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ORIGINAL RESEARCH

Disease Progression Stages and Burden in Patients with Duchenne Muscular Dystrophy Using Administrative Claims Supplemented by Electronic Medical Records

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ABSTRACT

Introduction: This study aims to identify stages of Duchenne muscular dystrophy (DMD) and assess the disease burden by progression stage using real-world administrative claims supplemented by relevant electronic medical record (EMR) data.

Methods: Claims and EMR data from the Decision Resources Group's Real World Data Repository (2011–2020) were used to identify patients with DMD by diagnosis code and to stratify them into four disease stages by diagnosis and procedure markers reflective of DMD progression. Clinical and medical history data from the Cooperative International Neuromuscular Research Group (CINRG) were used to validate the developed claims-based staging algorithm. The distribution and drivers by disease stage, as well as disease burden, were examined.

Results: A total of 938 (94%) of patients with DMD identified in claims/EMR data had sufficient information for stage classification. Patients were classified by stage based on patient characteristics and the presence or absence of progression markers such as genetic testing, wheelchair usage, scoliosis treatment, or ventilation assistance. Average ages at stages 1–4 are 7, 13, 18, and 23 years, respectively. Using natural history data, the claims-based staging algorithm was validated with high sensitivity and specificity rates. Both healthcare resource utilization and medical charges increased by stage. For example, the average annualized total charges were $17,688 (stage 1), $36,868 (stage 2), $72,801 (stage 3), and $167,285 (stage 4).

Conclusions: Large-scale claims data supplemented by EMR data can be used to characterize DMD progression and evaluate disease burden which may inform the design of future real-world studies about DMD.

Keywords: Disease stages; Disease burden; Duchenne muscular dystrophy

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Key Summary Points

Why carry out this study?

As a result of the rarity of Duchenne muscular dystrophy (DMD), a significant challenge in research is to adequately characterize DMD disease progression stages and capture the burden of illness across different stages.

This study develops a validated disease progression algorithm for patients with DMD using claims data.

What was learned from the study?

Patients were classified into four progression stages using large-scale claims data supplemented by electromedical record data.

The study found that patient healthcare resource utilization and medical charge increased by disease stage.

INTRODUCTION

Duchenne muscular dystrophy (DMD) is a rare, X-linked, neuromuscular disease characterized by a progressive deterioration of muscle due to mutations in the dystrophin gene [1]. Muscle damage due to the loss of the dystrophin protein may be apparent early in the disease course [2], but physical deficits can be masked by delays in the typical pattern of early childhood growth and achievement of motor milestones. Nonetheless, there has been increasing recognition of the progressive and predictable stages of DMD as patients age, requiring complex and resource-intensive multidisciplinary care [3, 4].

Patients with DMD experience progressive loss of muscle fiber, ambulation, and self-care skills over time and ultimately cardiopulmonary impairment leading to mortality. The loss of ambulation and cardiopulmonary function necessitates wheelchair use, ventilation devices, and reliance on caregivers [5], leading to declining quality of life over time [6]. Historically, the standard of care has centered on the use of corticosteroids for symptomatic relief, despite the recognized side effects [7]. Although considerable improvements have been made in the development of targeted therapies, effective disease-modifying therapies are limited to patients with certain types of mutations [8, 9]. Nevertheless, early use of molecular diagnostics and administration of comprehensive interventions prior to significant milestone impairment has resulted in prolonged survival [10, 11], making it possible for patients with DMD to live past early adulthood [12] and even enter their fourth decade [10]. This improved survival has motivated patients with DMD to consider continued participation in school and vocational attainment despite physical limitations [13].

With ongoing research on characterizing the trajectory of DMD and evaluating clinical outcomes following treatment to improve care [14–17], a significant challenge in DMD research still remains, as a result of the rarity of the condition, to adequately characterize DMD disease progression stages and capture the burden of illness across different stages. To date, most of the available literature on DMD centers on clinical trials [18, 19] and natural history data sources [20–22] with small sample sizes. Therefore, there is an emerging need for large-scale real-world characterization of DMD progression and burden [17] using, for example, administrative claims and electronic medical records (EMR) to provide healthcare stakeholders with valuable insight. However, previous studies in such data sources had only relied on age [5] to define stage, failing to account for the variability in disease course experienced by patients. Clinically measured function tests (e.g., ambulatory ability and lung capacity) [21] would ideally be available to define stages but these are not consistently recorded outside of clinical trial or registry settings. Additionally, the lack of specific diagnosis codes based on the International Classification of Diseases, Ninth/Tenth Revision (ICD-9/10) to identify patients with DMD has limited the real-world characterization of the progression of DMD, since

even the most current ICD-10 codes do not distinguish DMD from slower-progressing Becker's muscular dystrophy (BMD) [23].

To overcome these challenges, using administrative claims data supplemented by relevant EMR data, this study aimed to develop a staging algorithm to stratify patients with DMD on the basis of disease severity, assess real-world stage distribution, and evaluate clinical and economic burden of DMD by disease stage. In addition, the developed staging algorithm was validated using patient data from the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG-DNHS) [21].

METHODS

Data Sources

In this retrospective analysis, administrative claims and EMR data from the Decision Resources Group's (DRG's) Real World Data Repository (January 1, 2011 to March 21, 2020) were used. The validation analysis used natural history data from CINRG-DNHS (2006 to 2014). For CINRG data (NCT00468832, https://cinrgresearch.org/), the institutional or ethics review boards at each participating institution approved the study protocol and the consent/assent documents. Informed consent/assent was obtained from each participant or caregiver as appropriate prior to conducting the study procedures. DRG data do not require institutional review board review as it only contains de-identified data. The authors have obtained permission to access and use the data from the owners of the data.

DRG Data

The DRG database comprised open-source medical and pharmacy claims from multiple electronic data interchanges and EMRs from a major EMR vendor in the USA. Data from all sources were directly matched at the patient level over time, which thus facilitated the study of DMD progression. The database included over 300 million patients in the USA from 2011 onward. Multiple patient demographic characteristics and a variety of DMD-related progression or health and resource utilization (HRU) outcome measures were available from DRG.

CINRG Data

The CINRG-DNHS [21, 22] enrolled patients with documented DMD aged 2–28 years at more than 20 centers in nine countries between 2006 and 2009. Additional patients aged 4–8 years were recruited from 2012 to 2016. Ambulatory patients were assessed at baseline and months 3, 6, 9, and 12. Non-ambulatory patients were assessed at baseline and months 6 and 12. Long-term follow-up visits were conducted at months 18, 24, and annually thereafter. CINRG performed timed function tests among ambulatory patients, including time to rise from supine (RFS), time to climb four stairs, time to run or walk 10 m (10MWR), and 6-min walk test, measured forced vital capacity (FVC), and calculated forced vital capacity percentage predicted (FVC%p) at each visit. All these variables were used to define progression stages in the validation analysis. Additionally, CINRG also collected rich information regarding patients' health status and medical history through health status history interviews based on DMD-care guidelines and expert opinions from clinicians and researchers.

Study Design

An advantage of the DRG data set was that it allowed for further identification of patients with DMD using the Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT) code. In the analysis, patients with at least one SNOMED-CT code of 7667001 were identified as patients with DMD, allowing for distinguishing them from patients with BMD. As the SNOMED-CT code was only available in EMR data, this identification strategy limited patients in this analysis to those with both claims and EMR data in DRG. Patients were excluded if total observation length was shorter than 12 months or if

claims were observed in fewer than six individual months.

Disease Stage Identification

Patients were classified into the following four stages of DMD progression: early ambulatory (stage 1), late ambulatory (stage 2), early non-ambulatory (stage 3), and late non-ambulatory (stage 4) [5]. Each stage was determined on the basis of both patient characteristics and a combination of signal markers of DMD progression. More details are discussed below.

The *early ambulatory* stage was mainly identified by age (less than 8 years) combined with the absence of markers characteristic of later stages as noted below. Without observing markers of later stages, encounters such as genetic testing and counselling, psychosocial management, and rehabilitation were also used to identify this stage.

For patients at the *late ambulatory* stage, expected progression markers included assistive devices such as manual or power-assisted wheelchairs, scooters, and cough assist devices. Patients in this stage were still ambulatory but needed help from these assistive devices to restore independent mobility. Many patients at this stage were also expected to be characterized by use of corticosteroid treatments—including but not limited to prednisone and deflazacort—in combination with cardiac medications such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and beta blockers. Therefore, combined use of steroids and cardiac medications, defined as observations of both steroid and cardiac medications within a 3-month window, was also considered an indicator for late ambulatory stage. Unfortunately, steroid dosing and frequency is not observed in claims and EMR data, so we cannot distinguish daily use glucocorticoids for strength maintenance versus steroid inhalers for preventing of pulmonary complications in data.

The *early non-ambulatory* stage included patients who lost ambulation and required more advanced assistive treatments consistently for mobility and periodically for breathing. Therefore, this stage was identified by patients transitioning to motorized wheelchair use, indicated by either a combination of motorized wheelchair and cardiac medication use, or motorized wheelchair use on its own for at least 6 months. Patients were also classified into this stage if they underwent certain corrective procedures intended to treat scoliosis, or initiated pulmonary management services that were typically needed to assist with normal functioning. Patients at this stage may have also initiated bisphosphonate therapies to prevent fractures and continue cardiac medication use. Therefore, combined use of bisphosphonate therapies and cardiac medication was considered as a marker of this stage where the combined use was defined as observations of both medications within a 4-month window.

The final *late non-ambulatory* stage was defined by patients losing several essential muscular functions including pulmonary and gastrointestinal capabilities. This stage was identified by tracheostomy events, regular assisted ventilation, and the insertion of a gastrostomy tube with enteral nutrition supplements. It was not atypical for patients at this stage of DMD to transition completely to hospice or supervised home care, which was thus also used as a marker for this stage. The full list of markers used and the definition of each stage are summarized in Table 1.

All indicators were flagged on a claim-by-claim basis using a combination of ICD-9/10 codes for diagnosis and procedures; Current Procedural Terminology (CPT) and Healthcare Common Procedure Coding System (HCPCS) codes for procedures; and National Drug Code (NDC) codes for pharmaceutical therapies. The full list of codes used for each marker was provided in Appendix Table 1 (Supplementary Material). Specific code-based determinants of health stage were validated through expert clinical inputs. Disease stages using the selected indicators were assessed monthly for each patient with DMD from DRG. The identified stage was carried forward until a more severe stage was identified and patients were assumed not to revert to an earlier stage. The time preceding the first identified stage was assumed to be in the stage one level down the first identified stage. Patients aged 0–8 without any disease stage indicators observed during their entire

Table 1 Progression markers for stage definition

Stage 1 (Early Ambulatory)		
0–8 years old and lacking later stage markers		
OR satisfying one of the following criteria		
Maker #1 OR #2		
(Marker #3 AND #4) OR #4		
No	**Marker**	**Description**
#1	Genetic testing	DMD/BMD deletion/duplication or sequencing genetic testing
#2	Genetic counselling	Genetic counselling services and Molecular pathology procedure
#3	Psychosocial management	Speech/hearing therapy
#4	Rehabilitation management	Therapeutic activities
Stage 2 (Later Ambulatory)		
Satisfying one of the following criteria:		
#1 OR #2 OR #3		
#4 OR (#5 AND age 9-13)		
#6 AND #7		
No	**Marker**	**Description**
#1	Manual wheelchair	Manual wheelchair, components, and adjustments
#2	Power assist wheelchair	Manual wheelchair push-rim power system
#3	Scooter	Power operated vehicle
#4	Cough assist device	Cough stimulating or interface for cough stimulating device
#5	Orthotic or prosthetic therapy	Footplate, ankle motion, inner boot etc.
#6	Steroid	Prednisone or Deflazacort
#7	Cardiac medication	ACE/ARB + beta blocker
Stage 3 (Early Non-ambulatory)		
Satisfying one of the following criteria		
(#1 AND #7) OR (#1 for longer than 6 months)		
#2 OR #3 OR #4 OR #5		
≥ 2 #7 OR (#7 + #8)		
No	**Marker**	**Description**
#1	Motorized wheelchair	Motorized wheelchair and accessories
#2	Scoliosis	Scoliosis
#3	Orthopedic management	Bone density study and axial skeleton
#4	Rehabilitation management	Occupational therapy evaluation
#5	Hospital bed or mattress	Hospital bed or mattress

Table 1 continued

Stage 3 (Early Non-ambulatory)		
Satisfying one of the following criteria		
(#1 AND #7) OR (#1 for longer than 6 months)		
#2 OR #3 OR #4 OR #5		
≥ 2 #7 OR (#7 + #8)		
No	**Marker**	**Description**
#6	Pulmonary management	Nasal, positive airway, and breathing devices
#7	Cardiac medication	ACE/ARB + beta blocker
#8	Bisphosphonate therapy	Bisphosphonate therapies
Stage 4 (Late Non-ambulatory)		
Satisfying one of the following criteria		
#1 OR #2 OR #4 OR #5 OR #6		
#3 AND (age ≥ 10 years old)		
No	**Marker**	**Description**
#1	Tracheostomy	Tracheostomy and tracheostomy related procedures
#2	G-tube	Gastrostomy tube and gastro/jejunostomy tube
#3	Gastrointestinal management	Enteral formula, enteral nutrition infusion pump
#4	Hospice and home health care	Hospice or home care
#5	Pulmonary management	Nasal, positive airway, breathing devices etc.
#6	Assisted ventilation	Ventilation procedure and devices

ACE angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *BMD* Becker muscular dystrophy, *DMD* Duchenne muscular dystrophy, *G-tube* gastrostomy tube

observation period were assigned to the stage 1, with a required minimum observation length to ensure that the absence of disease indicators was not caused by a short observation period or missing data. As a result of incomplete coverage of the DRG claims and EMR data over a patient's medical care history, we may not be able to stage a patient to the suitable stage at their first observation. Therefore, we allowed for 12 months from the patient's first observation to assess the stage distribution by then.

Validation of Staging Algorithm Using CINRG Data

To evaluate the specificity and sensitivity of the staging algorithm developed on the basis of claims and EMR data, a validation analysis was conducted. Specifically, CINRG data was used to classify patients into stages using both clinical function tests and the physician-recorded fields that correspond to claims-based identifiers, and then the classified stages based on the two methods were compared.

Based on prior literature [21], clinical expert inputs, and data availability, disease stages were defined on the basis of a patient's ability to perform two timed function tests as well as the results of their pulmonary function tests in CINRG (as summarized in Table 2).

Although CINRG did not include claims or EMR data, physician-recorded medical history data fields were available and corresponded to

Table 2 Stage definition using clinical tests

	Criteria 1		Criteria 2
Stage 1 (Early ambulatory)	Able to perform 10MWR	AND	Able to perform RFS
Stage 2 (Late ambulatory)	Able to perform 10MWR	AND	Unable to perform RFS
Stage 3 (Early non-ambulatory)	Unable to perform 10MWR	AND	FVC%p $>$ 50%
Stage 4 (Late non-ambulatory)	Unable to perform 10MWR	AND	FVC%p $\leq$ 50% (Confirmed by two consecutive visits)

10MWR 10 m walk run test, *RFS* rise from supine, *FVC%p* forced vital capacity percentage predicted

most of the claims and EMR-based stage identifiers, therefore were used in the validation analysis. For example, answering "yes" to the "use manual wheelchair" question in CINRG corresponded to "manual wheelchair" marker in the claims-based staging algorithm. Appendix Table 2 (Supplementary Material) detailed the identified physician-recorded data fields in CINRG that corresponded to each stage identifier in the developed claims-based staging algorithm.

After patients in the CINRG data were classified to stages based on the two aforementioned methods, the specificity and sensitivity of the staging method based on physician-recorded fields were evaluated by comparing to the stages defined by clinical function tests, which were considered the gold standards of staging classification. Specifically, stage concordance was defined as, when a patient transitions to a new stage by clinical determinations, the stage defined by physician-recorded fields classifies the patient to the same stage within $\pm$ 1 visit. The main validation analysis used US patients in CINRG data. A sensitivity scenario analysis that included CINRG patients from all nine countries was also performed.

Disease Burden

This study also provided assessments of disease burden by disease progression stage. Disease burden was evaluated by both DMD HRU events and total medical care charges. The DMD HRU events included (1) adjusted emergency room (ER) encounters, (2) ER days, (3) adjusted hospital encounters, (4) hospital days, (5) adjusted intensive care unit (ICU) encounters, (6) ICU days, (7) pulmonary management, (8) motorized wheelchair use, (9) scoliosis, (10) cardiac management, (11) tracheostomy, (12) cough assist device use, and (13) assisted ventilation. Adjusted ER encounters, hospital encounters, and ICU encounters were defined as number of unique claims each day for ER visits, hospital stays, and ICU stays. For each patient at each stage, annualized rates were calculated on the basis of the length of stay in a particular stage. Average annualized rates and standard deviations by stage were reported. Total charges, as the sum of charges from both medical and pharmaceutical claims, were calculated on an annualized basis and inflated to 2020 USD for each patient at each stage. Average annualized charge and standard deviations by stage were reported. Additionally, the overall average annual total charges for a patient with DMD over time was also reported. To reduce noise, the burden analysis excluded observations when patients spend no more than 3 months in a particular stage.

Table 3 Health stage and age distribution at 12th month

Health stage	Distribution, *N* (%)	Age, mean	Age, median
1	363 (38.7%)	7.4	6
2	242 (25.8%)	13.1	12
3	215 (22.9%)	18.1	18
4	118 (12.6%)	23.2	23
Total	938		

Table 4 Stage concordance of two staging methods

		Stages defined by clinical function tests N (%)				
		1	2	3	4	Total
Stages defined by Physician-recorded fields N (%)	1	80 (91%)	6 (18%)	0 (0%)	0 (0%)	86
	2	7 (8%)	25 (74%)	4 (6%)	0 (0%)	36
	3	1 (1%)	1 (3%)	57 (89%)	35 (49%)	94
	4	0 (0%)	2 (6%)	3 (5%)	36 (51%)	41
	Total	88	34	64	71	**257**

RESULTS

Disease Progression Stage Distribution

Of the 993 patients with DMD identified using SNOMED code in EMR data, 94% had sufficient claims data and procedural markers observed for stage stratification. The age and distribution of patients according to health stage at the 12th month following the initial observation are summarized in Table 3. Most patients were classified as stage 1 (38.7%) compared to stage 2 (25.8%), stage 3 (22.9%), and stage 4 (12.6%). In general, both mean and median age of patients increased with advancing disease stages.

Patients were classified as stage 1 mainly by age and absence of later stage markers. Other than that, the most common markers to classify patients to stage 1 were genetic testing (16%) and rehabilitation management (15%). For patients classified as stage 2, the three most common drivers were manual wheelchair (51%), steroid and cardiac medication (26%), and orthotic or prosthetic therapy (20%). For patients classified as stage 3, scoliosis (30%), cardiac medications (22%), and motorized wheelchair (14%) were the three most common drivers. For patients classified as stage 4, the three most common drivers were assisted ventilation (56%), pulmonary management (26%), and tracheostomy (24%).

Validation of Staging Algorithm Using CINRG Data

Validation of the claims-based staging algorithm using CINRG data among US patients (169 patients with 257 stage transitions) is reported in Table 4. A patient can contribute multiple times if they have more than one stage transition. In general, the concordance between the two staging methods was high, particularly for stages 1–3 (with sensitivity rates 91%, 74%,

Table 5 Annualized rate of HRU events by stage

DMD-related medical events (mean, SD)	Stage 1	Stage 2	Stage 3	Stage 4
Adjusted emergency room encounter	0.38 (0.90)	0.44 (1.55)	0.65 (2.37)	1.76 (6.68)
Emergency room days	0.25 (0.53)	0.29 (0.95)	0.38 (1.26)	1.11 (6.18)
Adjusted hospital encounter	0.79 (1.80)	1.19 (3.08)	3.95 (18.17)	14.05 (104.39)
Hospital days	0.51 (1.07)	0.72 (1.77)	1.73 (4.54)	4.95 (11.69)
Adjusted ICU	0.01 (0.07)	0.04 (0.37)	0.10 (0.71)	1.09 (9.25)
ICU days	0.00 (0.05)	0.02 (0.21)	0.09 (0.59)	0.92 (6.99)
Pulmonary management	0.00 (0.00)	0.00 (0.00)	0.23 (1.15)	4.39 (6.64)
Motorized wheelchair claim	0.00 (0.05)	1.10 (3.50)	0.66 (1.39)	1.01 (1.95)
Scoliosis	0.00 (0.00)	0.00 (0.00)	0.84 (2.77)	1.84 (6.30)
Cardiac management	0.45 (1.12)	0.83 (2.21)	1.45 (2.91)	2.09 (6.78)
Tracheostomy	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	9.13 (20.58)
Cough assist device	0.00 (0.00)	0.28 (1.64)	0.33 (1.26)	1.16 (2.26)
Assisted ventilation	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	7.18 (11.81)

DMD Duchenne muscular dystrophy, *HRU* healthcare resource utilization, *ICU* intensive care unit, *SD* standard deviation

and 89%, respectively). The observed concordance for stage 4 (51%) was lower, apparently because of missing ventilation data in CINRG. The specificity (i.e., true negatives) for stages 1–4 was 95%, 96%, 96%, and 84%, respectively. Results from the sensitivity analysis including patients outside of the USA (435 patients with 671 stage transitions) were consistent (Appendix Table 3, Supplementary Material).

Disease Burden by Stage

Overall, the average annualized rate of all HRU events increased with more severe disease stages (Table 5), and the magnitude of increase was also larger for later stages. For example, average annualized hospital days increased from 0.51 at stage 1 to 0.72 at stage 2, to 1.73 at stage 3, and to 4.95 at stage 4. Some events only appeared in later stages by definition, such as scoliosis, which, as a marker for stage 3, only started to appear among patients at stage 3.

Similarly, annualized costs increased with disease stage (Table 6). For patients classified as stage 1, the average per-patient annualized total charges were $17,688 and roughly doubled for patients classified as stage 2 ($36,868). The average annual cost of medical care for a patient with DMD, weighted by the length of stay at each stage, was $71,451.

DISCUSSION

This retrospective study extended the current body of DMD research by characterizing DMD disease progression stages and describing the magnitude of the burden of illness by disease stage using real-world, large-scale claims data supplemented with EMR data. The ability to reliably define stages of DMD progression is a relevant component of clinical and economic

Table 6 Health stage distribution and average per-patient annualized health care costs by stage

Health stage at 12th month	Distribution *N* (%)	Average per-patient annualized total charges, mean (SD)
1	363 (38.7%)	$17,688.48 ($104,157.74)
2	242 (25.8%)	$36,867.81 ($162,917.88)
3	215 (22. 9%)	$72,800.97 ($342,693.74)
4	118 (12.6%)	$167,284.62 ($331,378.95)
Total	938	

SD standard deviation

evaluations [24]. However, literature to date has generally relied upon clinical functional measures using data from clinical trials [18, 19], natural history sources [20–22], and medical centers [17]. While these data are informative, they typically involve small samples and rarely include data on HRU and cost, which are of interest to many stakeholders. Large-scale claims and EMR data have the potential to provide more information, but the clinical functional measures historically used for DMD stage definition are usually not available within these sources. This study addresses this gap by providing a novel approach to classify the progression stage of patients with DMD using diagnosis, procedure, and medication markers in real-world claims and EMR data.

This study found that over one-third of identified patients were classified to stage 1, roughly one-quarter of patients were classified to stages 2 and 3, and 13% were classified to stage 4 at the 12th month after their first observation. This distribution is generally consistent with an earlier observation of disease stage distribution based on only age [5]. The lower share in stage 4 in the current study may relate to advances in clinical care over time and/or to patients lost to follow-up in the DRG data set (e.g., if Medicaid fee-for-service coverage is more common in stage 4; and if patients in stage 4 have much less frequent medical care visits because of physical limitations, economic reasons, or geographic isolations), although additional research to confirm this hypothesis is warranted.

The staging algorithm is also validated indirectly using CINRG data, suggesting that the staging algorithm developed in this study can successfully identify stages of DMD using claims and EMR data that correspond to those that would be classified by clinical function markers if available. In the validation analysis, the sensitivity or concordance and specificity between the two staging methods were high, particularly for stages 1–3. The lower rates for stage 4 were primarily driven by missing ventilation data in CINRG, therefore likely underestimating the actual performance of the claim-based staging algorithm with unambiguous reporting of ventilation assistance in claims and EMR data. Even with the ventilation data limitation in CINRG, the sensitivity and specificity align with thresholds that have been reported in several studies across various disease areas [25–28].

Results also revealed an increase in HRU and costs as DMD stage advanced, which aligns with prior research documenting the increased need for assistive therapies to navigate the disability loss of muscle function [5, 29] and increased cost with disease progression [5, 29–33]. Overall, the observed medical care costs align with the annual total medical costs associated with DMD previously reported for the USA, Germany, UK, and Italy.

This study should be considered within the context of certain limitations. First, the claims data corresponded to prescriptions and may not correlate with compliance or extent of utilization of the interventions. Second, as a result of incomplete coverage of the DRG claims data and EMR data over a patient's medical care

history, we were unable to stage all patients at their first observation. To overcome this limitation, we allowed 12 months from the patient's first observation to assign patient stage and assess the stage distribution. Third, in the validation analysis, not every claim- or EMR-based stage classifier had a comparable physician-recorded data field available in CINRG. However, these markers play a minimal role in stage classification in DRG data. Further, as more natural history data that cover the same period with the claims data become available, future studies using these data sets, such as such as the c-TAP and c-Path data, to further validate the algorithm would contribute to add more evidence in understanding of the real-world evidence using claims data. Finally, the amount charged was used to calculate economic burden due to lack of paid amounts. Charge amounts are not an ideal metric for healthcare costs as the amount charged to a provider often exceeds final paid amounts.

CONCLUSION

This study classified US patients with DMD by progression stage using administrative claims data supplemented by EMR data. The staging algorithm was validated to show good sensitivity and specificity using CINRG data. These findings demonstrate that claims data, supplemented by EMR data, have the potential to offer healthcare stakeholders critical insight regarding DMD progression and the disease burden. Results indicated that patients with severe stages of DMD had higher HRU and greater medical care costs. These results may serve as a benchmark for US patients in future research.

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Compliance with Ethics Guidelines. For CINRG data (NCT00468832, https://cinrgresearch.org/), the institutional or ethics review boards at each participating institution approved the study protocol and the consent/assent documents. Informed consent/assent was obtained from each participant or caregiver as appropriate prior to conducting the study procedures. DRG data do not require institutional review board review as it only contains de-identified data. The authors have obtained permission to access and use the data from the owners of the data.

Data Availability. The data sets generated during and/or analyzed during the current study are not publicly available due to data usage agreement between DRG, CINRG, and Sarepta.

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