PCR183

Diagnosis, treatment and the burden of disease for Duchenne muscular dystrophy (DMD) in females: A targeted literature review (TLR)

Raúl Juntas Morales, MD, PhD;[1] Alessandra Ferlini, MD, PhD;[2] Florencia Giliberto, PhD;[3] Igor Beitia Ortiz de Zarate, PhD;[4] Sara Graziadio, PhD, Mphil;[5] Mary Edwards, BA, MA;[5] Mick Arber, BA, MA;[5] Iria Nieto Vázquez, PhD;[6] Ioannis Tomazos, PhD, MBA;[7] Paul Castellano, PharmD, MBA;[7] Rongrong Zhang, MSc;[8]

[1] Vall d'Hebron University Hospital. Vall d'Hebron Institut de Recerca (VHIR).Barcelona. Spain;[2] Medical Genetics Unit, University of Ferrara, Ferrara, Italy; [3] Laboratorio de Distrofinopatías, Cátedra de Genética, FFyB-UBA; INIGEM UBA-CONICET, Buenos Aires, Argentina; [4] PTC Therapeutics France SAS, 41-43 rue Pergolèse, F-75116 Paris, France;[5] York Health Economics Consortium, York, UK; [6] PTC Therapeutics Spain S.L . Paseo de la Castellana nº 135, 6th floor, 28046, Madrid, Spain;[7] PTC Therapeutics Inc, 500 Warren Corporate Center Drive, Warren, N.J. 07059, USA;[8] PTC Therapeutics Sweden AB, Askim, Sweden

1. Background & Objectives:

Duchenne muscular dystrophy (**DMD**) is caused by **mutations in the DMD gene**, leading to a lack of functional dystrophin protein. → Results in progressive **muscle weakness** and **premature death** due to cardiorespiratory complications.[1]

DMD is inherited in an X-linked recessive pattern and thereby **predominantly affects males**.[1] Female carriers typically do not present with symptoms due to the presence of an unmutated DMD gene on their other X chromosome.[2]

New recommendations have been proposed to limit the term "*DMD*-carrier" to describe asymptomatic females, while symptomatic individuals are termed 'patients with dystrophinopathy'.[5]

2.5%-10% of females heterozygous for a DMD pathogenic variant develop symptoms, ranging from muscle cramps to severe muscle weakness.[3,4]

- Although some female *DMD*-carriers are symptomatic, research primarily focuses on males; guidelines for managing DMD in females focus on access to testing, with no treatment recommendations.
- The use of medications (including corticosteroids, ACE inhibitors, and ataluren[6,7]) and other care strategies for female *DMD*-carriers or patients with DMD dystrophinopathy are not well established.[8,9] There remains a need to determine the best identification strategies and therapies for female carriers and patients.

A targeted literature review (TLR) was conducted to characterize the burden and management of female *DMD*-carriers and female patients with DMD dystrophinopathy

2. Methods:

Search strategy and study selection

- A search was conducted in June 2023 in:
  - MEDLINE(R) ALL
  - Cochrane Database of Systematic Reviews (CDSR)
  - Cochrane Central Register of Controlled Trials (CENTRAL)
  - HTA Database
  - Epistemonikos
  - Embase
  - Conference Proceedings Citation Index – Science (CPCI-S)
  - ClinicalTrials.gov
- Searches identified studies published in any language in the last 10 years.
  - MEDLINE strategy comprised two concepts: DMD AND females. Variant terms were included for each concept. The MEDLINE strategy was restricted to studies published in any language in the last 10 years
  - The MEDLINE strategy was translated appropriately for the other resources searched.
- All retrieved records were screened against the PICOS criteria (**Figure 1**) for eligibility.

Figure 1. Summary of PICOS criteria.

Population*
Female *DMD*-carriers (without dystrophinopathy), female patients with DMD dystrophinopathy, and females considered at risk of carrying a heterozygous pathogenic variant for DMD

Interventions/Comparators
For studies of treatment outcome: ataluren, other pharmaceutical treatments. For other studies: No limitations or restrictions were applied for intervention/comparator.

Outcome
One or more of the following outcomes: burden of disease, diagnostic pathways in clinical practice, treatment pathways, treatment outcomes.

Study design
Any study designs were eligible, including case series and case reports. Preprints, editorials and news items, SLRs, narrative reviews, and conference abstract only were not eligible.

Abbreviations: DMD = Duchenne muscular dystrophy; SLR = systematic literature review.
*Studies in mixed populations, where no separate results were reported for the subgroup of female *DMD*-carriers or female patients with DMD dystrophinopathy, were not eligible for inclusion in the review unless 80% or more of the study population met the review's eligibility criteria. Studies that did not report the gender of the participants in the title or abstract were excluded at title and abstract screening but were tagged as 'gender NR'

Data extraction and synthesis

- Newer papers (**2015-2023**) reporting on higher numbers of patients, with either detailed data or >1 outcome reported, were prioritised for extraction.
- Key guidelines were also synthesised
- Methods and results of each study were summarised in outcome categories including burden of disease (cardiac, muscular, cognitive) and disease management (diagnosis and treatment).
  - Where separate data are available for female DMD-carriers and female patients with DMD dystrophinopathy, these patient groups are reported separately.

.

4. Discussion & Conclusions:

Findings from this review highlight the considerable disease burden for female patients with DMD dystrophinopathy and *DMD*-carriers, especially cardiac issues and muscular and/or cognitive difficulties.

Given the broad scope of the review, evidence was captured describing previously undiagnosed cardiac, muscular, and cognitive issues among female carriers, aligning with new definitions from the European NeuroMuscle Centre and emphasizing the clinical significance of these findings.

Some studies compared female carriers with non-carriers or a healthy control population, providing valuable comparative data.

However, the evidence base was limited by sparse reporting of baseline characteristics and study population selection processes; as such, the representativeness of the study samples is challenging to assess relative to the general female *DMD*-carrier population.

Data on diagnostic pathways used was also limited, and pathways followed did not always reflect best practice.

Due to their low patient numbers, case reports were not extracted as part of this review, even though these types of publications appear to provide the best (albeit limited) available evidence on treatment pathways for female patients with DMD dystrophinopathy.

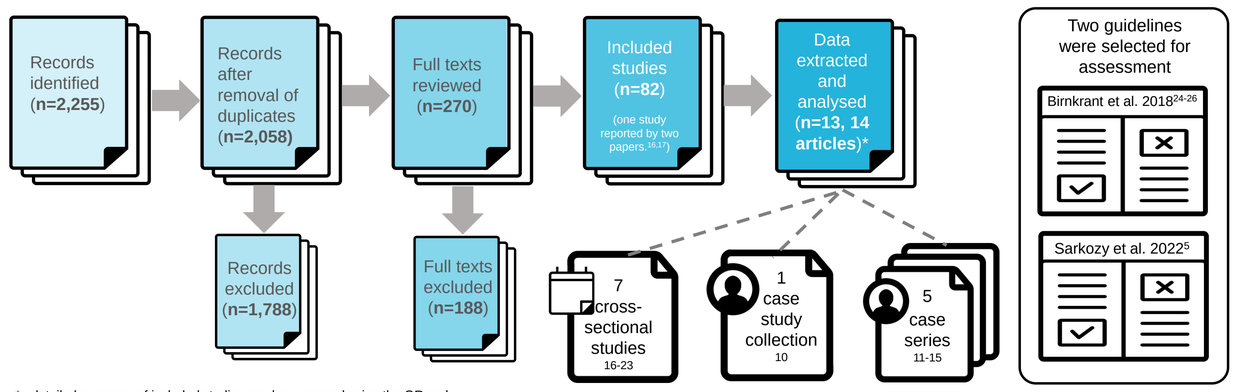
Future efforts could include extracting and analysing case reports to fill existing data gaps.

Despite being under-investigated, a considerable proportion of female DMD carriers have high disease burden, particularly in terms of cardiac issues, as well as muscular and/or cognitive deficits.

- Additional research is needed to fill the substantial gap in the literature to characterize this population.
- Primary studies should be targeted to better understand the quality of life, mortality, and burden of disease in females, as well as the efficacy and safety of available treatments.

3. Results:

Study characteristics



*a detailed summary of included studies can be accessed using the QR code

Summary of guidelines

- Guidelines emphasise genetic counselling, testing, cardiac surveillance, providing resources to help carriers communicate their diagnosis to family members and potential newborn screening due to emerging therapies.[5,24-26]
  - Both Sarkozy 2022;[5] Birnkrant 2018[24-26]: recommend regular cardiac and neuromuscular assessments for female *DMD*-carriers.
  - Sarkozy 2022[5]: heart medications should begin as soon as left ventricular dysfunction is found regardless of symptoms; use of ACE inhibitors or angiotensin receptor blockers to manage high blood pressure, reduce the risk of cardiomyopathy.

Burden of disease

Cardiac burden findings

- Cardiac outcomes were common in female carriers; cardiac abnormality rate (variously defined) was 50% to 100% among 90 carriers across 4 studies; whether cardiac symptoms were treated was largely unreported (**Table 1**).

Table 1. Summary of studies reporting cardiac outcomes

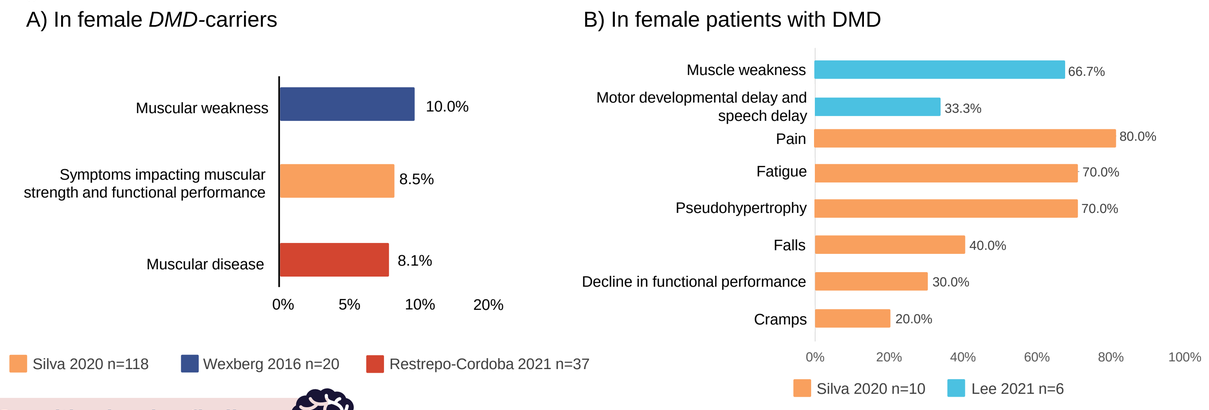
Author, year	Population	Description of cardiac finding
Female *DMD*-carriers		
Restrepo-Cordoba 2021[13]	N = 37 (without severe skeletal myopathy)	**32.4%** with dilated cardiomyopathy diagnosed by ECG and echocardiography
Solheim 2021[22]	N = 33	**69.7%** with DMD specific cardiac abnormality diagnosed by ECG
Schelhorn 2015[20]	N = 15 (asymptomatic)	**100%** with cardiac abnormalities diagnosed by MRI
Wexberg 2016[15]	N = 20; 17 (85%) were clinically asymptomatic	**65%** with abnormal ECV values diagnosed by MRI
Lang 2015[19]	N = 22 (symptomatic or asymptomatic)	**50%** with self-reported cardiovascular symptoms **35%** with LGE diagnosed by MRI
MUNI/A/1493/2018[16,17]	N = 44 (asymptomatic)	**Systolic parameters significantly different** in comparison with the age matched healthy controls on echocardiogram **LV diastolic parameters were significantly different** in comparison with the age-matched healthy controls on echocardiogram
Shehta 2021[21]	N = 25 (mothers or female relatives of male DMD patients)	**Trans-thoracic echocardiography** and **12 lead ECG findings were significantly different** from healthy controls
Girls with DMD		
Lee 2021[12]	N = 6 (had elevated CK levels later diagnosed with DMD or DMD/BMD)	**0%** with abnormal findings on echocardiogram

Abbreviations: BMD=Becker muscular dystrophy; CK=creatine kinase; DMD=Duchenne muscular dystrophy; ECG=electrocardiogram; ECV=extracellular Volume; LGE=late gadolinium enhancement; LV=left ventricular; MRI=magnetic resonance imaging

Muscular burden findings

- Among female carriers, 8-10% had muscle symptoms (2 studies) (**Figure 3**).
- Among female patients with DMD, muscle symptoms were common and varied from muscle weakness to falls and motor developmental delays (**Figure 3**).

Figure 3. Prevalence of muscular burden



Cognitive burden findings

- Two studies, both using cognitive assessment tools in female carriers and non-carriers, described reduced cognitive performance on some sub-domains among carriers relative to non-carriers (**Table 2**).

Table 2. Summary of studies reporting cognitive outcomes for *DMD*-carrier mothers

Author, year	Population	Summary of cognitive findings
Thangarajh 2019[23]	N=11* biological mothers of children with DMD who are *DMD*-carriers N=8* biological mothers of children with DMD who are non-*DMD*-carriers	**Non-carrier mothers scored significantly better on all NIHTB-CB cognitive task measures compared to carriers**, including: • Attention (Cohen's d score**: 1.2), • Episodic memory (Cohen's d score: 0.5), • Processing speed (Cohen's d score: 0.1), • Reading (Cohen's d score: -0.7), • Fluid cognition composite score) Cohen's d score: -0.7), • Crystalized cognition composite score (Cohen's d score: -0.7), and • Total composite score (Cohen's d score: -1.0).
Demirci 2020[18]	N= 31 *DMD*-carrier mothers of patients with DMD	**Controls performed better on all cognitive outcome measures compared to carrier mothers**, including MMSE (p=0.007), attention (p=0.005), language (p=0.006), verbal memory (p=0.006 to p<0.001), visuospatial functions (p=0.001), and executive functions (p=0.013 to p<0.001)

Abbreviations: DMD = Duchenne muscular dystrophy; MMSE = Mini mental state examination
*Note that N of 11 and 8 are uncertain as it is unclear how 3 mothers who reported no knowledge of their carrier status, and / or mothers for which data were not available, were accounted for.
**Cohen suggested that d = 0.2 be considered a "small" effect size, 0.5 represents a "medium" effect size and 0.8 a "large" effect size[28]

Disease management

- Across four studies reporting diagnostic pathways, methods of diagnosis were not systematic.
  - The pathways followed did not always reflect best practice guidelines for genetic testing in dystrophinopathies, which recommend a testing strategy for manifesting females equivalent to that outlined for males.[27]
  - In a study comparing female carriers to males with a likely *DMD* mutation, mean age at dilated cardiomyopathy diagnosis was significantly later for females (p<0.001).[13]
- No analyzed studies reported on treatment outcomes.

References

The reference list can be accessed using the QR code

FUNDING & DISCLOSURES: This study was funded by PTC Therapeutics, Inc. RJM, AF, FG acted as consultants on DMD clinical trials for PTC Therapeutics. IBOZ, INV, IT, PC, and RZ are employees of PTC Therapeutics and may own stocks in the company. SG, ME, MA are employees of York Health Economics Consortium which received funding from PTC Therapeutics for this work. Medical writing support was provided by Broadstreet HEOR, Vancouver, Canada, and was funded by PTC Therapeutics.

CONTACT INFORMATION: ytomazos@ptcbio.com

THE INTERNATIONAL SOCIETY FOR PHARMACOECONOMICS AND OUTCOMES RESEARCH (ISPOR) EUROPEAN CONFERENCE, BARCELONA, SPAIN, NOVEMBER 17-20, 2024

Supplementary Material:

References

1. Crisafulli S et al. *Orphanet J Rare Dis*. 2020.15(1):141.
2. Edwards JH. *J Med Genet.* 1986.23(6):521-30.
3. Lee SH et al. *J Clin Neurol.* 2015.11(3):248-51.
4. Zhong J et al. *Mol Med Rep.* 2019.19(4):3035-44.
5. Sarkozy A et al. *Neuromuscul Disord.* 2023. 03 2023; 274-84.
6. Weber FJ et al. *Muscle Nerve*. 2022.66(4):462-70.
7. National Institute for Health and Care Excellence. *Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene.* 2023.
8. Bourke J et al. *Open Heart.* 2022.9(2):e001977.
9. Ishizaki M et al. *Neuromuscul Disord.* 2018.28(7):572-81.
10. Apkon S et al. *J Neuromuscul Dis.* 2021; 315-22.
11. Eekhoff L et al. *J Genet Couns*. 2019.28(5):993-1002.
12. Lee T et al. *Clin Chim Acta.* 2021.519:198-203.
13. Restrepo-Cordoba MA et al. *Eur J Heart Fail.* 2021.23(8):1276-86.
14. Silva THd et al. *Arq Neuropsiquiatr.* 2020.78(3):143-48.
15. Wexberg P, et al. *J Cardiovasc Magn Reson.* 2016.18(1):61.
16. Masarova L, et al. *JACC Cardiovasc Imaging*. 2021.14(5):1070-72.
17. Kincl V et al. *Sci Rep.* 2020.10(1):20794.
18. Demirci H et al. *Muscle Nerve.* 2020.62(6):710-16.
19. Lang SM et al. *Pediatr Cardiol.* 2015.36(7):1495-501.
20. Schelhorn J et al. *Eur Radiol.* 2015.25(10):3066-72.
21. Shehta M et al. *Egypt Heart J.* 2021.73(1):91.
22. Solheim TA et al. *Front Neurol.* 2021.12:707838.
23. Thangarajh M et al. *Ann Clin Transl Neurol*. 2019.6(9):1696-706.
24. Birnkrant DJ et al. *Lancet Neurol.* 2018.17(4):347-61.
25. Birnkrant DJ et al. Lancet Neurol. 2018.17(5):445-55.
26. Birnkrant et al. *Lancet Neurol*. 2018.17(3):251-67.
27. Fratter C et al. *Eur J Hum Genet.* 2020.28(9):1141-59.
28. Sullivan GM et al. *J Grad Med Educ*. 2012.4(3):279-82.

Table A1. Summary of included studies.

Author, year	Population	Date of study	Location of study (n)/countries)	Size of study
Case series				
Eekhoff 2019[11]	DMD carriers	August and December 2017 (data collection)	Online and telephone study of registrants of the Duchenne Registry in the United States	60 survey respondents, 11 interviewees
Lee 2021[12]	Girls with elevated creatine kinase levels (no cause identified at baseline) and no family history of neuromuscular diseases who were subsequently diagnosed with DMD	Patients referred between April 2014 and August 2018	Single site in Tokyo, Japan (Department of Pediatrics, Hyogo College of Medicine Hospital)	14, of which 6 were eligible for this review (5 were DMD-carriers, and one was "BMD / DMD")
Restrepo-Cordoba 2021[13]	Female carriers with a pathogenic or likely pathogenic DMD mutation and without severe skeletal myopathy	Data reviewed / collected from 1987 to 2018 (first clinical evaluation of patients ranged from to 1987 to 2018)	26 sites across Europe and Israel (Czech Republic, Denmark, France, Germany, Israel, Italy, Romania, Spain, Netherlands, UK)	223 of which 37 were female
Silva 2020[14]	DMD-carriers	June 2008 to August 2015	Single site (Physiotherapy Service of the Human Genome Research Center, Universidade de São Paulo), Brazil	118 of which 10 were symptomatic and had burden of disease data
Wexberg 2016[15]	Adult female DMD-carrier	First patient enrolled Sept 2012	Single site in Austria (Gottfried von Preyer Children's Hospital)	22
Cross-sectional studies				
MUNI/A/1493/2018 2020[16]	Asymptomatic DMD female carriers	NR	NR but suggests single site in the Czech Republic (St. Anne's University Hospital, Brno)	37 asymptomatic female carriers plus 20 healthy controls (not eligible for this review)
MUNI/A/1493/2018 2020[17]	Asymptomatic female subjects with genetically diagnosed presence of *DMD* allele	NR	Single site in the Czech Republic (University Hospital Brno)	44 female DMD-carriers plus 17 controls (not eligible for this review)
Demirci 2020[18]	Genetically tested carrier mothers of DMD patients	NR	Single site in Istanbul, Turkey (Neuromuscular Disease Unit in the Neurology Department of Istanbul University, Istanbul Faculty of Medicine)	90 of which 31 were eligible carrier females
Lang 2015[19]	*DMD*-carriers	Retrospective chart review of patients who underwent CMRI study between 6 December 2006 and 28 August 2013	Cincinnati Children's Hospital Medical Center, USA	22
Schelhorn 2015[20]	Genetically confirmed asymptomatic female heterozygous carriers of *DMD*	February to October 2013	Single site in Essen, Germany (University Hospital Essen)	15
Shehta 2021[21]	Female asymptomatic genetically tested *DMD*-carriers who were mothers or female relatives of male DMD patients	Patient recruitment between July 2019 and July 2020	Single site, site NR: study was conducted in "a tertiary care university hospital" and all authors' institutional addresses are Ain Shams University, Cairo, Egypt	106 of which 25 were eligible
Solheim 2021[22]	Genetically verified female carriers of pathogenic *DMD* variants	December 2016 to April 2018	Single site in Copenhagen, Denmark (Neuromuscular Clinic, Department of Clinical Genetics, Rigshospitalet)	53
Thangarajh 2019[23]	Biological mothers of DMD-diagnosed children	NR	Two regional academic institutions in the US (not specified)	25 of which 11 mothers were eligible
Case reports				
Apkon 2021[10]	Symptomatic females	Conference at which the cases were presented was 26-27 June 2019; date of individual cases NR	Conference was in Orlando, Florida, USA. Unclear where individual cases were from.	9 separate case reports including a total of 10 patients

Abbreviations: BMD- Becker muscular dystrophy, CMRI- Cardiac magnetic resonance imaging, DMD- Duchenne muscular dystrophy, DCM- Dilated cardiomyopathy, LVF- Left ventricular failure, NR- Not reported.