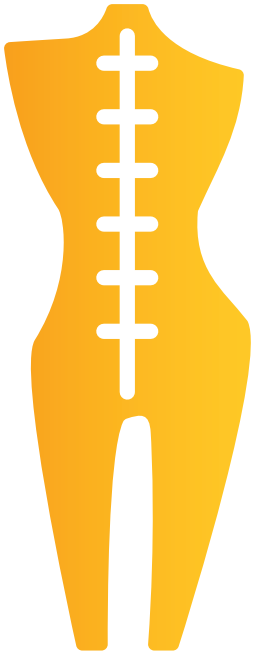
VOL 16 / ANNO 2021 / PAG 13-30

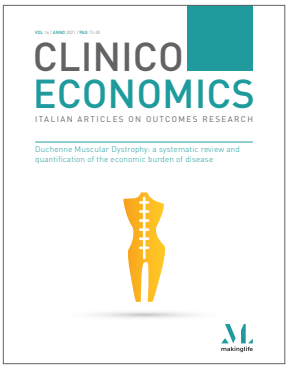
CLINICO ECONOMICS

ITALIAN ARTICLES ON OUTCOMES RESEARCH

Duchenne Muscular Dystrophy: a systematic review and quantification of the economic burden of disease



makinglife



ClinicoEconomics è una rivista peer-reviewed di farmacoeconomia e di outcomes research sulle conseguenze economiche e di politica sanitaria di dispositivi medici e strategie farmacologiche.
Obiettivo della Rivista è quello di pubblicare in modo rapido e conciso lavori sull'impatto clinico ed economico in tutte le principali aree terapeutiche, valutazioni in tema di sicurezza, di efficacia nella pratica clinica, di costo-efficacia, di costo-utilità e di costo-beneficio nell'uso sostenibile dei farmaci e dei dispositivi medici.
www.clinicoeconomics.eu

Progetto grafico e impaginazione
newattitude comunicazione

Stampa
Starprint Srl

makinglife

www.makinglife.it

Volume n. 16 / 2021 alla Pubblicazione peer-reviewed open access
ClinicoEconomics Italian Articles on Outcomes Research (Print ISSN 2282-8087; Online ISSN 2282-8095) è una rivista annuale pubblicata da MakingLife S.r.l. via P. Paleocapa 6, 20121 Milano, Italia.
Registrazione del Tribunale di Milano n. 368 del 14/07/2011

CLINICO ECONOMICS

Duchenne Muscular Dystrophy: a systematic review and quantification of the economic burden of disease

G.L. Colombo[1] | **G.M. Bruno**[2] | **S. Di Matteo**[3] | **C. Martinotti**[3]

[1] CEFAT - center of pharmaceuticals economics and medical technologies evaluation, Drug Science Department, Pavia University, Pavia, Italy

[2] Drug science department, Pavia University, Pavia, Italy

[3] S.A.V.E. Studi Analisi Valutazioni Economiche S.r.l, Milan, Italy

Correspondence:

Giorgio L. Colombo. CEFAT, University of Pavia. c/o S.A.V.E. Studi Analisi Valutazioni Economiche, Via G. Previati 74, 20149 Milan, Italy.

Tel: +39 02.48519230. Fax: +39 02.73960369. E-mail: giorgio.colombo@unipv.it

ABSTRACT

INTRODUCTION

Duchenne muscular dystrophy (DMD) is a lethal X-linked recessive neuromuscular disorder caused by mutations in the dystrophin gene that result in absent or insufficient functional dystrophin, a cytoskeletal protein essential for the development, stabilization and function of myofibers. Consequently, progressive skeletal, smooth and cardiac muscle damage and degeneration occur in DMD patients, developing in atrophy and muscle weakness, motor delays, loss of ambulation, respiratory impairment, and cardiomyopathy.

Our goal has been to collect the available evidence regarding DMD's cost of illness, in order to see what is missing, what common aspects emerge, which are in contrast (and understand why), and, finally, in order to address choices and new future analyses.

MAIN BODY

The results of our systematic review allow confirming the substantial economic burden related to Duchenne Muscular Dystrophy. The included studies identify the cost of DMD in ten (10) countries characterized by different healthcare systems.

All the studies reported on total direct costs as the main cost item and have highlighted the prominent role of direct non-medical costs on direct medical costs. It is noteworthy that the total direct cost for DMD patients has been reported up to sixteen (16) times higher than the mean per-capita health expenditure in analysed countries (eg the UK).

Authors info:

Giacomo M. Bruno
giacomomatteo.bruno@unipv.it

Sergio Di Matteo
sergio.dimatteo@savestudi.it

Chiara Martinotti
chiara.martinotti@savestudi.it

CONCLUSION

The variation of cost estimates for different studies and countries highlights the need to clearly understand and address the financial burden of DMD disease. On the basis of the research conducted for this review, we believe it is necessary that future cost-of-illness studies in DMD follow a quality standard protocol with transparent and clearly defined cost components and separate estimates by disease severity and age.

KEYWORDS

Cost analysis, pharmacoeconomics, cost of illness, economic impact, economic evaluation.

INTRODUCTION

Duchenne muscular dystrophy (DMD) is a lethal X-linked recessive neuromuscular disorder caused by mutations in the dystrophin gene that result in absent or insufficient functional dystrophin, a cytoskeletal protein essential for the development, stabilization and function of myofibers.[1] Consequently, progressive skeletal, smooth and cardiac muscle damage and degeneration occur in DMD patients, developing in atrophy and muscle weakness, motor delays, loss of ambulation, respiratory impairment, and cardiomyopathy. Clinical course of skeletal muscle and the cardiac involvement can be variable; however, even with medical care, most of the people with DMD die from cardiac or respiratory failure before or during their third decade.[1,2,3] Duchenne muscular dystrophy is a rare disease, in fact, its prevalence has been reported between 15.9 and 19.5 per 100,000 live births, with a global estimate of about 300,000 subjects affected, with 1500 in Italy.[1,4,5,6]

The first signs of the disease appear at around 2.5 years of age, although symptoms may first be noticed in babies less than 12 months old.[7,8] Age at diagnosis is not defined homogeneously in the literature; in Italy, a large dystrophinopathic cohort has reported the mean age as 4 years.[9] Diagnosis is often delayed because the symptoms are not recognised or appropriately evaluated, resulting in delays to provision of appropriate care and monitoring.[10,11] The progressive loss of muscle function in DMD causes a series of increasingly severe skeletal muscle symptoms. These symptoms include altered gait, proximal weakness, falls, difficulty in climbing stairs and enlarged calf muscles.[1,12,13] Muscle deterioration continues during childhood, with loss of ambulation (LOA) and complete wheelchair reliance, occurring by approximately 13-14 years of age, followed by the gradual loss of upper limb function throughout the teenage years and the twenties.[1,14,15] Orthopaedic complications, such as scoliosis, tendon contractures and bone fractures, arise in concert with skeletal muscle complications, and scoliosis appears in almost all DMD patients, if not treated with corticosteroids (CS).[16] Timing of loss of ambulation is related to the rate of disease progression and onset of further DMD associated complications; moreover, the loss of ambulation has resulted in association with an increased mortality risk.[17,18]

Respiratory insufficiency and cardiovascular complications are leading causes of disease-related morbidity and mortality among DMD patients.[19] During the final stages of the disease, patients have mostly lost all muscle function, which also affects breathing, chewing and swallowing, leading to need of ventilation, nutritional issues and malnutrition. The physical, cognitive and social limitations of patients with DMD can lead to depression and anxiety not only in patients but also in caregivers and family members.[20] Duchenne prognosis, progressive loss of motor function, the numerous complications and limitations in activities of daily living impact the quality of life of patients and of their caregivers.[21,22] Indeed, DMD patients require increasing assistance with even the most basic of daily activities, resulting in loss of independence and a decrease in health-related quality of life (HR-QoL), that escalates over the course of the disease. With the worsening of the disease and loss of patient independence, burden on caregivers increases, exerting emotional, health, social and financial effects.[23,24]

The clinical management occurs with drugs, mainly steroids and cardiological/respiratory medication, and with rehabilitative treatments.[25]

This integrated and multidisciplinary approach has improved quality of life and increased life expectancy, making DMD no longer an exclusively paediatric pathology, so much that it has been associated with an "adulthood" disease.[3,18,26,27] In this regard, two European long-term retrospective cohort studies have shown a significant increase in life expectancy over the years. Specifically, a French study by Kieny has reported a median survival of about 25.8 years for patients born between 1955 and 1969, rose to 40.9 years for patients born after 1970.[27] In line with this study, Passamano et al have observed the overall mortality percentage at age 20 and 25 for patients born in the 1960s, 1970s and

1980s respectively. For patients born in the 1960s, 76.7% died by the age of 20 and 86.5% by the age of 25; for those born in the 1980s, the percentage of patients that died by the age of 20 has been reduced to 40.2% and by the age of 25 to 50.8%.[3] Despite improvements in clinical management, there is still no cure for DMD patients, who universally suffer a reduced lifespan and require complex, costly, and life-long multidisciplinary care to cope with the loss of muscle function and with several complications of the disease. This in turn entails a significant impact on both family and society, with serious management problems when welfare support is not adequate or lacking. The multidisciplinary care team must aim to alleviate respiratory, cardiac, nutritional, endocrine, gastrointestinal and musculoskeletal complications, to provide for physical therapy and surgical intervention for scoliosis and contractures, to perform cognitive assessment and speech therapy and to deliver psychological support. Currently, corticosteroids are the standard of care for DMD, which can delay the onset of functional, pulmonary and cardiac decline to an extent; however, they do not address the disease cause.[20,28] Moreover, although corticosteroids offer benefit for DMD patients, the long-term adverse effects, such as weight gain, behavioural changes, immunosuppression, diabetes and hirsutism, can make care more complex and challenging. Availability of safe, well-tolerated and effective medications, capable of targeting the underlying pathophysiologic changes in DMD, represent a significant unmet need.[29] Recently, advancements in genetics and molecular biology have provided new therapeutic options for DMD, offering hope to patients. These new medications, such as stop codon readthrough agents and exon-skipping agents, have been targeted to act on the mutations responsible for DMD. In August 2014, the European Commission granted ataluren a conditional marketing authorisation for use in the European Union, targeting the approximately 11% of boys with DMD caused by a stop codon in the dystrophin gene.[1,15] In September 2016, the US Food and Drug Administration (FDA) approved use of eteplirsen, which targets the approximately 13% of boys with a mutation in the dystrophin gene that is amenable to exon 51 skipping, through an accelerated approval pathway, while not yet approved in the European Union.[1,31,32]

Ataluren and eteplirsen are the first of a series of mutation-specific therapies to gain regulatory approval. Other dystrophin restoration therapies are in development and some are near or already in regulatory review. New treatments can increase dystrophin levels and delay loss of ambulation and declines in clinical outcomes in patients with DMD; however, currently, they are still not able to cure the patient, although they can improve the quality of life.[20,33] The cost of these orphan drugs is another item to be taken into account. In the last few years, the increasing number of licensed medicines for rare diseases has brought to a growing debate regarding high costs and affordability for national healthcare systems. Based on the previous considerations, it is clear how DMD disease characteristics and its course make it a rare pathology, with a high economic impact from the point of view of both health systems and society.

For complex management diseases, such as DMD, cost of illness studies (COI) play an import role. They offer a systematic quantification of the economic burden of disease on both the individual and on society and help to identify direct budgetary consequences of diseases in the health system and indirect costs related to patient or caregiver productivity loss.[34] Cost-of-illness studies can be used as a public policy tool to assist in prioritization and justification of healthcare and prevention policies. They can highlight interventions that are more valuable by comparing averted economic burden, and so, consequently, they can lead to shifts in distribution of public and private investments.[35] This study type is useful to identify main disease cost-drivers, such as cost factors and patient's consumption behaviour depending on the severity or the stage of disease progression, providing information for other types of economic evaluations, including a framework for cost estimation in cost-utility and cost-effectiveness analyses, for policy makers.

Defining the cost of illness of rare diseases is very important because, despite their low prevalence, they can entail a huge expense due to the management complexity. Thus, it can be helpful to study a particular disease to understand the actual burden of the illness on society and economic amounts that could potentially be saved by slowing the progress of the disease or by promoting its eradication. Studies in different countries can show different outcomes depending on the health systems and population's specific characteristics, but are also useful for highlighting common aspects and for suggesting any interesting observation points.

Using this perspective, the aim of our analysis is to systematically review the relevant literature on the socio-economic burden of Duchenne Muscular Dystrophy and identify all costs, both direct and indirect, related to the disease from the perspective of National Healthcare Systems and society.

Specifically, we have tried to provide a critical review of the available literature, which identify the current state of knowledge in the DMD cost of illness area, and a synthesis of studies' results, highlighting strengths, limitations and common aspects among studies. We have concluded our review with the definition of items to be considered for the development of future economic evaluations.

MATERIAL AND METHODS

The review has been conducted following the general principles published in the Centre for Reviews and Dissemination (CRD)'s guidance for conducting systematic reviews and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. The inclusion and the evaluation of studies in this review has been based on PICOS (Population, Intervention, Comparators, Outcome and Study design).[36,37]

To facilitate the interpretation and the comparison of results from included studies, we have chosen to adopt a single categorization of costs, reporting results for direct cost, divided into medical and nonmedical direct cost when easily extractable, and indirect costs, plus any intangible costs listed, to end with the total annual cost per patient.

The distinction in direct medical and non-medical costs has not been reported in all studies, and there is no internationally shared classification; so, the cost components adopted in the individual studies have been variable. In health economics, the term "direct cost" refers to all costs, due to resource use, that are completely attributable to the use of a health care intervention or illness. Direct costs can be split into direct medical costs and direct non-medical costs. Direct medical costs include the cost of a defined intervention and all follow-up costs for other medication and health care interventions in ambulatory, inpatient and nursing care. All specialist and GP care, including emergency care, as well as rehabilitation and physiotherapy, are considered. Direct non-medical costs have been provided outside the medical care system and include, for instance: transportation costs, nursing home, home help, societal services costs and additional paid caregiver time.[38] The main direct cost items used have been: hospital admission, emergency visits, visits to physicians and other health care practitioners, nurse, tests, medications and outpatient care. Direct non-medical costs have been mainly associated with informal care and the use of informal services, aids, devices and investments for home adaptation. Informal care is defined as the performance of tasks by non-professional (typically parents or guardians) that help maintain or enhance patient independence.[39]

Informal care is associated with informal costs, which have been considered as cost outcome measures and extracted from studies. Informal costs refer to the amount of unpaid informal caregiver's time provided for care. Informal services are defined as the group of tasks or care provided by non-professional caregivers, who are often relatives but may also be friends or neighbours. Two main types of costs of informal care can be distinguished: out-of-pocket expenses, such as travel expenses, and time input of carers, also called

the objective burden of caregiving.[39,40] For informal costs' calculation, two main different methods are used: the replacement cost approach and the opportunity cost approach. The first one aims to assign a monetary value for informal care time based on the cost of care by professional caregivers (formal care). Instead, the opportunity cost approach is the value of the best forgone alternative for the informal caregiver; for example, lost leisure time or lost production. The included studies applied opportunity cost approach.

Indirect costs have been assessed as loss of productivity, which has been evaluated with different approaches, mainly with a human capital-based approach.[39,41,42]

As regards "intangible costs", in economic evaluations this term is used to indicate costs and consequences that are difficult to measure and monetise, although there is not always a clear consensus on what this encompasses.[43]

ELIGIBILITY

This review has included published cost of illness studies and economic evaluation conducted on Duchenne Muscular Dystrophy diagnosed patients and on their caregivers. We have considered studies following PRISMA-defined PICOS criteria:

- Participants: subjects with a diagnosis of DMD regardless of severity stage.
- Intervention: no specific type of treatment has been considered among inclusion criteria.
- Comparators: the main comparison is with the DMD patient's baseline data over time; the presence of a comparison cohort is considered admissible but not required for inclusion; if present, a comparison with a patient without DMD or with other disease has been allowed.
- Outcomes: the primary economic outcome evaluated is the total annual cost related to the disease, which consists of different cost components (direct medical-costs, direct non-medical costs, indirect costs, formal/informal costs, and intangible costs). In studies carrying out a stratification by cost subgroups, the main parameters considered for their effects on costs were age and disease severity stage.
- Studies: cost of illness and economic evaluation studies based on the analysis of DMD patients data (cross-sectional/prospective/retrospective observational studies including patients follow-up/medical records/registries/questionnaires or RCT) that can allow the extraction of an average total cost per patient during a specific period of time (eg one month, six months, one year etc.), normalized to total cost per patient per year; both societal and healthcare payer's (Medicare, NHS, National Health-care System) perspectives have been adopted for the inclusion.

SEARCH STRATEGY, SCREENING, AND DATA EXTRACTION

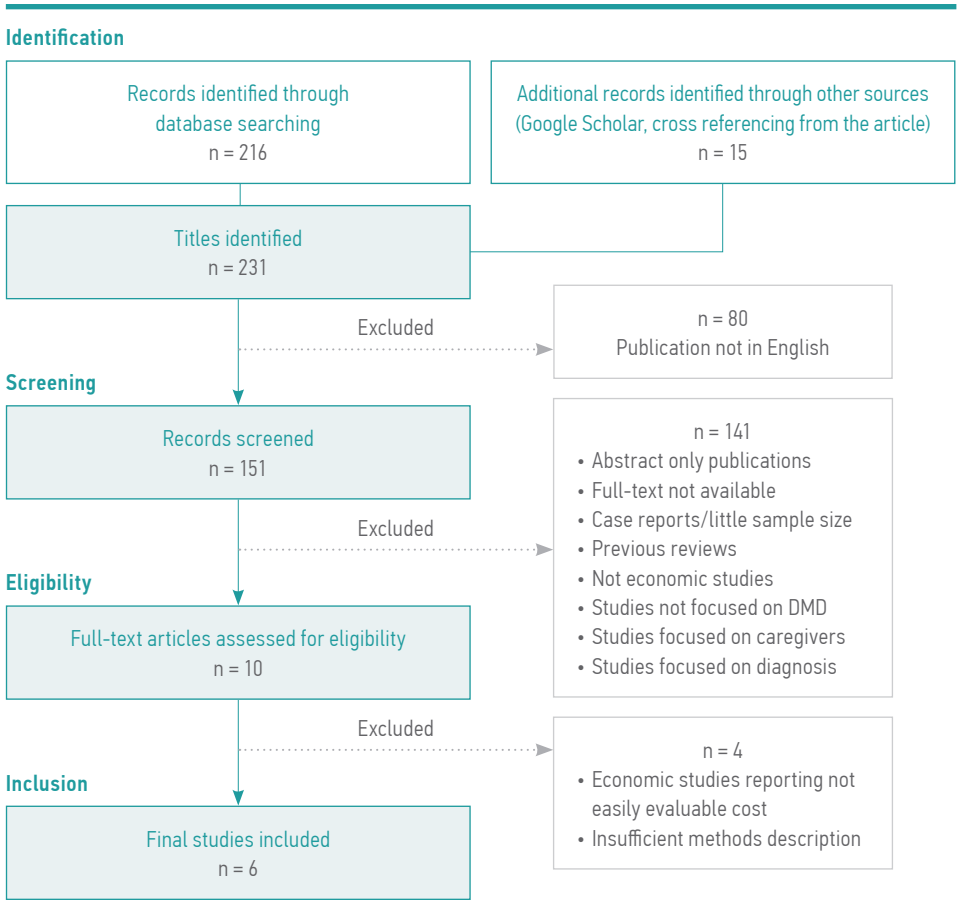
An electronic literature search about available articles meeting the inclusion criteria has been carried out using Medline (PubMed), the Cochrane Library and Google Scholar up to November 2019. In addition, cross-referencing from the articles found has been adopted to complete the search. The keywords used to search titles and abstracts were: Duchenne Muscular Dystrophy, cost of illness, economic impact, economic evaluation, cost analysis, burden of disease combined using the AND, OR Boolean operators. In the studies where multiple pathologies were included, we have extracted data related to DMD.

Case reports, purely descriptive studies, non-economic studies, studies not focused on DMD, studies focused on caregiver, studies focused on diagnosis and previous COI reviews (systematic or not) on this topic were excluded. Moreover, abstract-only publications were excluded due to lack of sufficiently detailed data (see Figure 1). Besides, economic studies reporting not easily evaluable cost and with insufficient methods' description were excluded (see Figure 1).

Only full text articles, published in English, were included.

Methodological quality of included studies has been

FIGURE 1
Flow diagram of the included studies' selection process: data identification, screening, eligibility and inclusion



evaluated using a quality assessment tool for economic evaluation, developed on the basis of a model described by Drummond et al and adapted to COI by Molinier et al Heterogeneity was not analysed and no quantitative pooling of data from these studies was undertaken. From all the articles that met the review criteria, basic information was extracted by an independent researcher and reported in summary tables created with Excel®. From each publication, the following data was extracted: authors, year of publication, country, study perspective, study design, population size, baseline characteristics (age, gender, disease severity, stratification by severity/age), cost evaluation methods (tools adopted to collect resource consumption and type of unit cost valuation) and cost items. For each study method used for DMD, severity evaluation was sought. Cost of complications was analysed as well, if included in study outcomes. In case studies offered subgroups analyses, we focused on changes in disease costs related to age and severity condition. For each study, we extracted costs per patient (or caregiver) related to the study period and the average total cost. To provide consistency in comparing results, we adopted an annual cost per patient as a summary measure. Studies characteristics' description, the main cost results extracted from the studies, and total annual cost for all population subgroups have been reported in summary tables. Because of methodological and clinical heterogeneity between studies, a narrative synthesis has been applied. Numbers of studies screened, assessed for eligibility, and included in the review have been reported with a flow diagram (Figure 1). Risk of bias assessment in the included studies was conducted at the outcome and study level; the internal and external validity have been texted. For each study, we have considered clarity and completeness in reporting information on study design and methods (description of design, setting, relevant dates). The sample size, patient's inclusion criteria, data

source and the level of precision in presenting results were the main aspects considered in the risk of bias assessment. Summary of descriptive statistics has been presented as mean ±standard deviation (SD) and n (%).

RESULTS

STUDY SELECTION

The study selection process is detailed in Figure 1. As shown in the flow diagram of the selection process below (Figure 1), 231 records were identified in the searching, through digital databases and, after the inclusion of additional records, through other sources (Google Scholar, cross-referencing from the articles). Eighty (80) texts were excluded because they were not published in English or because they were duplicates. Consequently, 151 abstracts were screened; 141 of these abstracts were considered not eligible, due to not meeting the inclusion criteria, mainly due to: abstract only publications, full-text not available, simple case report/descriptive analysis/previous reviews, non-economic studies or non-focusing on DMD, mainly focused on caregiver or treatment or diagnosis. Therefore, ten (10) full-text articles were assessed for eligibility. Six (6) articles were finally included in the review as four (4) did not meet the inclusion criteria (see Figure 1).[39,41,42,44,45,46]

INCLUDED STUDIES' CHARACTERISTICS

Five (5) studies were conducted from a societal perspective,[39,41,42,44,45] while only one adopted a healthcare payer's perspective.[46] The primary characteristics of the included studies are summarized in Table 1. Included DMD cost of illness studies were developed on the basis of observational data. For the observational studies included, data on DMD patient were provided from claims databases and surveys addressed to patients and/or their caregivers.

The six included studies were from the following countries: Germany (3),[39,41,45] USA (3),[41,44,46] Italy (2),[39,41] UK (2),[39,41] Australia (1),[42] Bulgaria (1),[39] France (1),[39] Hungary (1),[39] Spain (1),[39] Sweden (1).[39]

Two studies were multicentric and undertaken in more than one country.[39,41]

The size of the total population sample analysed in each study varied from a minimum of 75[46] to a maximum of 1,966[44]. As far as the multicentric studies are concerned, the total population sample has been obtained by numerical contributions varying between individual countries (min 2; max 284).

At the individual study level, depending on the different types of cost (direct, indirect and intangible), various sources have been adopted by questioning databases or individual patients with specific questionnaires.

The mean age varied among the studies; most of them showed a mean age in the range 12.2-14.8. The German study by Schreiber-Katz reported a median age of 11 (minimum age 1 and maximum 42).[45] Five (5) studies considered a stratification by severity and/or age.[39,41,42,45,46] All studies, except for the one conducted via the healthcare payer's perspective,[46] considered the impact of lost productivity and assistance provided by caregivers. Four (4) studies analysed patients' health related quality of life (HR-QoL) as well (see Table 1).[39,41,42,45]

COST ESTIMATES

Five (5) studies adopted a societal perspective, reporting at least direct costs and indirect costs;[39,41,42,44,45] moreover, in the study by Landfeldt et al,[41] intangible costs were reported as well. The healthcare payer's perspective has been considered in one included study, by Thayer et al,[46] and, in this case, direct costs have been analysed.

Table 2 summarizes the main cost results shown in the included studies.

DISCUSSION

The results of our systematic review allow confirming the substantial economic burden related to Duchenne Muscular Dystrophy. Our goal has been to collect the available evidence regarding DMD's cost of illness, in order to see what is missing, what common aspects

emerge, which are in contrast and understand why, and finally address choices and new future analyses.

Over the last few years, the attention paid to rare diseases and DMD has increased, and, consequently, more papers have been published on these issues. However, there still seem to be little awareness about the importance of managing these diseases in the best way to avoid a disease progression towards more serious and irreversible stages and to alleviate patients, caregivers and healthcare systems, being a worsening and debilitating disease that still lacks of a definitively resolutive cure.

In our analysis, six (6) studies have been included and it has been collected data from ten (10) countries, characterised by different healthcare systems. We have aimed to identify the annual cost per patient, focusing on disease severity stratification/age, and we have tried to analyse the impact of individual cost categories in order to identify the cost drivers of the disease and the differences/similarities between countries. Due to the lack of economic analyses based on randomized controlled trials, we have included observational retrospective studies assessing DMD's cost of illness. Cost simulation models lifelong based have been excluded to report real world economic data and try to reflect the real data as much as possible.

The included studies have shown results not always homogeneous, therefore not allowing generalizability, but useful to define general trends and to suggest possible improvements in the development of future economic studies. Some characteristics of the analysed studies influence cost estimates: type of healthcare system, study objectives, patient characteristics, included cost items and disease severity status/age. Therefore, comparison of the results can be achieved considering these specific elements.

The main outcome has been the annual mean cost of illness related to DMD, determined by the addition of cost items considered in each study in accordance with the perspective adopted. The main cost categorizations used have been direct (divided in medical and non-medical cost), indirect and intangible costs, if calculated. All the studies have reported total direct costs as the main cost item and highlighted the prominent role of direct non-medical costs on direct medical costs. It is noteworthy that the total direct cost for DMD patients has been reported up to sixteen (16) times higher than the mean per-capita health expenditure in the analysed countries (eg UK).[41] Among non-medical direct costs, the cost driver has been identified in informal care and in the investments necessary to assist patients as the illness progresses, highlighting increasing costs with disease severity progression. Informal care cost has shown a significant impact on total directs costs, although it varies between studies, up to 27% of the total DMD economic burden.[45]

The total direct annual cost reported in the studies has been in a range from a minimum of € 7657 for Hungary[39] up to a maximum of $ 54.270 in the USA.[41]

Indirect cost, measured as loss of productivity, has been an import cost item; a considerable variability has been reported in this case as well, due to different assessment methods, the quality of the analysis and characteristics of the population.

Intangible costs (costs due to pain, anxiety, social handicap, etc.), calculated only by Landfeldt's study,[41] have been estimated by assigning a monetary value to the loss in quality of life for patients and caregivers in relation to age and sex-specific mean quality of life in the general population.

Five (5) studies have considered the impact of disease progression and of DMD population's age on costs; this has been an important aspect to assess, given the nature of the disease and the growing needs for the patient with advancing age, loss of ambulation and other typical cardiovascular and respiratory complications. It emerged that the transition from stage I (early ambulatory with mild impairment) to stage III (non-ambulatory with confinement to bed) could result in a cost increase of more than five (5) times.[45] The increase in severity requests more assistance and special conditions to allow daily living activities; moreover, it leads to compli-

TABLE 1
Primary characteristics of included studies

Author	Year	Country	Perspective	Study design	Population size (n)	Age
Landfeldt	2014	Multicentric Germany Italy UK USA	Societal	Cross-sectional international observational study, data from online questionnaire addressed to patients entered in national DMD registries which form part of in TREAT-NMD network	770 Germany = 173 Italy = 122 UK = 191 USA = 284	 13 12 12 12
Larkindale	2014	USA	Societal	Retrospective observational study, Commercial and Medicare claims data for direct medical cost and cost of illness surveys for nonmedical cost and indirect cost	199 Medicare recors 1,966 Commercial plan 131 COI survey responses	-
Schreiber-Katz	2014	Germany	Societal	Cross-section retrospective observational study, data from German dystrophinopathy registry	248 patient/parent pairs	Median: 11 min: 1 ma: 42
Cavazza	2016	Multicentric Bulgaria France Germany Hungary Italy Spain Sweden UK	Societal	Cross-section observational international retrospective study, data from questionnaire completed by patients and their caregivers	268 patients/154 caregivers 14; 6 2; 2 25; 11 57; 28 87; 61 58; 33 7; 3 18; 10	 23.9 17 13.1 12.1 13.5 16.2 11.3 21.1 70% - 2/17 y
Thayer	2017	USA	Healthcare payer	Cross-section observational international retrospective study, data from claims database and enrollment information from health plan	DMD cohort n = 75 control cohort n = 750	13.1
Teoh	2016	Australia	Societal	Cross-section observational international retrospective study, data from surveys addressed to households with DMD child	104 households with DMD child	13.3

cations and it causes hospitalizations, resulting in an increase in direct costs. In Teoh's study,[42] the highest health costs have been largely driven by overnight hospital admissions related to a few major surgical procedures, respiratory conditions, and cardiac complications. These admissions contributed to 78% of the total hospital cost in this population; in this case, 10% of the individuals accounted for approximately 51% of the total healthcare costs for this population.[42] Considering these aspects is important, since DMD patients needed in-patient treatments at an average age of 14 years, osteoporosis occurs early in DMD and requires treatment in 39%, DMD patients became full-time wheelchair bound at the age of 14-15 years and 50% in stages IV and V use an invasive or non-invasive ventilator device.[45]

Based on the information gathered from the included studies, it is possible to define the main cost items that affect the total cost of the disease.

A first aspect concerns the duration of the illness since, with the progression of severity, complications increase and autonomy is reduced; in this view, it is important

Stratification by severity/age		Loss productivity	Cost analysis for caregiver	QoL evaluation	
Yes/No	Severity status			Yes/No	Measure
Y	Ambulation status and age 4 groups early ambulatory (5-7 y), late ambulatory (8-11 y), early nonambulatory (12-15 y), late nonambulatory (≥16 y)	Y	Y	Y	Health Utilities Index
N	-	Y	Y	N	-
Y	Stage I, n: 49 pairs Stage II, n: 70 pairs Stage III, n: 11 pairs Stage IV, n: 92 pairs Stage V, n: 26 pairs	Y	Y	Y	PedsQL
N	Age subclassification children (age <18 y) adult (≥18 y)	Y	Y	Y	EQ- 5D
	Age subclassification 0-7 y 8-13 y 14-17 y 18-29 y	N	N	N	-
	Age subclassification 0-4 y 5-14 y 15-24 y 25-34 y	Y	Y	Y	PedsQL

to consider the role of early diagnosis, which allows to face the disease course immediately. This first aspect is correlated to the other, corresponding to cost items determined by the progress of disease severity: loss of ambulation, need for a wheelchair and for home/car wheelchair adaptation, need for monitoring of cardiac and respiratory functions, surgical operations, need for invasive or non-invasive ventilator device. These issues accompany with an increase in direct healthcare costs, due to a greater consumption of resources, in non-medical costs, and, as evidenced, in particular in costs for informal assistance and investments in home adaptation.

Despite the variability in costs ranges among studies, it is possible to identify common trends (Table 2). All studies have reported a substantial economic burden related to DMD, highlighting the many different costs that accompany a rare condition, such as DMD, and a significant economic impact on families and society, often underestimated, in addition to healthcare costs.

The total annual cost of DMD, including direct and in-

TABLE 2
Main cost results from the included studies

Study	Cost items Summary	Currency		Main cost results Annual cost per patient in general population or in subgroups (severity stage, age)							
				Germany	*Italy*	*UK*	*USA*				
Landfeldt 2014	Direct cost	$	2012	42,360	23,920	54,160	54,270				
	Indirect cost			20,770	18,220	18,700	21,550				
	Total annual costs			63,140	42,140	72,870	75,820				
	Intangible cost			45,860	37,980	46,080	45,080				
	Total burden			**109,000**	**80,120**	**118,950**	**120,910**				
Larkindale 2014	Direct medical cost	$	2010	22,533							
	Direct nonmedical cost			12,939							
	Indirect cost			15,481							
	Total annual costs			**50,952**							
Schreiber-Katz 2014				*Mean*	*Stage I*	*Stage II*	*Stage III*	*Stage IV*	*Stage V*		
	Direct medical cost	€	2013	19,346	4,220	7,629	11,666	22,989	68,968		
	Direct nonmedical cost			30,884	11,646	10,684	29,238	49,834	62,980		
	Total direct cost			50,230	15,866	18,313	40,904	72,823	131,948		
	Indirect cost			28,683	13,078	14,955	8,046	25,778	32,907		
	Total annual costs			**78,913**	**28,944**	**33,268**	**48,950**	**98,601**	**164,855**		
Cavazza 2016				*Bulgaria*	*France*	*Germany*	*Hungary*	*Italy*	*Spain*	*Sweden*	*UK*
	Direct medical cost	€	2012	2117	19797	19779	808	9744	8954	9940	3887
	Direct nonmedical cost			6094	38907	35492	6849	31518	25154	33920	30771
	Total direct cost			8210	58704	55270	7657	41262	34108	43860	34658
	Indirect cost			956	-	-	-	285	495	-	-
	Total annual costs	*All population*		**9166**	**58,704**	**55,270**	**7657**	**41,547**	**34,606**	**43,860**	**34,658**
Subgruop analysis	**Total annual costs**	*Children*		**16,934**	**67,495**	**40,741**	**8454**	**34,543**	**36,970**	**60,003**	**41,130**
	Total annual costs	*Adult*		**4850**	**49,913**	**101,278**	**1963**	**63,559**	**29,892**	**3502**	**29,480**
Thayer 2017	Total direct cost	$	2010		*DMD*	*Control*					
				All ages	24,017	1,752					
				1-13 y	23,005	2,277					
				14-29 y	40,132	2,746					
Teoh 2016				*All ages*	*0-4 y*	*5-14 y*	*15-24 y*	*25-34 y*			
	Direct medical cost	AU$	2014	10,046	5,672	7,587	15,808	3,681			
	Direct nonmedical cost			33,557	21,523	18,955	50,909	95,404			
	Indirect costs			3,008	1,288	4,256	1,487	1,338			
	Total annual cost			**46,669**	**28,482**	**30,947**	**68,205**	**100,603**			

direct costs, has been shown to vary from a minimum of € 7657 in Hungary to a maximum of $ 75,820 in the USA, as reported in the studies by Cavazza et al[39] and by Landfeldt et al[41] respectively. These two studies are cross-sectional international observational retrospective studies and have involved four (4) (Germany, Italy, UK, USA) and eight (8) countries (Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden, UK), respectively. Germany, Italy and the UK have been included in both studies. The total cost (direct and indirect) of DMD in Germany, in Italy and in the UK have been equal to $ 63,140, $ 42,140 and $ 72,870 in Landfeldt's study,[41] while the study by Cavazza et al[39] has reported a total cost of € 55,270, € 41,547 and € 34,658 in Germany, in Italy and in the UK. These results are almost comparable for Germany, but less for Italy and, least of all, for the UK. Regarding France, Bulgaria, Spain and Sweden, Cavazza's study[39] has reported a total cost of about € 58,704, € 9166, € 34,606 and 43,860. The total cost of DMD in Germany and in the USA has been evaluated also in two other country-specific included studies and it has been shown equal to € 78,913 for Germany[45] and

$ 50,952 for the USA.[44] Moreover, the total annual cost in Australia has been reported by Teoh et al[42] and it has amounted to AU$ 46,669. Finally, the only included study conducted in the healthcare payer's perspective has presented total direct costs equal to $ 24,017 in the USA.[46] This total direct medical cost is a partial cost of illness, but resulted in line with the direct medical costs reported in the study by Larkindale et al ($ 22,533).[44] The average annual total costs, just reported, refer to the entire population adopted in the included studies; however, all of them, except for Larkindale et al,[44] have considered the cost effects on population subgroups stratified by state of severity or age.

As reported in Table 2, this type of analysis has evidently highlighted how the cost of the disease grows with increasing clinical severity and with the age of DMD patients. The total cost has been shown more than five times higher in the transition from stage I to V in Schreiber-Katz's study[45] and more than tripled comparing the age range 0-4 y with the age range 25-34 y in Teoh's study.[42]

Regarding individual cost categories' analysis, studies conducted according to the societal perspective have highlighted the significant impact of non-medical direct costs on the total cost of illness and, within the category the important role of informal cost, that has been expensive in all countries. All the studies developed from the societal perspective have reported a breakdown into healthcare direct medical costs, non-medical costs and indirect costs, with the exception of the study by Landfeldt et al,[41] where no specific distinction has been made between medical and non-medical direct costs categorization; however, all individual items referring to direct costs have been clearly reported to obtain a total direct cost, in addition to indirect and intangible costs. In this study, the largest individual cost component has been indirect costs in Germany, in Italy and in the United States and non-medical community services in the United Kingdom. However, assuming to add the single cost items pertaining to the category of direct healthcare medical costs, on the one hand, and those attributable to non-medical costs, on the other hand, within the macro category of the direct rights, also in this study the significant impact of the category of non-medical costs would be shown. In all the included studies, non-medical costs have been driven by informal care, aids and investments to move or adapt housing/vehicle (eg home renovations/modifications carried out to accommodate for their child's changing needs, purchase/adaptation of the home/vehicle for wheelchair access). In the included studies, it has been reported that most of the patients needed a carer, requiring informal assistance and causing loss of productivity for families. Indirect costs, calculated as loss of family income, have also shown an important impact and tend to increase with increasing severity, directly influenced by the level of informal care needed by the patients.

The study by Schreiber-Katz et al[45] has reported that indirect costs and informal care have caused 36% and 27% of total DMD economic burden. In all the studies, the total direct costs have represented the major cost component in the definition of the total cost of the disease and, within the category, non-medical direct costs are the main component.

To conclude, the findings of this review have been consistent with previous ones,[10,34] that had already considered DMD's cost of illness, but, compared to those, we have collected more and more recent evidences and we have highlighted the impact of individual cost components and disease progression on disease burden, offering an update and a search space, including studies from ten (10) countries and providing the identification of important cost driver.

LIMITATIONS

Our review has some limitations; it is to be noted that incidence-based economic models reporting lifetime costs have been excluded, such as studies analysing primarily cost of disease and informal care focusing on caregivers or considering muscular dystrophies in general. In addition, all articles not published in English have been excluded; for a comprehensive understand-

ing of DMD's cost of illness, the results of these studies might provide useful insights. Further limitations stay in the study design of the included studies, consisting in observational analyses presenting potential risk of selection bias in included patients and potential errors in data collection and patient responses, since input data have been collected from claims database or questionnaires addressed to patients/caregivers. Moreover, the sample size and the different populations considered didn't allowed pooled metanalysis.

CONCLUSIONS

The variation of cost estimates for different studies and countries highlights the need to clearly understand and address the financial burden of DMD disease. The need to improve economic assessments in the field of rare diseases, and, in particular, in DMD has been recently highlighted and some criticisms have been conducted by expert opinions regarding methods, development, exposure and evaluation of studies in literature.[47,48,49]

On the basis of the research conducted to carry out this review, we believe it is necessary that future cost-of-illness studies in DMD should follow a quality standard protocol with transparent and clearly defined cost components and separate estimates by disease severity and age, given the role of these aspects as cost driver.

DMD is a rare disease, and the increasing number of DMD trials is a challenge for clinical trial capacity because of the low numbers of patients who qualify for participation. The need to optimize patient recruitment is expected to promote initiatives supporting trial readiness, such as patient registries, identification of clinically significant outcome measures and natural history studies.[1] At the moment, there is no definitive cure for DMD; standard treatment options focus on the alleviation of symptoms and on the management of complications. However, nowadays, some orphan drugs, capable of slowing down the course of the disease by acting on genetic causes, are available. Although involving different therapeutic mechanisms, these interventions generally aim to reduce, halt, or reverse the rate of muscle degeneration, thereby delaying time to key disease milestones, including the loss of independent ambulation and the need of ventilation support for survival. However, these treatments are characterized by high costs that limit access and availability. Indeed, the role of economic evaluations, the development of analyses that test the effects of postponement of mortality and the improvement of the quality of life are fundamental to make the sustainability of new treatments.

DECLARATIONS

Ethics approval and consent to participate: NOT APPLICABLE

Consent for publication: NOT APPLICABLE

Data availability: NOT APPLICABLE

Funding: NOT APPLICABLE

Competing interests: NOT APPLICABLE

Authors' contributions: GLC supervised the review and the final paper, GMB and CM researched and prepared the review and the paper, SDM supervised all the comparison done in the review from statistical point of view.

Acknowledgements: NOT APPLICABLE

ABBREVIATIONS

DMD: Duchenne Muscular Dystrophy
LOA: loss of ambulation
CS: corticosteroid
FDA: Food and Drug Administration
COI: cost of illness
CRD: centre for reviews and dissemination
PRISMA: preferred reporting items for systematic reviews and meta-analyses
PICOS: population, intervention, comparators, outcome and study design
RCT: randomized controlled trial
NHS: national health service
SD: standard deviation
HR-QoL: health-related quality of life
GP: general practitioner

REFERENCES

1. Birnkrant DJ, Bushby K, Bann CM et al. *Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management.* Lancet Neurology. March 2018; 17(3): 251–267.
2. Landrum Peay H, Fischer R, Tzeng JP, et al. (2019) *Gene therapy as a potential therapeutic option for Duchenne muscular dystrophy: A qualitative preference study of patients and parents.* PLoS ONE 14(5): e0213649. https://doi.org/10.1371/journal.pone.0213649.
3. Passamano L, Taglia A, Palladino A, et al. *Improvement of survival in Duchenne Muscular Dystrophy: retrospective analysis of 835 patients.* Acta Myol. 2012 Oct;31(2):121-5.
4. Mendell JR, Shilling C, Leslie ND, et al. *Evidence-based path to newborn screening for Duchenne muscular dystrophy.* Ann Neurol. 2012; 71:304–13.
5. Moat SJ, Bradley DM, Salmon R, Clarke A, Hartley L. *Newborn bloodspot screening for Duchenne muscular dystrophy: 21 years experience in Wales (UK).* Eur J Hum Genet. 2013; 21:1049–53.
6. https://www.osservatoriomalattierare.it/distrofia-di-duchenne-che-cose. Distrofia Muscolare di Duchenne, tutta colpa di un gene. Diagnosi, terapie e prospettive future.
7. Ciafaloni E, Fox DJ, Pandia S, et al. *Delayed diagnosis in duchenne muscular dystrophy: data from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet).* 2009 J Pediatr, 155, 380-5.
8. Van Ruiten HJ, Straub V, Bushby K, et al. *Improving recognition of Duchenne muscular dystrophy: a retrospective case note review.* Arch Dis Child; 2014, 99, 1074-7.
9. Magri F, Govoni A, D'Angelo MG, et al. *Genotype and phenotype characterization in a large dystrophinopathic cohort with extended follow-up.* J Neurol. 2011;258(9):1610–23.
10. Ryder S, Leadley RM, Armstrong N et al. *The burden, epidemiology, costs and treatment for Duchenne muscular dystrophy: an evidence review.* Orphanet Journal of Rare Diseases, 2017;12,79.
11. Van Ruiten HJ, Marini Bettolo C, Cheetham T, et al. *Why are some patients with Duchenne muscular dystrophy dying young: An analysis of causes of death in North East England.* Eur J Paediatr Neurol. 2016 Nov;20(6):904-909.
12. Falzarano MS, Scotton C, Passarelli C, et al. *Duchenne Muscular Dystrophy: From Diagnosis to Therapy. Molecules*; 2015, 20, 18168-84.
13. Mercuri E, Muntoni F. *Muscular dystrophies.* Lancet. 2013 Mar 9;381(9869):845-60.
14. Verma S, Anziska Y, Cracco J. *Review of Duchenne muscular dystrophy (DMD) for the pediatricians in the community.* 2010 Clin Pediatr (Phila), 49, 1011-7.
15. McDonald CM, Henricson EK, Abresch RT, et al. *Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study.* Lancet. 2018 Feb 3;391(10119):451-461.
16. Archer JE, Gardner AC, Roper HP, et al. *Duchenne muscular dystrophy: the management of scoliosis.* 2016 J Spine Surg 2, 185-194.
17. Humbertclaude V, Hamround D, Bezzou K, et al. *Motor and respiratory heterogeneity in Duchenne patients: implication for clinical trials.* 2012 Eur J Paediatr Neurol, 16, 149-60.
18. Rall S, Grimm T. *Survival in Duchenne muscular dystrophy.* Acta Myol. 2012 Oct;31(2):117-20.
19. Birnkrant DJ, Bushby K, Bann CM, et al. *Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management.* Lancet Neurol. 2018 Apr; 17(4):347-361.
20. Bushby K, Finkel R, Birnkrant DJ et al. *Diagnosis and management of Duchenne muscular dystrophy, part*

1: diagnosis, and pharmacological and psychosocial management. Lancet Neurology. 2010 Jan;9(1):77-93.

21. Otto C, Steffensen BF, Højberg AL, et al. *Predictors of Health-Related Quality of Life in boys with Duchenne muscular dystrophy from six European countries.* J Neurol. 2017; 264(4):709–23.

22. Uzark K, King E, Cripe L, Spicer R, Sage J, Kinnett K, et al. *Health-related quality of life in children and adolescents with Duchenne muscular dystrophy. Pediatrics.* 2012.

23. de Moura MC, Wutzki HC, Voos MC, et al. *Is functional dependence of Duchenne muscular dystrophy patients determinant of the quality of life and burden of their caregivers?* Arq Neuropsiquiatr. 2015 Jan;73(1):52-7.

24. Magliano L, D'Angelo MG, Vita G, et al. *Psychological and practical difficulties among parents and healthy siblings of children with Duchenne vs. Becker muscular dystrophy: an Italian comparative study.* Acta Myol. 2014 Dec;33(3):136-43.

25. Bushby K, Finkel R, Birnkrant DJ, et al. *Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care.* Lancet Neurology 2010; 9:177-89.

26. Politano L, Scutifero M, Patalano M, et al. *Integrated care of muscular dystrophies in Italy. Part 1. Pharmacological treatment and rehabilitative interventions.* Acta Myol. 2017 Mar;36(1):19-24.

27. Kieny P, Chollet S, Delalande P, et al. *Evolution of life expectancy of patients with Duchenne muscular dystrophy at AFM Yolaine de Kepper centre between 1981 and 2011.* Ann Phys Rehabil Med. 2013;56(6):443–54.

28. Henricson EK, Abresch RT, Cnaan 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.

29. Reinig AM, Mirzaei S, Berlau DJ. *Advances in the Treatment of Duchenne Muscular Dystrophy: New and Emerging Pharmacotherapies.* Pharmacotherapy 2017;37(4):492–499.

30. McDonald CM, Campbell C, Torricelli RE, et al. *The Clinical Evaluator Training Group and the ACT DMD Study Group. Ataluren in patients with nonsense mutation Duchenne muscular dystrophy (ACT DMD): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial.* Lancet. 2017; 390:1489–98.

31. Mendell JR, Goemans N, Lowes LP, et al. *The Eteplirsen Study Group and Telethon Foundation DMD Italian Network. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy.* Ann Neurol. 2016; 79:257–71.

32. Niks EH, Aartsma-Rus A. *Exon skipping: a first in class strategy for Duchenne muscular dystrophy.* Expert Opin Biol Ther 2017; 17:225–36.

33. Kinane TB, Mayer OH, Duda PW, Lowes LP, Moody SL, Mendell JR. *Long-Term Pulmonary Function in Duchenne Muscular Dystrophy: Comparison of Eteplirsen-Treated Patients to Natural History.* J Neuromuscul Dis. 2018;5(1):47-58.

34. Angelis A, Tordrup D, Kanavos P, et al. *Socio-economic burden of rare diseases: A systematic review of cost of illness evidence.* Health Policy. 2015 Jul;119(7):964-79.

35. D. Rice *Cost of illness studies: what is good about them?* Injury Prevention, 6 (2000), pp. 177-179

36. Centre for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking reviews in healthcare.* 3rd ed. 2009.

37. Moher D, Liberati A, Tetzlaff J, et al. *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* PLoS Med. 2009 Jul 21;6(7): e1000097.

38. Kirch W. *Encyclopedia of Public Health: Volume 1: A - H Volume 2: I - Z* Springer Science & Business Media, 2008.

39. Cavazza M, Kodra Y, Armeni P, et al. *Social/economic costs and health-related quality of life in patients with Duchenne muscular dystrophy in Europe.* Eur J Health Econ. April 2016; 17 Suppl 1:19-29.

40. Hoefman, R.J., van Exel, J. & Brouwer, W. *How to Include Informal Care in Economic Evaluations.* PharmacoEconomics 31, 1105–1119 (2013).

41. Landfeldt E, Lindgren P, Bell CF, Schmitt C, Guglieri M, Straub V, Lochmüller H, Bushby K. *The burden of Duchenne muscular dystrophy: an international, cross-sectional study.* Neurology, 2014.

42. Teoh LJ, Geelhoed EA, Bayley K, Leonard H, Laing NG. *Health care utilization and costs for children and adults with duchenne muscular dystrophy.* Muscle & Nerve, 2015.

43. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health care Programmes*, 4th ed.; Oxford Univ Press: Oxford, UK, 2015; ISBN 0191643580.

44. Larkindale J, Yang W, Hogan PF, Simon CJ, Zhang Y, Jain A, Habeeb-Louks EM, Kennedy A, Cwik VA. *Cost of illness for neuromuscular diseases in the United States.* Muscle & Nerve, 2014.

45. Schreiber-Katz O, Klug C, Thiele S, Schorling E, Zowe J, Reilich P, Nagels KH, Walter MC. *Comparative cost of illness analysis and assessment of health care burden of Duchenne and Becker muscular dystrophies in Germany.* Orphanet Journal of Rare Diseases. (2014) 9:210-3.

46. Thayer S, Bell C, McDonald CM. *The Direct Cost of Managing a Rare Disease: Assessing Medical and Pharmacy Costs Associated with Duchenne Muscular Dystrophy in the United States.* Journal of Managed Care + Speciality Pharmacy, 2017.

47. Mercuri E, Baranello G, Battini R, Berardinelli A, Bertini E, Bruno C et al. *Registries versus tertiary care centers: how do we measure standards of care in Duchenne muscular dystrophy?* Neuromuscul Disord. 2016; 26: 261-263.

48. Landfeldt E et al. *Compliance to care guidelines for Duchenne muscular dystrophy in Italy.* Neuromuscular Disorders 28 (2018) 100.

49. Landfeldt E. *Extending Life in Duchenne Muscular Dystrophy: Implications for Appraisals of Cost-Effectiveness.* PharmacoEconomics - Open (2019) 3:279–280.

www.makinglife.it | info@makinglife.it