RWD128

# The burden of illness in Duchenne muscular dystrophy: evidence gaps and research needs


**Alex Simpson[1], Conor McCloskey[2] , Roberto Bonemei[2] , Sunita Nair[3] , Maria João Garcia[1]**

**1. Global Access, F. Hoffmann-La Roche Ltd, Switzerland, 2- Clarivate, UK, 3- Clarivate, India**


## Background

- Duchenne muscular dystrophy (DMD) is an X-linked, rare neuromuscular disease caused by mutations in the DMD gene that disrupt the production of functional dystrophin protein, leading to progressive muscle weakness, diminished quality of life and premature death. [1-3]
- While corticosteroids are a therapeutic option for patients with DMD to delay progression of muscle weakness and loss of function, the emergence of newer treatments, such as antisense oligonucleotides, exon skippers, enzyme inhibitors and gene therapies, have the potential to change the disease course by addressing the underlying cause of DMD.[1-3]
- Therefore, it is important to synthesize the evidence describing the burden of illness (BoI) of Duchenne muscular dystrophy (DMD) in order to contextualize the impact of the potential shift in the DMD treatment landscape.
- To this end, a targeted literature review (TLR) was conducted in 2022 to understand the current BoI and associated evidence gaps across the humanistic, clinical and economic domains

## Objectives

- Understand the BoI among patients with DMD in terms of humanistic, clinical and economic burden
- Identify research areas where the evidence is of poor quality or absent
- Provide recommendations and solutions for potentially filling aforementioned evidence gaps, in particular, estimating a present day lifetime economic burden of DMD

## Methods

### *Targeted Literature Review*

- Relevant studies reporting data on the epidemiology, natural history, and clinical, humanistic, and economic burden of disease in patients with DMD were identified using electronic databases (MEDLINE, Embase, and the Cochrane Library) and gray literature searches, performed on August 31st, 2022.
- Citations identified in the electronic database searches were screened by a single analyst to assess eligibility on the basis of the pre-defined inclusion criteria.
- Relevant data from included studies were extracted into pre-designed data extraction tables in Microsoft® Excel, and the data extraction was conducted by a single analyst and quality checked by a second analyst or project lead. Disputes were referred to a third analyst.

### *Estimating Total Lifetime Economic Burden of DMD*

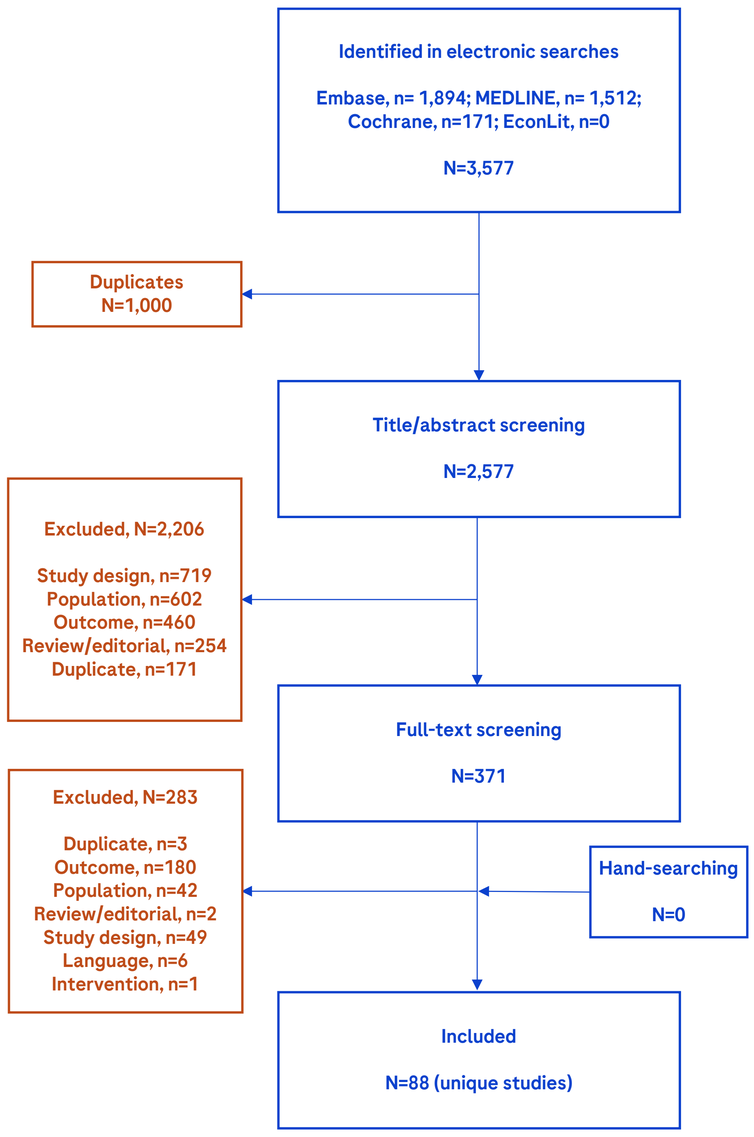
- Studies reporting economic burden were further assessed for their ability to inform a present day estimate of the lifetime economic burden of DMD, including direct medical costs, out-of-pocket expenses, and productivity losses (due to work impairment and lost earnings potential due to early mortality)
- We extrapolated costs from dated data collection efforts in an attempt to make them applicable and relevant to the present day
- Full details of this approach are set out in the Results section

## Results

### *Targeted Literature Review*

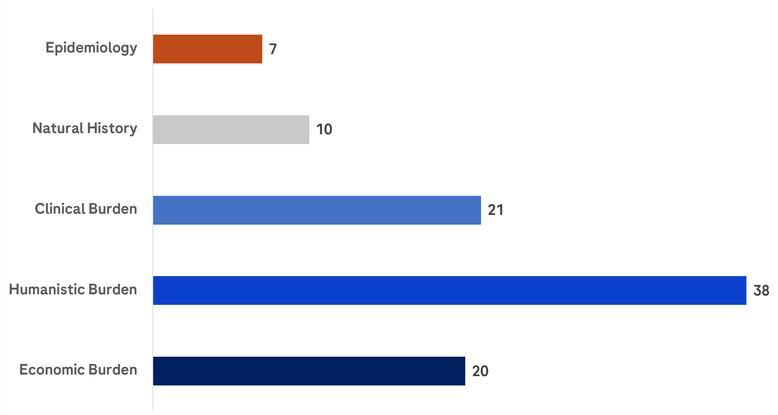
- The search strategy identified a total of 3,577 citations, of which 88 were included for data extraction and synthesis (**Figure 1**).
- Most of the studies reported data on the humanistic burden of DMD (**Figure 2**). Some publications provided information on more than one of these topics.

**Figure 1.** Study flow of included and excluded publications




## Results (cont.)

**Figure 2.** Number of studies reporting each type of BOI data for DMD




### *Epidemiology*

- Two studies[4,5] identified prevalence data from the USA, ranging from 1.18–1.60 per 10,000 males.
- One study[6] reported prevalence rates by age, finding that the 5- to 9-year-old age group had the highest prevalence (1.43–1.60) followed by 10- to 14-year-olds (1.29) and 15- to 19-year-olds (1.08).
- A similar DMD prevalence was also identified in Norway where one study found the prevalence of DMD to be 1.35 per 10,000 boys <18 years old.[7]
- Studies of DMD incidence were more limited, with one study being reported from Norway (1 in 4,967 live male births)[7] and one from Taiwan (1 in 8,710 live male births).[8]
- Similarly, studies that evaluated prevalence breakdown by race were also similarly limited, with only one such study being identified from the USA.[6]

➢ **Research need: Global epidemiologic studies of DMD that cover a broad range of geographies, populations, DMD stages and specific DMD mutations**

### *Natural History*

- The mean age at DMD diagnosis ranged from 2.8–4.6 years as assessed by five studies.[7,9-12]
- Patients' performance as assessed by the NSAA scale and timed function tests (e.g. 6MWT) generally increased between the ages of 3 and 6 years as patients grow, but at a slower rate than healthy controls;[13,14] performance subsequently declined between the ages of 7 and 13 years [15]
- Loss of ambulation (LOA) occurred in 35–64% of patients at a mean of 9.7–13.3 years.[7, 9-12] One large Dutch study (n=336)[12] reported that patients experiencing early LOA had scoliosis surgery and mechanical ventilation earlier than those with late LOA (both P <0.001).
- Only three studies described the decline in physical function with age, as assessed using specific tests such as the 6MWT and the NSAA scale, two of which involved US cohorts and one of which involved cohorts from the USA, UK, and Italy.
  - However, none of the studies investigated differences in the rate of physical decline according to mutation status.

➢ **Research need: Longitudinal natural history studies examining loss of motor function using precise tools (e.g., NSAA, 6MWT, TFT), and including mutation status**

### *Clinical Burden*

- Lower/upper limb and facial weakness are common physical symptoms of DMD,[16-18] with stiffness, fatigue, muscle contractures, and low-speech volume having a meaningful impact on daily living in at least a quarter of patients.[19]
- Pain is commonly experienced by patients with DMD and affected patients' mood with late LOA more than those with early LOA or those still ambulatory ($P$ =0.046).[20]
- Survival has improved decade on decade with survival rates at the age of 20 improving from 23% for patients born in the 1960s, to 54% and 60% for those born in the 1970s and 1980s, respectively, but there is a lack of recent data regarding DMD survival in the modern age and with the advent of treatment advances.[21]

➢ **Research Need: Up-to-date survival data in the context of treatment advances and DMD treatment in the modern age, in addition across multiple geographies**

### *Humanistic Burden*

- Significantly lower PedsQL scores were recorded in patients with DMD compared with controls;[22-26] scores ranged from 52.73[25] to 62.54[24] for patients with DMD and 82.64[24] to 87.05[25] for controls (out of 100).
- Eleven studies described the burden of caregivers of patients with DMD, where the estimated utilities ranged from 0.79 (Germany) to 0.84 (Italy).[27]
- Of the eight studies that were identified describing predictors or factors having a positive or negative impact on HRQoL, one study[28] found the most prominent decline between the transition from late ambulatory to early non-ambulatory disease.
- Most studies involved small patient numbers and thus may not be representative of all patients with DMD or take into account differences in symptoms.
- Most studies were cross-sectional and hence did not explore how HRQoL changes over the course of the disease.

➢ **Research Need: Longitudinal studies that chart precise changes in HRQoL over time and with correlation to loss of motor function. Studies in larger patient cohorts will also allow for the definition of HRQoL trajectory, factors which influence HRQoL on the humanistic burden of caregivers, and the possible impact of interventions that stabilise disease progression**

### *Economic burden*

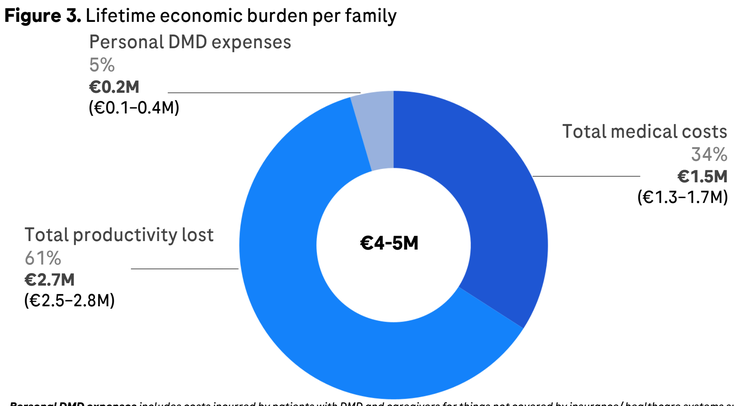
- Resource use and costs were found to increase with disease progression as illustrated by:
  - A US claims analysis in which mean (SD) per-patient annualized total costs increased with the severity of the disease from $17,688 ($104,157) for early ambulatory to $167,284 ($331,378) for late non-ambulatory disease.[29]
  - A German study, where total direct cost of illness was lowest for patients with early ambulatory disease with mild impairment (€15,866) and highest for patients with non-ambulatory disease confined to bed (€131,948), and the corresponding total indirect costs increased from €13,078 to €32,907.[28]
- Moreover, non-medical and indirect costs also constituted a large proportion of total costs and added to the already substantial burden of direct medical costs.
  - This was demonstrated most clearly in a pan-European study encompassing eight countries[30] which found that the main driver for total costs was direct non-healthcare costs, with the main cost element within this category being informal care with the exception of one country (Sweden).
  - Despite the substantial impact of caring for a child with DMD, only one study specifically investigated the economic impact of DMD from the caregiver's perspective, with an estimated annualized earning loss for caregivers ranging from $13,828–$23,995 for patients with ≤3 and ≥4 years of ambulation loss, respectively.[31]

➢ **Research Needs: Studies which consider the totality of economic burden including opportunity cost of productivity loss due to disease impacts at work and premature mortality. In addition, studies which cover multiple countries, particularly ex-US, to truly estimate the global burden of disease.**

## Results (cont.)

### *Estimating Total Lifetime Economic Burden of DMD*

**Figure 3.** Lifetime economic burden per family




***Personal DMD expenses*** *includes costs incurred by patients with DMD and caregivers for things not covered by insurance/ healthcare systems such as home or car modifications.* ***Total productivity lost*** *represents a composite of productivity lost due to work impairment due to disease/ illness (Landfeldt 2014) and productivity lost due to loss of work opportunity as a result of illness.* ***Total medical costs*** *represents all direct medical costs such as hospitalisations, specialist visits and tests/ procedures. The number in bold represents the average value between Germany, Italy and the UK, and the range represents the 95% CI around that value.*

- The study by Landfeldt et al. 2014[27] estimated total (direct and indirect) costs, out-of-pocket expenses, and productivity losses due to work impairment using cross sectional data from Germany, Italy and the UK collected in 2012.
- This study represented one of the most comprehensive sources of economic burden data on DMD that was identified from ~~our~~ this TLR.
- However, with the data being collected in 2012, and up to date estimates being required, we used this study as a basis to calculate a present day average lifetime economic burden of DMD figure with the following approach:

- Total annual cost of illness (direct medical costs only), out-of-pocket expenses, and patient/caregiver productivity loss (due to work impairment) were extracted (€/year)
  – These parameters represented tangible costs of illness and the main drivers of the economic burden of DMD
- As this data was collected in 2012, these values were adjusted to 2022 values using the CPI [32] (Table 1)
- As these values represented an annual estimate, we then multiplied this by the average life expectancy, 28 years,[33] to estimate an average lifetime burden of €2,378,790 (Table 1):

**Table 1.** 2022 Estimated Lifetime costs (€) of DMD based on 2012 values

| | Germany | Italy | UK | Average |
|---|---|---|---|---|
| Total medical costs | 1,553,765 | 813,089 | 2,066,962 | 1,477,939 |
| Productivity loss due to work impairment | 761,844 | 619,334 | 713,667 | 698,282 |
| Personal DMD expenses | 217,879 | 256,640 | 133,192 | 202,570 |
| **Total Lifetime Costs** | 2,533,488 | 1,689,062 | 2,913,821 | **2,378,790** |

*Total medical costs represents all direct medical costs such as hospitalisations, specialist visits and tests/ procedures. Productivity loss due to work impairment represents work impacts due to DMD whilst the patient is alive, but does not represent any opportunity loss of potential earnings due to illness/ disease. Personal DMD expenses represent costs incurred by patients with DMD and caregivers for things not fully covered by insurance/ healthcare systems such as home or car modifications. These numbers have been adjusted purely for inflation only, and do not reflect any other potential changes in DMD epidemiology or standards of care/ treatment advances*

- These estimates however do not yet represent the totality of the burden of disease as opportunity costs due to early mortality were not considered, i.e., potential earnings lost due to loss of work opportunity as a result of illness.
- The study by Innis et al. 2023[34] has previously estimated potential working years lost for patients with DMD (35.0 years) and their caregivers (4.3 years), based on a lifetime cost model in a US population using the human capital approach.
- Potential working years lost (39.3 years) was multiplied by the average income of Germany, Italy and the UK in 2022 (€50,165) to estimate a total productivity loss due to loss of work opportunity (€1,971,485)
- Combining €2,378,790 from the previous step and €1,971,485 then represents an estimate of the present day total lifetime economic burden of DMD as between **€4-5million** (Figure 1 and 4)

**Figure 4.** Calculating the total lifetime economic burden of DMD from Total Lifetime Costs and Productivity Loss due to mortality/ illness

**2,378,790** + 1,971,485 = **4,350,275**

(Total Lifetime Costs) + (Productivity loss opportunity cost) = **Total Lifetime Burden of DMD**

## Conclusions

- There is extensive evidence describing the burden of DMD, as experienced by patients and caregivers but there are considerable evidence gaps on the overall societal burden relating to outdated data, disparate populations, limited follow-up, and narrow scope.
- Whilst current estimates of the total lifetime economic burden of disease can be extrapolated from previously identified literature as we have done herein, recent and comprehensive economic burden studies that capture all aspects of the burden of disease are urgently required.

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## Abbreviations

6MWT, 6-minute walk test; BOI, burden of illness; CPI, Consumer Price Index; DMD, Duchenne muscular dystrophy; HRQoL, health-related quality of life; LOA, loss of ambulation; NSAA, North Star Ambulatory Assessment; PedsQL, Pediatric Quality of Life Inventory; SD, standard deviation; STS, supine to standing test; TLR, targeted literature review; UK, United Kingdom; US, United States; USA, United States of America.

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