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BRIEF REPORT

Observing the Clinical Course of Duchenne Muscular Dystrophy in Medicaid Real-World Healthcare Data

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ABSTRACT

Introduction: Duchenne muscular dystrophy (DMD) is a rare, severe progressive neuromuscular disease. Health insurance claims allow characterization of population-level real-world outcomes, based on observed healthcare resource use. An analysis of data specific to those with Medicaid insurance is presently unavailable. The objective was to describe the real-world clinical course of DMD based on claims data from Medicaid-insured individuals in the USA.

Methods: Individuals with DMD were identified from the MarketScan Multi-State Medicaid datasets (2013–2018). Diagnosis and procedure codes from healthcare claims were used to characterize the occurrence of DMD-relevant clinical observations; categories were scoliosis, cardiovascular-related, respiratory and severe respiratory-related, and neurologic/neuropsychiatric. Age-restricted analyses were conducted to focus on the ages at which DMD-relevant clinical observations were more likely to be captured, and to better understand the impact of both age and follow-up time.

Results: Of 2007 patients with DMD identified, median (interquartile range) age at index was 14 (9–20) years, and median follow-up was 3.1 (1.6–4.7) years. Neurologic and neuropsychiatric observations were most frequently identified, among 49.3% of the cohort; followed by cardiovascular (48.5%), respiratory (38.1%), scoliosis (36.3%), and severe respiratory (25.0%). Prevalence estimates for each category were higher when analyzed within age-restricted subgroups; and increased as follow-up time increased.

Conclusions: This study is the first to use diagnosis and procedure codes from real-world Medicaid claims to document the clinical course in DMD. Findings were consistent with previously published estimates from commercially insured populations and clinical registries; and contribute to the expanding body of real-world evidence around clinical progression of patients with DMD.

Keywords: Medicaid; Duchenne muscular dystrophy; DMD; Claims data; Rare disease

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Key Summary Points

Why carry out this study?

Duchenne muscular dystrophy (DMD) is a severe, childhood-onset, X-linked progressive neuromuscular disease. The progression of symptoms in DMD, including loss of ambulation (LOA), scoliosis, respiratory insufficiency, need for ventilation, and cardiomyopathy, typically culminates with premature mortality in the third or fourth decade of life.

This study sought to describe the real-world clinical course of DMD based on claims data from Medicaid-insured individuals in the US.

What was learned from the study?

The ages at observation of key clinical outcomes in DMD were consistent with previously published estimates.

This study offers real-world insight into the clinical course of DMD identified using Medicaid claims and highlights methodological considerations for using claims data to understand natural history.

INTRODUCTION

Duchenne muscular dystrophy (DMD) is a severe X-linked progressive neuromuscular disease. Robust data on the natural history of DMD are available from several well-documented clinical registries, including the Cooperative International Neuromuscular Research Group (CINRG) [1], Duchenne Registry [2], and Centers for Disease Control and Prevention's Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet) [3]. Studies using these data have described the frequency of key clinical milestones in DMD that occur throughout late childhood and adolescence, including loss of ambulation (LOA), scoliosis, respiratory insufficiency, need for ventilation, and onset of cardiomyopathy [4–8]. The progression of symptoms in DMD typically culminates with premature mortality in the third or fourth decade of life [9–11].

Despite the availability of estimates of the frequency and timing of these milestones from clinical cohorts, other real-world estimates are scarce. However, understanding how estimates of the clinical course from real-world populations compare to those from clinical trial or registry populations is important to understand the experience of patients in standard clinical practice settings; and also, to help understand the potential utility of existing real-world data to monitor the clinical burden and health resource utilization among patients with DMD over time.

The prevalence of selected clinical outcomes among commercially insured patients with DMD was documented in a recent real-world study using health insurance claims data based on healthcare resource use data from MarketScan [12]. However, these findings may have limited generalizability to populations with other insurance coverage, and updated USA-specific estimates are needed. The objective of this study was to describe the real-world clinical course of DMD, based on health insurance claims documenting healthcare resource use among Medicaid-insured patients in the USA.

METHODS

The study cohort and entry criteria employed were consistent with those previously described in the study examining the costs of care among patients with DMD with Medicaid coverage [13]. Briefly, MarketScan Multi-State Medicaid claims data from 2013 to 2018, which included data from 10 anonymized states, were used to identify men no more than 30 years old with muscular dystrophy (International Classification of Diseases [ICD] code 359.1), or DMD/Becker muscular dystrophy (ICD G71.0). All cohort members were enrolled at their index visit, which was the first inpatient or first of at least two outpatient visits with an MD or DMD/

Becker MD code. All cohort members were included regardless of treatment history and followed until death (if known), deregistration, or the end of the follow-up period. Baseline characteristics of the cohort are presented in the prior publication.

The prevalence and age at the capture of various clinical diagnosis or procedure codes related to key clinical outcomes in DMD were estimated. Definitions of these outcomes were described previously [13] as well as in Supplementary Table S1. Observations of these key clinical outcomes were categorized into:

- Scoliosis
- Neurologic/neuropsychiatric
- Cardiovascular-related
- Respiratory-related
- Severe respiratory-related

While wheelchair use characterizes later stages of DMD progression [14, 15], wheelchair possession alone is unable to confirm ambulatory status as it cannot provide information about the frequency or nature of wheelchair use. However, validated ICD or procedure codes are not available to assess loss of ambulation (LOA), which is an important clinical milestone in DMD. As such, wheelchair possession was instead investigated [15], in addition to the observations of key clinical outcomes noted above.

While respiratory-related observations could include any type of ventilation, code for respiratory insufficiency or failure, or tracheostomy, severe respiratory-related observations were restricted to tracheostomy and/or a diagnosis of respiratory failure (Table S1). Additionally, since the base case definition of cardiovascular-related observations included diagnosis codes for cardiomyopathy and heart failure as well as the use of relevant cardiac medications, an additional definition of cardiovascular-related observations based on diagnosis codes alone was explored (to avoid misclassifying patients being treated with cardiac medications prophylactically as having cardiomyopathy). Finally, while mortality is a key outcome of interest, it could not be assessed in this study as only inpatient deaths through 2016 were available in the database.

Analytic methods were also previously described [12]. In brief, the primary analysis summarized the occurrence of key clinical outcomes by tallying the proportion of patients who experienced each key clinical outcome, and the median age at first observation. Age-restricted analyses were then performed within clinically relevant time windows to understand the impact of both follow-up time and age on the likelihood of capturing observations of claims related to key clinical outcomes within the cohort. Observations of wheelchair possession, scoliosis, and neurologic/neuropsychiatric were examined among those who were aged 8–10 and 11–13 years at cohort entry. Cardiovascular-, respiratory-, and severe respiratory-related observations were examined among those aged 14–16 and 17–19 years at cohort entry. These clinically relevant time windows for analysis were selected based on published evidence from North America on the mean age at occurrence of LOA [16, 17], cardiomyopathy [5, 18], and respiratory involvement [18, 19]. Among patients who have a minimum of 1-year follow-up, the frequency and age at first captured observation were explored.

Estimates of the prevalence of observations for key clinical outcomes were compared between the age-restricted cohorts and the overall cohort. Sensitivity analyses, in which no minimum duration of follow-up was imposed, were conducted to:

1. Remove the minimum 1-year requirement.
2. Explore these outcomes over the first year, rather than the first 2 years, after cohort entry.

Kaplan–Meier (KM) analyses stratified by age category at cohort entry were conducted to better understand the prevalence of events captured by follow-up time available.

Data in the MarketScan commercial databases are de-identified and are compliant with the Health Insurance Portability and Accountability Act (HIPAA) regulations; thus, institutional review board approval was not required to conduct this study. This work was supported by Sarepta Therapeutics, Inc.

Table 1 Percentage and median age of observations of key clinical outcomes among Medicaid patients with DMD, overall and stratified by age

Age at cohort entry	Median (IQR) of follow-up duration included	Observations of key clinical outcomes	*N* (%)*	Median (IQR) age at first observation
Primary analyses (non-age stratified)				
n = 2007	3.1 (1.6–4.7)	Wheelchair possession	1129 (56.3)	16 (11–20)
		Scoliosis	728 (36.3)	16 (12–19)
		Neurologic/neuropsychiatric	989 (49.3)	12 (8–17)
		Respiratory-related	765 (38.1)	19 (15–23)
		Severe respiratory-related	502 (25.0)	21 (17–25)
		Cardiovascular-related	974 (48.5)	17 (13–22)
		Cardiovascular-related (defined by diagnosis codes only)	634 (31.6)	19 (15–23)
2-year observation window, among those with a minimum follow-up of 1 year (main age-restricted analysis)				
8–10 years	2.0 (2.0–2.0)	Wheelchair possession	165 (64.2)	10 (9–11)
(*n* = 257, 12.8% of total cohort)		Scoliosis	89 (34.6)	10 (9–11)
		Neurologic/neuropsychiatric	179 (69.6)	9 (8–10)
11–13 years	2.0 (2.0–2.0)	Wheelchair possession	173 (74.9)	13 (12–14)
(*n* = 231, 11.5% of total cohort)		Scoliosis	123 (53.2)	13 (12–14)
		Neurologic/neuropsychiatric	137 (59.3)	12 (12–13)
14–16 years	2.0 (2.0–2.0)	Respiratory-related	123 (49.4)	16 (15–17)
(*n* = 249, 12.4% of total cohort)		Severe respiratory-related	69 (27.7)	16 (15 to 18)
		Cardiovascular-related	164 (65.9)	15.5 (15–16)
		Cardiovascular-related (defined by diagnosis codes only)	108 (43.4)	16 (15–17)

Table 1 continued

Age at cohort entry	Median (IQR) of follow-up duration included	Observations of key clinical outcomes	*N* (%)*	Median (IQR) age at first observation
17–19 years	2.0 (2.0–2.0)	Respiratory-related	138 (52.5)	19 (18–20)
(*n* = 269, 13.1% of total cohort)		Severe respiratory-related	89 (33.8)	19 (18–20)
		Cardiovascular-related	172 (65.4)	18 (17–19)
		Cardiovascular-related (defined by diagnosis codes only)	125 (47.5)	19 (18–19)
Sensitivity analysis variation #1: 2-year observation window; no minimum follow-up imposed				
8–10 years	2.0 (1.9–2.0)	Wheelchair possession	142 (50.7)	10 (9–10)
(*n* = 280, 14.0% of the total cohort)		Scoliosis	72 (25.7)	10 (9–10)
		Neurologic/neuropsychiatric	175 (62.5)	9 (8–10)
11–13 years	2.0 (2.0–2.0)	Wheelchair possession	164 (64.6)	13 (12–13)
(*n* = 254, 12.7% of the total cohort)		Scoliosis	107 (42.1)	13 (12–13)
		Neurologic/neuropsychiatric	133 (52.4)	12 (11–13)
14–16 years	2.0 (2.0–2.0)	Respiratory-related	113 (42.6)	16 (15–16)
(*n* = 265, 13.2% of the total cohort)		Severe respiratory-related	56 (21.1)	16 (15 to 17)
		Cardiovascular-related	162 (61.1)	15 (15–16)
		Cardiovascular-related (defined by diagnosis codes only)	100 (37.7)	15.5 (14.75–16)
17–19 years	2.0 (2.0–2.0)	Respiratory-related	131 (43.2)	19 (18–19)
(*n* = 303, 15.1% of the total cohort)		Severe respiratory-related	82 (27.1)	19 (18–19)
		Cardiovascular-related	180 (59.4)	18 (17–19)
		Cardiovascular-related (defined by diagnosis codes only)	128 (42.2)	19 (18–19)

Table 1 continued

Age at cohort entry	Median (IQR) of follow-up duration included	Observations of key clinical outcomes	*N* (%)*	Median (IQR) age at first observation
Sensitivity analysis variation #2: 1-year observation window; no minimum follow-up imposed				
8–10 years	1.0 (1.0–1.0)	Wheelchair possession	119 (42.5)	10 (9–10)
(*n* = 280, 14.0% of the total cohort)		Scoliosis	58 (20.7)	9.5 (9–10)
		Neurologic/neuropsychiatric	161 (57.5)	9 (8–10)
11–13 years	1.0 (1.0–1.0)	Wheelchair possession	145 (57.1)	12 (12–13)
(*n* = 254, 12.7% of the total cohort)		Scoliosis	93 (36.6)	12 (12–13)
		Neurologic/neuropsychiatric	120 (47.2)	12 (11–13)
14–16 years	1.0 (1.0–1.0)	Respiratory-related	91 (34.3)	15 (15–16)
(*n* = 265, 13.2% of the total cohort)		Severe respiratory-related	42 (15.8)	15.5 (15–16)
		Cardiovascular-related	154 (58.1)	15 (15–16)
		Cardiovascular-related (defined by diagnosis codes only)	84 (31.7)	15 (14–16)
17–19 years	1.0 (1.0–1.0)	Respiratory-related	114 (37.6)	18 (18–19)
(*n* = 303, 15.1% of the total cohort)		Severe respiratory-related	69 (22.8)	18 (18–19)
		Cardiovascular-related	171 (56.4)	18 (17–19)
		Cardiovascular-related (defined by diagnosis codes only)	107 (35.3)	19 (18–19)

IQR interquartile range

*Denominator: all patients within the age range at baseline; additional cohort characteristics including health status, healthcare resource use, and costs of the cohort over the follow-up period were summarized previously in the study by Klimchak et al. [13]

RESULTS

From the 2007 patients with DMD identified, the median (IQR) age was 14 (9–20) years at cohort entry, and follow-up was 3.1 (1.6–4.7) years.

In the primary analysis, observations of wheelchair possession were the most frequent (56.3%), and severe respiratory-related observations the most infrequent (25.0%; Table 1). The corresponding median (IQR) age at first observation among the cohort was 16 (11–20) years for wheelchair possession and 21 (17–25) years for severe respiratory-related observations. In the age-restricted analysis taking into consideration the window during which each key

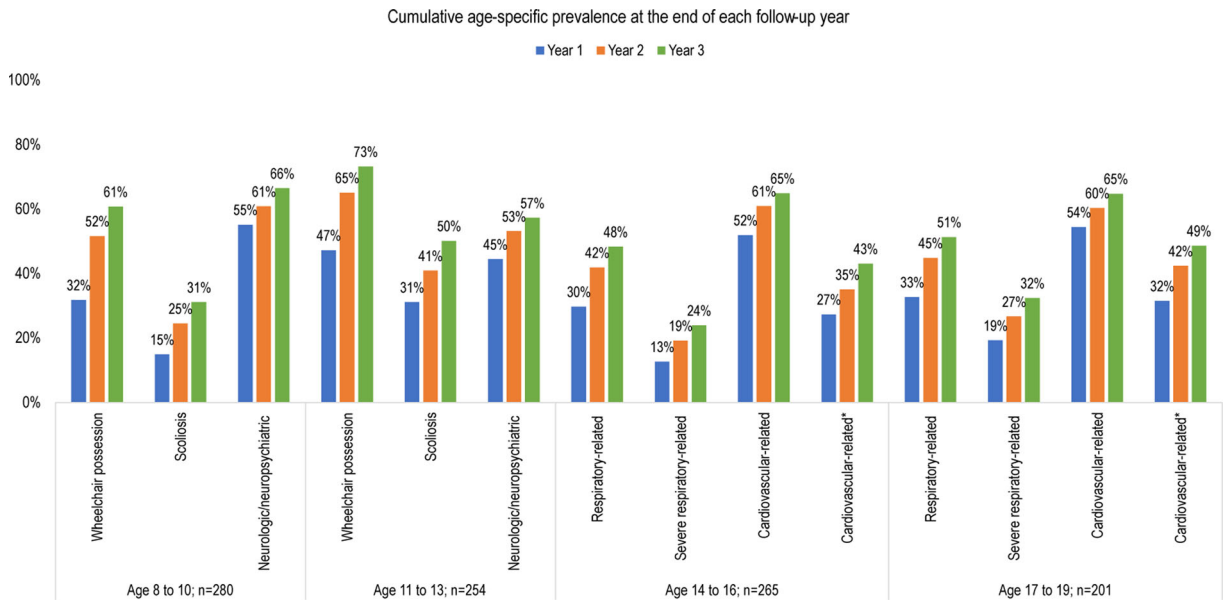

Fig. 1 Estimates from Kaplan–Meier analysis of age-specific prevalence by follow-up time among patients with DMD. *Defined by diagnosis codes only (i.e. use of medications were not included as part of the definition). These estimates from the set of Kaplan–Meier analyses showed that after adjusting for loss of follow-up (varying follow-up length), the prevalence of outcomes increased with follow-up length and age

clinical outcome is most likely to take place, the prevalence of observations in each specific age group was higher compared to the results of the primary analysis (Table 1). For instance, the prevalence of wheelchair possession, scoliosis, and neurologic/neuropsychiatric observations over a 2-year period among those aged 8–-13 years (with at least 1 year of follow-up) was up to 20% higher than the estimates from the primary analysis. Similarly, the prevalence of respiratory- and cardiovascular-related observations from the age-restricted analyses among those aged 14–19 years of age (with at least 1 year of follow-up) at cohort entry were approximately 10% higher compared to the main analyses.

The KM analyses showed that the prevalence of observations is higher with longer follow-up and is generally higher among those in older age groups (Fig. 1). For instance, the prevalence of patients with observations for wheelchair possession during follow-up approximately doubled from 31.8% by the end of year 1 to 60.7% by the end of year 3 among those aged 8–10 at baseline. Among patients aged 11–13 years at baseline, the prevalence of patients with observations for wheelchair possession increased from 47.2% by the end of year 1 to 73.2% by the end of year 3. Some tapering of prevalence was observed for neurologic/neuropsychiatric and cardiovascular-related observations, with the majority of these captured within the first year of follow-up. This finding of higher prevalence with longer follow-up was supported by the findings from sensitivity analyses: when removing the minimum follow-up requirement and/or reduced observation window length, the prevalence generally decreased.

DISCUSSION

The study explored the use of diagnosis and procedural coding data within health insurance claims to characterize the clinical course of DMD among Medicaid-insured patients. The findings extend on existing data from commercially insured patients and add to the growing body of evidence describing outcomes among patients with DMD, at the population

level, in the real world [4, 20–22]. Understanding the clinical characteristics and outcomes of this large cohort of patients with DMD with Medicaid coverage is important for increasing the generalizability of these results, particularly in interest of the uncertainty of whether the populations may differ clinically and a substantial proportion of patients with DMD in the USA access care through Medicaid [13].

Consistent with previous findings from analyses among commercially insured patients with DMD in the USA [12], the results of the primary (non-age-restricted) analyses reported slightly older median ages at the first observation of key clinical outcomes, compared with published estimates from clinical studies [4–8]. This suggests that the first observation for individual clinical outcomes in a cut of administrative health insurance claims data may not necessarily reflect an initial diagnosis of that milestone, but instead reflects the first captured event within the dataset. This highlights an important limitation to the use of such claims data to understand health outcomes at the individual level. With relatively short follow-up per patient, as is common in US health insurance claims data [13], it is challenging to determine if the first observation of an outcome in the database reflects when the outcome first occurred (i.e. it was an incident event) or merely reflects the first documentation of an outcome that was pre-existing in that individual patient. That many of the first instances of clinical outcomes observed in the current study were not incident is supported by the relatively late median age at cohort entry of 14 years. By that age, on average, previous research shows that many patients with DMD would already be regularly using a wheelchair, have been diagnosed with scoliosis, and potentially experienced early respiratory and cardiac involvement [14]. As a result, some of the observations for key clinical outcomes where one would expect a relatively early onset, such as use of a wheelchair and scoliosis, may appear to have occurred later than they actually did if the patient was first documented within the database after the outcome occurred. In addition, some outcomes may not necessarily be documented again within claims after initial documentation. For example, if a patient first obtained a wheelchair prior to cohort entry, but did not proceed to have any maintenance or replacement during follow-up, this patient would not contribute to the count of patients with wheelchair possession within this study. Similarly for scoliosis, if corrective surgery had occurred prior to cohort entry, these patients may not proceed to have additional diagnosis codes or other claims codes indicative of scoliosis during the follow-up. As a result, both the length of, and age during, the observation window will impact the prevalence and age estimates, and could lead to an underestimation of the prevalence of or age at which these outcomes occur.

These challenges support the use of the age-restricted analyses, in which the frequencies of observations for key clinical outcomes were higher, which is as expected given that the age-restricted analyses focused on the time windows during which these outcomes were more likely to occur. Indeed, the findings from these analyses were more comparable to estimates from the published literature. Up to 75% of the cohort aged 8–13 years had a record of wheelchair possession within 2 years of follow-up, which falls within the range of published estimates of age at LOA (from 30% by 10 years [4] through 95% by 15 years of age) [5]. Scoliosis was documented in up to 50% of young teenagers over their first 2 years of follow-up, consistent with published estimates suggesting 60% of patients with DMD have scoliosis by 15 years [5]. Neurologic and/or neuropsychiatric observations were documented in 60–70% of children and young teenagers within 2 years, which is also broadly consistent with published estimates of the age at diagnosis of common neuropsychiatric complications in DMD [23]. Respiratory-related observations were documented in approximately half of the cohort of older teenagers within 2 years of follow-up, aligning with published estimates of 40–50% of patients requiring ventilation over 20 years of age [8, 20]. Severe respiratory-related observations had a slightly lower estimated prevalence of approximately 30% within 2 years of follow-up. Estimates of cardiovascular-related observations were on the lower end of published estimates (68–93% cardiomyopathy by 20 years of

age) [5–7]. The difference was more pronounced when cardiovascular-related observations were restricted to exclude the use of cardioprotective medications. It is important to bear in mind that some of these key clinical outcomes under investigation—such as scoliosis, or neurologic and/or neuropsychiatric observations—would not be expected to be observed among all of those with DMD, even if patients were followed throughout the entirety of their disease course [24].

The strengths of the study stem from the use of a well-validated dataset that provided a large sample size of patients with DMD, including children and adults over an average follow-up period of 3 years. The algorithm to identify the cohort was previously used in similar studies to understand clinical outcomes [12, 13, 25, 26]. In addition, this study offers insights into the prevalence of key DMD outcomes observed among patients covered by Medicaid.

However, the generalizability to the entire Medicaid population in the USA may still be limited, given that these data comprise a random selection of 10 states from the USA. Additional limitations include that there may be misclassification due to coding error as these data are collected for reimbursement not research, and clinical data to validate patient characteristics and outcomes are not available. For instance, while the patient identification algorithm was based on previously published studies [12, 13, 25, 26], it has not been clinically validated and may result in misclassification of patients with other types of muscular dystrophy as DMD. In particular, as a result of the shared use of the ICD-10-CM code of G71.01 for DMD/BMD, the risk of including patients with BMD within the DMD cohort may be higher than for other types of muscular dystrophy. However, sensitivity analyses were conducted to explore the effects of potential misclassification and findings were comparable to the main analyses (Table S2).

Further, while the observation of study outcomes was dependent on diagnosis and/or procedure codes, the presence of a code cannot confirm any specific clinical pathology nor can severity be definitively assessed as the underlying reasons for a physician selecting a particular code are unavailable. For instance, treatment with cardioprotective medications may indicate cardiomyopathy or heart failure in some patients with DMD; however, it is unclear based on claims data alone whether these medications were prescribed to an individual for cardiomyopathy prophylaxis or treatment. Similarly, while the presence of diagnosis codes for respiratory or heart failure would indicate at least some degree of involvement, these codes cannot be used to infer symptom severity. As another example, while codes for purchasing a wheelchair can indicate progression to requiring walking aids, they cannot indicate the frequency and timing of wheelchair use or degree of reliance; thus, they cannot be used to characterize a patient's lower limb functional status. Additionally, wheelchair purchases from outside of insurance would not be recorded.

An additional consideration is that the lack of a code for an outcome of interest does not necessarily mean that outcome did not occur. Longer observation windows result in higher prevalence estimates; and there are specific age ranges in which certain key clinical outcomes are most likely to occur. Given that the cohort had an average follow-up of less than 4 years, the data do not allow for a full longitudinal understanding of progression at the patient level nor ascertainment of the timing of onset of clinical outcomes. These issues have implications for the design of studies to measure real-world outcomes for those with DMD over time and should be carefully considered particularly when following a closed lifetime cohort is not possible. Finally, this study did not seek to look at time to clinical events adjusted for medication exposure; however, recent evidence has shown delays in time to certain milestones due to the use of DMD treatments [5, 27–29].

CONCLUSION

This study reports the observed clinical course of DMD via claims diagnosis and procedures codes from real-world Medicaid-insured data. The ages at observation of key clinical outcomes in DMD were consistent with previously published estimates. However, limitations remain

in using claims data to characterize clinical outcomes, and the study findings need to be interpreted in that context while also considering the clinical heterogeneity in the timing of key clinical outcomes experienced by those with DMD. The findings from this study can help identify the types of outcomes that can be observed through cohort studies using Medicaid claims data, and highlight considerations on methodology required. These data also contribute to the body of real-world evidence around clinical progression of DMD at the population level.

Authorship All authors (Christina Qian, Alexa C Klimchak, Shelagh M Szabo, Evan Popoff, Susan T Iannaccone, and Katherine L Gooch) contributed to the study conception and design. Material preparation, data collection and analysis were performed by Christina Qian and Evan Popoff. The first draft of the manuscript was written by Christina Qian and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest. Christina Qian and Shelagh M Szabo are employees, and Evan Popoff was an employee, of Broadstreet HEOR, which received funds from Sarepta Therapeutics Inc for this work. Alexa C Klimchak and Katherine L Gooch are employees of Sarepta Therapeutics Inc. and may hold stock/options. Susan T Iannaccone has received research funding or consulting fees from Avexis, Biogen, Fibrogen, Mallinckrodt, Regeneron, Sarepta, Scholar Rock, PTC Therapeutics, Pfizer, MDA, CureSMA, NIH, Genentech-Roche, and BCBS.

Ethical Approval. Data were provided by Merative™, for access to a cut of data from the MarketScan® Multi-State Medicaid databases. Data are de-identified and are compliant with the Health Insurance Portability and Accountability Act (HIPAA) regulations; thus, institutional review board approval was not required to conduct this study.

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