et al. Deflazacort or prednisone treatment for duchenne muscular dystrophy: A meta-analysis of disease progression rates in two multicenter clinical trials. Annals of Neurology. 2019; 86 (Supplement 23):S128–S9. https://doi.org/10.1002/ana.25736 PMID: 31599456

167. Gupta VA, Abbott L, Cheshhyre M, Main M, Baranello G, Scoto M, et al. DMD & BMD—CLINICAL: P.59 Functional progression in young DMD. Neuromuscular Disorders. 2020; 30 (Supplement 1):S65.

168. Goemans N, Tulinius M, Kroksmark A, Van Den Hauwe M, Lin Z, Wang SC, G. Longitudinal Effect of Drisapersen Versus Historical Controls on Ambulation in Duchenne Muscular Dystrophy. J Neuromuscul Dis. 2016; 3(S1):S137.

169. Goemans NM, Tulinius M, Van den Hauwe M, Kroksmark A-K, Buyse G, Wilson RJ, et al. Long-term efficacy, safety, and pharmacokinetics of drisapersen in Duchenne muscular dystrophy: results from an open-label extension study. PloS one. 2016; 11(9):e0161955. https://doi.org/10.1371/journal.pone.0161955 PMID: 27588424
170. Ricotti V, Ridout DA, Scott E, Quinlivan R, Robb SA, Manzur AY, et al. Long-term benefits and adverse effects of intermittent versus daily glucocorticoids in boys with Duchenne muscular dystrophy. J Neurol Neurosurg Psychiatry. 2013; 84(6):698–705. https://doi.org/10.1136/jnnp-2012-303902 PMID: 23250964

171. Schreiber A, Brochard S, Rippet P, Fontaine-Carbonnel S, Payan C, Poirot I, et al. Corticosteroids in Duchenne muscular dystrophy: impact on the motor function measure sensitivity to change and implications for clinical trials. Developmental Medicine & Child Neurology. 2018; 60(2):185–91. https://doi.org/10.1111/dmcn.13590 PMID: 28990163

172. Schreiber-Bontemps A, Brochard S, Fontaine-Carbonnel S, Chabrier S, Gautheron V, Peudenier S, et al. Promoting the use of Motor Function Measure (MFM) as outcome measure in patients with Duchenne Muscular Dystrophy (DMD) treated by corticosteroids. Annals of Physical and Rehabilitation Medicine. 2015; 58(Suppl 1):e139–e40.

173. Schreiber A, Brochard S, Rippert P, Fontaine-Carbonnel S, Payan C, et al. The natural history of Duchenne muscular dystrophy with corticosteroids using the Motor Function Measure. Developmental Medicine & Child Neurology. 2016; 58(S6):22–6.

174. Alfano L, Miller N, Iammarino M, Moore-Clingenpeel M, Waldrop M, Flanigan K, et al. The 100 meter timed test: responsiveness to change, predicting loss of ambulation, and data-driven phenotypes. Neuromuscular Disorders. 2019; 29(Suppl 1):S105.

175. Goemans N, vanden Hauwe M, Signorovitch J, Swallow E, Song J, Collaborative Trajectory Analysis P. Individualized Prediction of Changes in 6-Minute Walk Distance for Patients with Duchenne Muscular Dystrophy. PLOS ONE. 2016; 11(10):e0164684. https://doi.org/10.1371/journal.pone.0164684 PMID: 27737016

176. Goemans N, Vanden Hauwe M, Signorovitch J, Sajeev G, Yao Z, Jenkins M, et al. Development of a prognostic model for 1-year change in timed 4 stair-climb in duchenne patients. J Neuromuscul Dis. 2018; 5(Suppl 1):S196.

177. Mazzone ES, Pane M, Sivo S, Palermo C, Sormani MP, Messina S, et al. Long-term natural history data in ambulant boys with Duchenne muscular dystrophy: 36month changes. Neuromuscular Disorders. 2014; 24(9):861.

178. Shieh P O'Mara E, Elfring G, Trifillis P, Santos C, Parsons J, et al. Meta-analyses of deflazacort vs prednisone/prednisolone in patients with nonsense mutation dystrophinopathy. Muscle & Nerve. 2014; 50(4):477–87. https://doi.org/10.1002/mus.24332 PMID: 25042182

179. Mah JK, Selby K, Campbell C, Reha A, Elfring G, Morsy M, et al. Safety and Efficacy of low-dose ataluren in boys with nonsense mutation dystrophinopathy. Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques. 2011; 38(Suppl 1):S21.

180. McDonald CM, Hendricson EK, Abresch RT, Elfring GL, Barth J, Peltz SW, et al. P.11.19 Phase 2b, dose-ranging study of ataluren (PTC124®) in nonsense mutation Duchenne muscular dystrophy—results of a post hoc analysis of change in %-predicted 6-min walk distance. Neuromuscular Disorders. 2013; 23(9):804.

181. McDonald CM, Wei L-J, Elfring G, Spiegel R. T.P.5: Timed function tests and other physical function outcomes in ataluren-treated patients with nonsense mutation Duchenne Muscular Dystrophy (nmDMD). Neuromuscular Disorders. 2014; 24(9):861.

182. McDonald CM, Wei L, Elfring G, Peltz SW, Spiegel R. T.P.5: Timed function tests and other physical function outcomes in ataluren-treated patients with nonsense mutation Duchenne Muscular Dystrophy (nmDMD). 2014; 76(Suppl 18):S236–S7.

183. McDonald CM, Campbell C, Torricelli RE, Finkel RS, Flanigan KM, Goemans N, 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(10101):1489–98. https://doi.org/10.1016/S0140-6736(17)31611-2 PMID: 28728956

184. McDonald C, Wei L, Elfring G, Schilling T, Trifillis P, McIntosh J, et al. Preservation of Function over time as Measured by North Star Ambulatory Assessment in Ambulatory Boys with Nonsense Mutation Muscular Dystrophy Treated with Ataluren (SS1.004). Neurology. 2019; 92(Suppl 15):S51.004.

185. McDonald C, Wei L, Elfring G, Trifillis P, Able R, Souza M, et al. Preservation of function over time as measured by North Star ambulatory assessment in ambulatory boys with nonsense mutation muscular dystrophy treated with ataluren. Muscle and Nerve. 2019; 60 (SUPPL 1):S58.
188. Bushby K, Kirschner J, Luo X, Elfring G, Kroger H, Riebling P, et al. Results of North Star Ambulatory Assessments (NSAA) in the Phase 3 Ataluren Confirmatory Trial in Patients with Nonsense Mutation Duchenne Muscular Dystrophy (ACT DMD) (I15.008). Neurology. 2016; 86(16 Supplement):I15.008.

189. McDonald CM, Riebling P, Souza M, Elfring GL, McIntosh J, Ong T, et al. Use of ≥ 5-second threshold in baseline time to stand from supine to predict disease progression in Duchenne muscular dystrophy. European Journal of Paediatric Neurology. 2017; 21(Suppl 1):e237.

190. McDonald CM, Souza M, Elfring GL, McIntosh J, Werner C, Trifillis P, et al. Use of a ≥5-second threshold in baseline time to stand from supine to predict disease progression in Duchenne muscular dystrophy. Neuromuscular Disorders. 2018; 28(Suppl 1):S12.

191. McDonald CM, Souza M, Elfring GL, McIntosh J, Peltz SW, et al. Use of a ≥5-second threshold in baseline time to stand from supine to predict progression in DMD. J Neuromuscul Dis. 2018; 5(Suppl 1):S199.

192. Mercuri E, Buccella F, Desguerre I, Kirschner J, Muntoni F, Nascimiento Osorio A, et al. Timed-function test data in patients with duchenne muscular dystrophy from the strategic targeting of registries and international database of excellence (STRIDE) registry and the CINRG natural history study: A matched cohort analysis. Annals of Neurology. 2019; 86 (Supplement 23):S126–S7.

193. Muntoni F, Buccella F, Desguerre I, Kirschner J, Mercuri E, Nascimiento Osorio A, et al. Age at loss of ambulation in patients with duchenne muscular dystrophy from the stride registry and the CINRG natural history study: A matched cohort analysis. Annals of Neurology. 2019; 86 (Supplement 23):S127.

194. Brogna C, Coratti G, Pane M, Ricotti V, Messina S, D’Amico A, 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(6):e0218683. https://doi.org/10.1371/journal.pone.0218683 PMID: 31237898

195. Brogna C, Coratti G, Pane M, Ricotti V, Messina S, Bruno C, et al. P.148 Long-term natural history data in Duchenne muscular dystrophy ambulant patients with mutations amenable to skip exons 44, 45, 51 and 53. Neuromuscular Disorders. 2019; 29(Suppl 1):S91.

196. Komaki H, Maegaki Y, Matsumura T, Shiraishi KA, H.;, Nakamura A, Kinoshita S, et al. Early phase 2 trial of TAS-205 in patients with Duchenne muscular dystrophy. Annals of Clinical and Translational Neurology. 2020; 7(2):181–90. https://doi.org/10.1002/acn3.50976 PMID: 31957953

197. Hoffman EP, Schwartz BD, Mengle-Gaw LJ, Smith EC, Castro D, Mah JK, et al. Vamorolone trial in Duchenne muscular dystrophy shows dose-related improvement of muscle function. Neurology. 2019; 93(13):E1312–E23. https://doi.org/10.1212/WNL.0000000000008166 PMID: 31451516

198. Smith EC, Conklin LS, Hoffman EP, Clemens PR, Mah JK, Finkel RS, et al. Efficacy and safety of vamorolone in Duchenne muscular dystrophy: An 18-month interim analysis of a non-randomized open-label extension study. PLoS Med. 2020; 17(9):e1003222. https://doi.org/10.1371/journal.pmed.1003222 PMID: 32956407

199. Koeks Z, Bladen CL, Salgado D, Van Zwet E, Pogoryelova O, McMacken G, 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(4):293–306. https://doi.org/10.3233/JND-170280 PMID: 29125504

200. Voit T, Topaloglu H, Straub V, Muntoni F, Deconinck N, Campion G, 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(10):987–96. https://doi.org/10.1016/S1474-4422(14)70195-4 PMID: 25209738

201. McDonald C, Goemans N, Voit T, Wilson R, Wardell C, Campion G. Drisapersen: An overview of the EXON51 skipping antisense oligonucleotide clinical program to date in duchenne muscular dystrophy (DMD). Neurology Conference: 67th American Academy of Neurology Annual Meeting, AAN. 2015; 84(S14).

202. McDonald C, Mercuri E, Goemans N, Voit T, Wilson R, Wardell C, et al. Drisapersen: An overview of the clinical programme to date in Duchenne Muscular Dystrophy (DMD). Neuromuscular Disorders. 2014; 24(9–10):922.

203. Mayer OH, Leinonen M, Rummey C, Meier T, Buyse GM. Efficacy of Idebenone to Preserve Respiratory Function above Clinically Meaningful Thresholds for Forced Vital Capacity (FVC) in Patients with Duchenne Muscular Dystrophy. J Neuromuscul Dis. 2017; 4(3):189–98. https://doi.org/10.3233/JND-170245 PMID: 28869486