HHS Public Access

Author manuscript

J Child Neurol. Author manuscript; available in PMC 2020 January 01.

Published in final edited form as:

J Child Neurol. 2019 January ; 34(1): 44–53. doi:10.1177/0883073818801704.

A Review of MD STAR*net*'s Research Contributions to Pediatric-Onset Dystrophinopathy in the United States; 2002–2017

Kashika M. Sahay, PhD[1], **Tiffany Smith, MPH**[1], **Kristin M. Conway, PhD**[2], **Paul A. Romitti, PhD**[2], **Molly M. Lamb, PhD**[3], **Jennifer Andrews, PhD**[4], **Shree Pandya, DPT**[5], **Joyce Oleszek, MD**[6], **Christopher Cunniff, MD**[7], **Rodolfo Valdez, PhD**[8], and **on behalf of the MD STAR*net***

[1]Centers for Disease Control and Prevention, Atlanta, GA, USA

[2]Department of Epidemiology, University of Iowa, Iowa City, IA, USA

[3]Department of Epidemiology, University of Colorado, Aurora, CO, USA

[4]Department of Pediatrics, University of Arizona, Tucson, AZ, USA

[5]Department of Neurology, University of Rochester, Rochester, NY, USA

[6]Department of Physical Medicine and Rehabilitation, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, CO, USA

[7]Department of Pediatrics, Weill Cornell Medical College, New York, NY, USA

[8]Centers for Disease Control and Prevention, National Center for Birth Defects and Developmental Disabilities, DHDD, Rare Disorders and Health Outcomes team, Atlanta, GA, USA

Abstract

Population studies of rare disorders, such as Duchenne and Becker muscular dystrophies (dystrophinopathies), are challenging due to diagnostic delay and heterogeneity in disorder milestones. To address these challenges, the Centers for Disease Control and Prevention established the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*) in 2002 in the United States. From 2002 to 2012, MD STAR*net* longitudinally tracked the prevalence, clinical, and health care outcomes of 1054 individuals born from 1982 to 2011 with pediatric-onset dystrophinopathy through medical record abstraction and survey data collection. This article summarizes 31 MD STAR*net* peer-reviewed publications. MD STAR*net* provided the first population-based prevalence estimates of childhood-onset dystrophinopathy in

Corresponding Author: Tiffany Smith, MPH, 4770 Buford Highway, MS-E88, Atlanta, GA 30341-3717, USA. ync1@cdc.gov.

Author Contributions

KS led the development of this manuscript. KS and TS conceptualized and drafted the manuscript. KC and PR provided extensive feedback and drafted sections of the manuscript. ML and JA provided extensive feedback and assisted with creating the figures. All authors critically revised the manuscript, checked references and findings included in Table 2, and approved the final version.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Paul Romitti has received support from PTC Therapeutics Inc. The remaining authors have no conflicts of interest to disclose.

Ethical Approval

Each published manuscript included in this review article utilized data from MD STAR*net* which had been previously approved by institutional review boards or public health authority in Arizona, Hawaii, Colorado, Georgia, Iowa, and western New York.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

the United States. Additional publications provided insights into diagnostic delay, dystrophinopathy-specific growth charts, and health services use. Ongoing population-based surveillance continually improves our understanding of clinical and diagnostic outcomes of rare disorders.

Keywords

dystrophinopathy; muscular dystrophy; population-based; public health surveillance; rare disorders

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are dystrophinopathies, rare disorders characterized by progressive muscle weakness due to X-linked mutations of the dystrophin gene, leading to reduced/dysfunctional dystrophin production.[1] Clinical characteristics of the most severely affected include loss of ambulation and cardiopulmonary distress and potentially reduced life span. Although incurable, management and treatment options have improved the life span of individuals with dystrophinopathies.[1]

Dystrophinopathies are associated with high health care costs and long-term disability, making them an important focus for population-level surveillance and intervention efforts, yet they are difficult to study.[2] Studies of muscular dystrophy are an early example of research prompted by advocacy efforts. In 2001, the US Congress amended the Public Health Service Act to authorize the Muscular Dystrophy Community Assistance, Research, and Education Act (MD-CARE Act) (reauthorized in 2008, 2014). The MD-CARE Act legislated the establishment of a National Epidemiology Program by the Centers for Disease Control and Prevention (CDC) for "carrying out epidemiological activities regarding Duchenne and other forms of muscular dystrophies, including collecting and analyzing information on the number, incidence, correlates, and symptoms of cases." In response to the MD-CARE Act, the CDC created the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*) in 2002 to conduct population-based medical record surveillance of dystrophinopathies.[3]

MD STAR*net* is a population-based surveillance program that collects information on the health status of the total population with dystrophinopathy in specific areas of the United States. The data sources for MD STAR*net* include neuromuscular clinics, hospitals and hospital discharge databases, private physicians, specialized clinics, service units for children with special health care needs, birth defects surveillance programs, and birth and death certificates. This is a unique network as other networks have concentrated their effort on a variety of issues in the population served by clinics. For example, the Cooperative International Neuromuscular Research Group (CINRG) works on observational studies, clinical trials, and post-marketing surveillance.[4] The Translational Research in Europe for the Assessment and Treatment of Neuromuscular Diseases (TREAT NMD) is a large international network of academic institutions, patient groups, and pharmaceutical companies covering a variety of aspects related to research and treatment of these diseases.[5] TREAT NMD seeks to standardize patient registries, organize patient databases and biobanks for clinical trials, produce treatment guidelines for standards of care, develop

international consensus on animal and cellular models of neuromuscular diseases, standardize outcome measures, and produce consensus statements on clinical diagnosis and treatment protocols. The research activities of TREAT NMD include clinical trials, epidemiology, natural history, surveillance, genotype/phenotype analysis, and health care services.[5] Finally, the Canadian Neuromuscular Disease Registry (CNDR) is a network of clinics and investigators, part of the TREAT NMD network, whose main activity is to plan and recruit patients for clinical trials. They also conduct epidemiologic and natural history studies.[6]

This article summarizes the first 15 years of clinical and public health contributions of MD STAR*net* in relation to the MD-CARE Act. This summary is presented in a format relevant to clinicians, patients, and advocacy groups.

Design Considerations for Surveillance

Pediatric-onset dystrophinopathies were ascertained for MD STAR*net* using International Classification of Diseases (ICD) codes (ICD-9: 359.1; ICD-10: G71.0) and other criteria in a population-based cohort from 6 sites (Arizona [AZ], Colorado [CO], Iowa [IA], western New York State [wNY], Georgia [GA], Hawaii [HI]). Additional eligibility criteria were residence in a MD STAR*net* surveillance site following diagnosis, birth year (1982–2011), and pediatric onset (diagnosed before age 21 years).[7,8] Case definitions were created to assign diagnostic confidence (definite, probable, possible, manifesting female, or asymptomatic) based on clinical symptoms, clinical laboratory data, and/or evidence of X-linked family history (Figure 1).[9] Cases were further classified as DMD or BMD based on clinical presentation.

Abstractors were systematically trained to abstract relevant medical record data on all eligible cases. Clinical information was collected through medical record abstraction primarily from neuromuscular clinics. Authority for medical record review was obtained through state public health authority or institutional review board approval or exemption.[8] Data were quality checked, compiled, and deidentified prior to submission to the MD STAR*net* data coordinating center. From 2007 to 2012, selected primary caregivers and individuals with MD participated in voluntary survey research that collected information on personal experiences, such as quality of life, health care transition, and health care services (Table 1).

MD STAR*net* has several strengths, including a populationbased approach to identify individuals with MD living within eligible catchment areas.[7] Clinical and laboratory data were extracted directly from medical charts and reviewed by neuromuscular specialists. This approach limits case misclassification, because eligibility for inclusion in MD STAR*net* is based on clinician review of relevant clinical and laboratory data. Despite these strengths, MD STAR*net* faces the typical limitations of rare disorder surveillance, namely, small sample size, diagnostic delays, and difficulties with case ascertainment. Additionally, retrospective medical record review may miss important factors that could have influenced the current health status of patients with DBMD but were not part of this record. Finally, although MD STAR*net* attempts to cover specific areas completely, the generalizability of

the findings is compromised by the incomplete availability of clinical and vital information for individuals who migrate in or out of an MD STAR*net* surveillance region, and by the lack of electronic medical records for older individuals. It is also important to note that each primary or secondary study (eg, survey) based on the MD STAR*net* population has its own set of limitations depending on study design, sample size, the outcome selected, the availability of data, and the subpopulation examined.

Findings

As of October 2017, 31 peer-reviewed journal articles have been published on behalf of MD STAR*net* (Table 2). This narrative summarizes selected analytical findings from these papers.

Epidemiologic Insights

The first population-based prevalence estimates of pediatriconset dystrophinopathies in the United States were reported by MD STAR*net*.[8] A prevalence estimate of 1.38 per 10 000 was published in 2010 based on 649 males with a definite or probable diagnosis from each of the 6 sites. Prevalence was higher for Hispanic than non-Hispanic white or non-Hispanic black males and for DMD compared to BMD.[8]

Genetic Testing

Genetic information is increasingly necessary for clinical trials and estimating the numbers of individuals with various mutations who may be eligible for specific molecular therapies. In recent years, genetic testing for diagnosing mutations in the *DMD* gene has increased across MD STAR*net* sites.[10] In a 2009 study of 470 males, 41 (8.7%) had no mutation analysis done, and a *DMD* mutation was documented for 345 individuals (73.4%); the remaining 84 individuals (17.9%) had inconclusive or insufficient information. Of the mutations, deletions were the most common (n = 270, 78.3%), followed by duplications (n = 39, 11.3%) and point mutations (n = 36, 10.4%).

Diagnostic Process and Disease Progression

Delays in diagnosing a rare disorder provide challenges in developing and implementing early interventions that may reduce disease severity. The retrospective cohort design of MD STAR*net* has allowed for studies of the diagnostic process. Specifically, a study of diagnostic delay among males without family history of a neuromuscular disorder showed an average delay of 2.5 years from first signs and symptoms (mean age 2.5 years) to a definitive diagnosis (mean age 4.9 years).[11] Another study reported on racial and ethnic disparities in the diagnostic process, with non-Hispanic black and Hispanic males evaluated later than non-Hispanic white males.[13]

Diagnosis of a pediatric-onset dystrophinopathy in a male child also appeared to influence future reproductive patterns. Birth certificate data were linked within 3 MD STAR*net* sites to construct reproductive histories.[15] Based on these histories, 40% of mothers had another live birth after the birth of their oldest affected male in MD STAR*net*, and 18% had a birth after

the diagnosis of their affected child. These mothers were more likely to be younger and nonwhite compared to mothers with no live births after having a son diagnosed with pediatric-onset dystrophinopathy.[15]

Characterizing patterns of disease progression is important for determining clinically meaningful endpoints to evaluate treatments. An analysis of 825 males in MD STAR*net* led to the observation that early onset of signs and symptoms (<18 months of age) was associated with earlier loss of ambulation than among those with later onset of signs and symptoms (>5 years of age).[27] Overall, there was a 10% reduction in annual risk of loss of ambulation (LOA) for every 1-year delay in onset of the appearance of symptoms.[27] In comparing 60 pairs of affected brothers, investigators found that the age at which ambulation ceased was similar, with a median difference of 2 months; however, age at onset of other outcomes, such as scoliosis (median difference of 8 months) and cardiomyopathy (median difference of 2 years), was more varied.[18]

Growth

US standard growth charts do not accurately reflect the growth trajectories of males with pediatric-onset dystrophinopathies due to characteristic muscle wasting and shortened stature.[17,28] Therefore, MD STAR*net* investigators developed weight-, height-, and body mass index (BMI)-for-age growth charts for steroid-naïve, ambulatory males from heights and weights recorded at each neuromuscular clinic visit.[17] Comparisons of the dystrophinopathy-derived growth charts to the general US pediatric population illustrated that steroid-naïve, ambulatory males with a pediatric-onset dystrophinopathy were shorter and tended toward the extremes of weight and BMI than steroid-treated boys.[17] Furthermore, ambulatory males who were treated with steroids for at least 6 months were shorter than those who were steroid-naïve[28] (Figure 2).

Corticosteroid Patterns of Use and Clinical Outcomes

As corticosteroids are often used to preserve functional status, MD STAR*net* examined corticosteroid treatment patterns including percentages of users, age at initiation, and dosing schedules.[9,21] Among males born from 1984 to 1998 in 4 MD STAR*net* sites (AZ, CO, IA, wNY), the average percentage of males across all sites who had ever used corticosteroids was 47.1% in 2005, and the median dosages were 0.729 mg/kg for prednisone/prednisolone and 0.831 mg/kg for deflazacort.[9] A more recent analysis of corticosteroid use in 6 sites (IA, CO, GA, HI, IA, wNY) found that 60% of males had ever used corticosteroids, and recent birth cohorts tended to start steroid treatment at younger ages (8.2 years 1982–1986; 7.1 years 1997–2001) and continue for longer durations.[21]

Findings from MD STAR*net* studies suggest variable associations between corticosteroid use and clinical outcomes.[24,27,34] Investigators who recently analyzed data from all 6 MD STAR*net* sites reported a complex association between duration of corticosteroid use and LOA, with lower annual risk of LOA among long-term (>3 years) users, but higher annual risk among short-term ($0.25 > X < 3.0$ years) users, compared to an untreated group.[24] Using data from 5 sites (IA, CO, GA, IA, wNY), Barber et al[16] reported delayed onset of

cardiomyopathy among corticosteroid users. Further examination of timing of corticosteroid use showed that males who initiated treatment at 5 years of age or younger had a higher rate of fracture and earlier onset of cardiomyopathy compared to those who initiated steroid treatment after age 5 years.[34] These results point to a need for additional epidemiologic studies of treatment practices that minimize adverse events relating to steroid use, while optimizing clinical outcomes.

Neurobehavioral Comorbidities

Neurobehavioral comorbidities are of concern to individuals affected with a pediatric-onset dystrophinopathy and their families. In a sample of 765 oldest affected males, 45% had at least 1 documented neurobehavioral morbidity, which included behavior problems (43%), attention-deficit/hyperactivity disorder (23%), or a depressed mood (51%). Of the 344 males with at least 1 neurobehavioral concern, 69% received neuropsychiatric medication, counseling, or both; however, variability in the mode of interventions was found across type of neurobehavioral concern.[23] In addition to males with pediatric-onset dystrophinopathies, MD STAR*net* has described the symptom profiles of 9 manifesting females highlighting potential areas of intervention beyond neuromuscular management in this population, and noted neurobehavioral problems as a component of disease.[20] These findings emphasize the importance of comprehensive programs that support the neurobehavioral sequelae of individuals with pediatric-onset dystrophinopathies.

Multidisciplinary Care Recommendations

Individuals with pediatric-onset dystrophinopathy require multidisciplinary care that includes monitoring of neuromuscular, pulmonary, and cardiac systems.[25,29] Data from interviews of caregivers of affected males followed through MD STAR*net* indicated patterns of cardiac care were more consistent with care recommendations than those for pulmonary care, and the types of specialists patients saw and services they received varied among sites.[25] MD STAR*net* surveillance data suggested that less than one-half of interviewed adolescents received the recommended biannual pulmonary function assessments, although approximately two-thirds had annual monitoring of hypoventilation.[29]

Scientific Impact and Future Directions

In addition to epidemiologic findings, MD STAR*net* data have provided important clinical information for use by federal and state agencies. Population-based frequencies of affected males under age 18 years from MD STAR*net* contributed to evidence used by the US Food and Drug Administration (FDA) to designate dystrophinopathy a rare pediatric condition. The US FDA also used MD STAR*net* data in its review process for a drug targeting a subpopulation of muscular dystrophy patients. Additionally, MD STAR*net* data has been used to estimate the number of potential DMD patients with varied genetic profiles who may be eligible for drug treatments.

Future clinical outcomes to be examined by MD STAR*net* will include survival, natural history of scoliosis, endocrine function, bone health, and left ventricular dysfunction among

adults living with a dystrophinopathy diagnosis. In addition, surveillance has been expanded to collect epidemiologic and clinical information on limb girdle, congenital, facioscapulohumeral, myotonic, oculopharyngeal, distal, and Emery-Dreifuss muscular dystrophies. Future initiatives of MD STAR*net* may focus on tracking the implementation of newly developed ICD-11 codes for dystrophinopathies and facioscapulohumeral dystrophy.

Conclusion

MD STAR*net* has made important multidisciplinary contributions to pediatric-onset dystrophinopathy research –in epidemiology, early detection and diagnosis, genetic testing, growth, comorbidities, and disease management experiences of individuals living with dystrophinopathy. Current and future population-based surveillance efforts will continue to monitor clinical trajectories of individuals with muscular dystrophies in the US in accordance with the MD-CARE Act.

Acknowledgments

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This publication was supported by the Cooperative Agreement numbers, DD000187, DD000189, DD000190, DD000191, DD000392, DD001126, DD001119, DD001123, funded by the Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services.

References

1. Emery AE. The muscular dystrophies. Lancet. 2002;359(9307): 687–695. [PubMed: 11879882]
2. Gooch CL, Pracht E, Borenstein AR. The burden of neurological disease in the United States: a summary report and call to action. Ann Neurol. 2017;81(4):479–484. [PubMed: 28198092]
3. GovTrack. H.R. 717 (107th): MD-CARE Act. https://www.govtrack.us/congress/bills/107/hr717. Published 2001. Accessed October 17, 2017.
4. Cooperative International Neuromuscular Research Group (CINRG). http://www.cinrgresearch.org/. Published 2018. Accessed June 26, 2018.
5. Translational Research in Europe for the Assessment and Treatment of Neuromuscular Diseases. http://www.treat-nmd.eu/. Published 2018. Accessed June 26, 2018.
6. Canadian Neuromuscular Disease Registry (CNDR). https://cndr.org/. Published 2018 Accessed June 26, 2018.
7. Miller LA, Romitti PA, Cunniff C, et al. The Muscular Dystrophy Surveillance Tracking and Research Network (MD STARnet): surveillance methodology. Birth Defects Res A Clin Mol Teratol. 2006;76(11):793–797. [PubMed: 17036307]
8. Romitti PA, Zhu Y, Puzhankara S, et al. Prevalence of Duchenne and Becker muscular dystrophies in the United States. Pediatrics. 2015;135(3):513–521. [PubMed: 25687144]
9. Matthews DJ, James KA, Miller LA, et al. Use of corticosteroids in a population-based cohort of boys with Duchenne and Becker muscular dystrophy. J Child Neurol. 2010;25(11):1319–1324. [PubMed: 20207610]
10. Cunniff C, Andrews J, Meaney FJ, et al. Mutation analysis in a population-based cohort of boys with Duchenne or Becker muscular dystrophy. J Child Neurol. 2009;24(4):425–430. [PubMed: 19074751]
11. Ciafaloni E, Fox DJ, Pandya S, et al. Delayed diagnosis in Duchenne muscular dystrophy: data from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet). J Pediatr. 2009;155(3):380–385. [PubMed: 19394035]

12. Centers for Disease Control and Prevention. Prevalence of Duchenne/Becker muscular dystrophy among males aged 5–24 years—four states, 2007. MMWR Morb Mortal Wkly Rep. 2009;58(40): 1119–1122. [PubMed: 19834452]
13. Holtzer C, Meaney FJ, Andrews J, et al. Disparities in the diagnostic process of Duchenne and Becker muscular dystrophy. Genet Med. 2011;13(11):942–947. [PubMed: 21836521]
14. Nabukera SK, Romitti PA, Campbell KA, et al. Use of complementary and alternative medicine by males with Duchenne or Becker muscular dystrophy. J Child Neurol. 2012;27(6):734–740. [PubMed: 22156783]
15. Nabukera SK, Romitti PA, Caspers KM, et al. Reproductive patterns among mothers of males diagnosed with Duchenne or Becker muscular dystrophy. Am J Med Genet A. 2013;161(1):70–75.
16. Barber BJ, Andrews JG, Lu Z, et al. Oral corticosteroids and onset of cardiomyopathy in Duchenne muscular dystrophy. J Pediatr. 2013;163(4):1080–1084.e1. [PubMed: 23866715]
17. West NA, Yang ML, Weitzenkamp DA, et al. Patterns of growth in ambulatory males with Duchenne muscular dystrophy. J Pediatr. 2013;163(6):1759–1763.e1. [PubMed: 24103921]
18. Pettygrove S, Lu Z, Andrews JG, et al. Sibling concordance for clinical features of Duchenne and Becker muscular dystrophies. Muscle Nerve. 2014;49(6):814–821. [PubMed: 24030636]
19. Zhu Y, Romitti PA, Conway KM, et al. Complementary and alternative medicine for Duchenne and Becker muscular dystrophies: characteristics of users and caregivers. Pediatr Neurol. 2014;51(1): 71–77. [PubMed: 24785967]
20. Imbornoni L, Price ET, Andrews J, Meaney FJ, Ciafaloni E, Cunniff C. Diagnostic and clinical characteristics of earlymanifesting females with Duchenne or Becker muscular dystrophy. Am J Med Genet A. 2014;164(11):2769–2774.
21. Fox DJ, Kumar A, West NA, et al. Trends with corticosteroid use in males with Duchenne muscular dystrophy born 1982–2001. J Child Neurol. 2015;30(1):21–26. [PubMed: 24682290]
22. Zhu Y, Romitti PA, Caspers Conway KM, et al. Genitourinary health in a population-based cohort of males with Duchenne and Becker muscular dystrophies. Muscle Nerve. 2015;52(1):22–27. [PubMed: 25297835]
23. Caspers Conway K, Mathews KD, Paramsothy P, et al. Neurobehavioral concerns among males with dystrophinopathy using population-based surveillance data from the muscular dystrophy surveillance, tracking, and research network. J Dev Behav Pediatr. 2015;36(6):455–463. [PubMed: 26020585]
24. Kim S, Campbell KA, Fox DJ, Matthews DJ, Valdez R, MD STAR*net*. Corticosteroid treatments in males with Duchenne muscular dystrophy: treatment duration and time to loss of ambulation. J Child Neurol. 2015;30(10):1275–1280. [PubMed: 25414237]
25. Pandya SK, Campbell KA, Andrews JG, Meaney FJ, Ciafaloni E. Health services received by individuals with Duchenne/Becker muscular dystrophy. Muscle Nerve. 2016;53(2):191–197. [PubMed: 26044770]
26. Pandya S, Andrews J, Campbell K, Meaney FJ. Rehabilitative technology use among individuals with Duchenne/Becker muscular dystrophy. J Pediatr Rehabil Med. 2016;9(1):45–53. [PubMed: 26966800]
27. Ciafaloni E, Kumar A, Liu K, et al. Age at onset of first signs or symptoms predicts age at loss of ambulation in Duchenne and Becker Muscular Dystrophy: Data from the MD STAR*net*. J Pediatr Rehabil Med. 2016;9(1):5–11. [PubMed: 26966795]
28. Lamb MM, West NA, Ouyang L, et al. Corticosteroid treatment and growth patterns in ambulatory males with Duchenne muscular dystrophy. J Pediatr. 2016;173:207–213.e3. [PubMed: 27039228]
29. Andrews JG, Soim A, Pandya S, et al. Respiratory care received by individuals with Duchenne muscular dystrophy from 2000 to 2011. Respir Care. 2016;61(10):1349–1359. [PubMed: 27507176]
30. Soim A, Lamb M, Campbell K, et al. A cross-sectional study of school experiences of boys with Duchenne and Becker muscular dystrophy. Phys Disabil Educ Relat Serv. 2016;35(2):1.
31. Frishman N, Conway KC, Andrews J, et al. Perceived quality of life among caregivers of children with a childhood-onset dystrophinopathy: a double ABCX model of caregiver stressors and perceived resources. Health Qual Life Outcomes. 2017;15(1):33. [PubMed: 28187773]

32. Latimer R, Street N, Conway KC, et al. Secondary conditions among males with Duchenne or Becker muscular dystrophy. J Child Neurol. 2017;32(7):663–670. [PubMed: 28393671]

33. Conway KM, Ciafaloni E, Matthews D, et al. Application of the International Classification of Functioning, Disability and Health system to symptoms of the Duchenne and Becker muscular dystrophies. Disabil Rehabil. 2018;40: 1773–1780. [PubMed: 28395534]

34. Kim S, Zhu Y, Romitti PA, et al. Associations between timing of corticosteroid treatment initiation and clinical outcomes in Duchenne muscular dystrophy. Neuromuscul Disord. 2017;27(8): 730–737. [PubMed: 28645460]

35. Gissy JJ, Johnson T, Fox DJ, et al. Delayed onset of ambulation in boys with Duchenne muscular dystrophy: potential use as an end-point in clinical trials. Neuromuscul Disord. 2017;27(10): 905–910. [PubMed: 28739181]

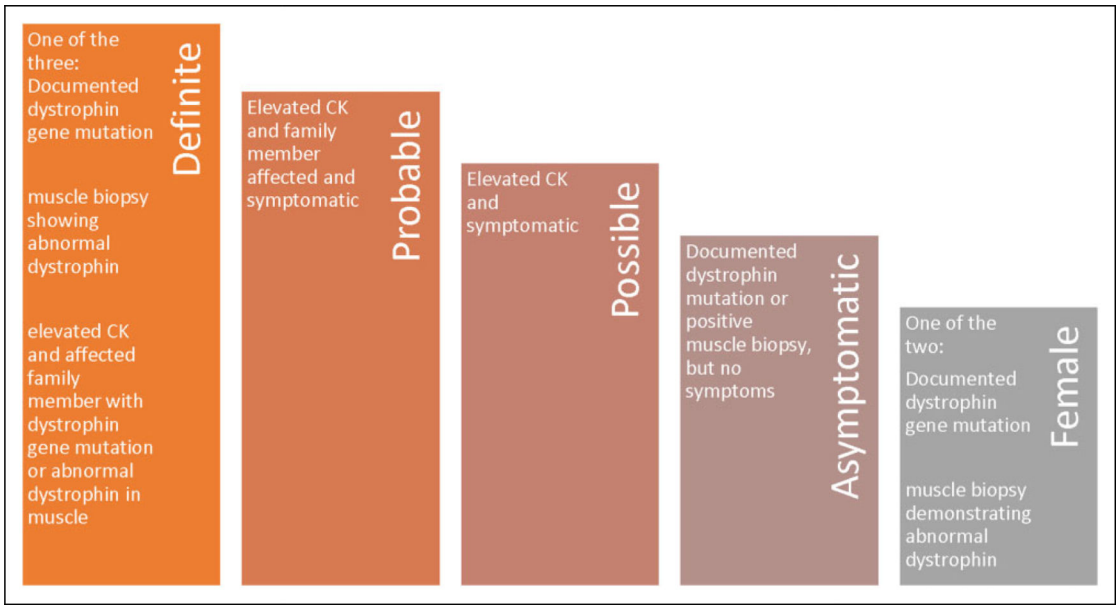

Figure 1.

Case[a] definitions of childhood-onset dystrophinopathy in population-based surveillance systems—definite, probable, possible, asymptomatic, and manifesting female, United States, 2002–2011.

[a] Cases were found through searches for ICD-9 code 359.1 in medical records and ICD-10 code G71.0 in death records.

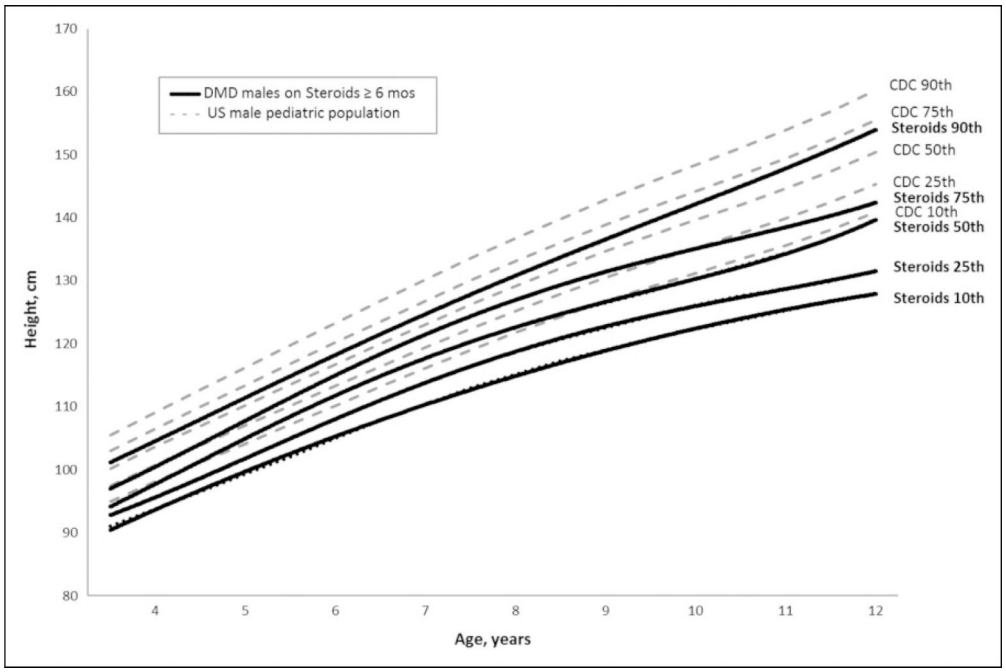

Figure 2.

Growth curves comparison for steroid-treated boys with Duchenne muscular dystrophy (DMD) as compared to CDC US Standard growth curves, adapted from Lamb et al (2016).[28]

Table 1.

Details on the Surveys and Interviews Conducted as Part of MD STAR*net*.[a]

Survey Name	Caregiver interview	Needs assessment	Family quality of life	Health care transitions and other life experiences survey
Eligibility/sampling[b]	Caregivers of living or deceased males who met definite/probable case definition within MD STAR*net*	Caregivers of living males and affected males ages 18 y or older who met definite/ probable case definition within MD STAR*net*	Caregivers of living males who met definite/probable case definition within MD STAR*net*	Caregivers of living males and affected males ages 16 y or older who met definite/ probable case definition within MD STAR*net*
Survey mode	Computer-assisted Telephone Interview	Mailed survey	Mailed survey	Online or telephone survey
Eligibility and participation[c]	362 completed caregiver interviews 379 not complete	272 completed caregiver interviews 248 not complete	209 completed caregiver interviews 251 not complete	91 completed caregiver interviews 155 not complete Adult males living 16 and older 65 complete 193 not complete
Dates survey conducted	2007–2012	2008–2012	2011–2012	2013

[a] All eligible caregivers and affected individuals were required to be current residents of an MD STAR*net* site at the time of recruitment.

[b] Caregivers and affected males were excluded from recruitment if no further contact was requested at any phase of recruitment.

[c] Sites went through appropriate institutional review board approval for surveys.

J Child Neurol. Author manuscript; available in PMC 2020 January 01.

Table 2.

Key Findings From MD STAR*net* Citations, Selected Sites Within the United States, 2002–2017.

Article	Cohort and sample size	Key findings[a]
Miller, 2006[7]	N/A	This is the first MD STAR*net* publication, which presents case definitions, population-based surveillance protocol, methodology, and strengths/limitations of MD STAR*net*.
Cunniff, 2009[10]	Born 1982–2004; n = 470	The use of muscle biopsy has declined over time as mutation analysis is becoming more common. DMD mutation was documented for 73.4% of cases. Of cases with a confirmatory analysis, 78.3% had a deletion, 11.3% had a duplication, and 10.4% had a point mutation.
Ciafaloni, 2009[11]	Born 1982–2004, no family history; n = 156	The average age at first signs and symptoms was 2½ y, first clinic visit 3½ y, and diagnosis was nearly 5 (4.9) y. There was a delay of 1 year from first signs and symptoms to evaluation by clinician and a delay of 1½ y from first clinical visit to diagnosis.
CDC, 2009[12]	Born 1983–2002 and deaths through 2007; n = 452	Population-based prevalence of 0.3–1.8 per 10 000 males aged 5–24 y with either DMD or BMD; more than 90% of males >15 used wheelchairs; nearly 60% of males born 1983–1987 had survived through 2007.
Mathews, 2010[9]	Born 1982–2009; n = 815	Within this study, 674 (82%) cases were classified as either “definite” or “probable.” Genetic testing increased from 67% in the oldest cohort born 1982–1987 to 94% in the cohort born 2004–2009.
Matthews, 2010[9]	Born 1984–1998; n = 351	Among cases with complete corticosteroid information from 1991 to 2005, the most commonly prescribed steroid was prednisone with a median dose of 0.729 mg/kg. Steroid usage increased over time across cohorts. The most common change in dosage was an increase in dose due to child growth. The most common reasons for steroid discontinuation were weight gain, behavioral side effects, and loss of ambulation.
Holtzer, 2011[13]	Born before 2001, identified before 2009; n = 375	Models were adjusted for family history of dystrophinopathy. There was an association between race/ethnicity and diagnosis. Black and Hispanic race/ethnicity were associated with later age at initial evaluation and CK/DNA diagnostic testing, whereas living in an area of high poverty and previous positive family history were associated with younger ages at evaluation.
Nabukera, 2012[14]	Survey of caregivers of males living or deceased in MD STAR*net* sites identified from April 2004 to August 2006; n = 200	80% of caregivers reported using CAM at some point for their DMD children. The most common CAMs reported were aquatherapy, prayer, and special diets.
Nabukera, 2013[15]	Mothers of males with DMD born 1982–2006; n = 239	Nearly 1 in 5 mothers (18%) had a live birth after their oldest affected male child was diagnosed with a dystrophinopathy. Mothers who had a live birth after a dystrophinopathy diagnosis were more likely to be younger and minority race as compared to mothers with no live birth after dystrophinopathy diagnosis.
Barber, 2013[16]	1982–2005; DMD only; n = 462	The average age of cardiomyopathy onset symptoms was delayed by an average of 2.1 y for boys treated with corticosteroids. Based on survival analysis, by age 14.3, only one-third of boys (36%) treated with steroids had developed cardiomyopathy, as compared to nearly two-thirds (63%) of nontreated boys.
West, 2013[17]	Born 1982–2008, with a growth record between ages 2 and 12; DMD only; n = 513	Growth curves were presented for steroid-naïve ambulatory DMD males. As compared to the general US pediatric male population, DMD males were more likely to be in the extremeweight categories (<10th and >90th percentile); average heights were comparable. Steroid-naïve DMD males are shorter and have higher BMIs on average than the US general pediatric male population.
Pettygrove, 2014[18]	Born 1982–2006; 60 pairs of brothers	Ambulation cessation is correlated between brothers, but other outcomes such as scoliosis and cardiomyopathy can vary widely between siblings.
Zhu, 2014[19]	Caregiver survey; n = 362 caregivers	75% of caregivers reported some use of CAM therapies. CAM use was more common among non-Hispanic whites, higher income and high education. Mind-body medicine—eg, aquatherapy, prayer, and/or blessing—was the most frequently used modality. CAM use was associated with earlier onset of symptoms and wheelchair use.
Imbornoni, 2014[20]	Born 1982–2011; n = 9 females	Symptomatic females with dystrophinopathy have a longer diagnostic delay than boys with no family history of dystrophinopathy. Detailed descriptive case notes, diagnostic and clinical criteria, and some genetic data are presented.

Article	Cohort and sample size	Key findings[a]
Fox, 2015[21]	Born 1982–2001, first-born DMD only with complete clinical history past age 7; n = 521	Steroid usage has increased over time. Boys with a family history of DMD are less likely to use steroids as compared to boys without a family history. Blacks and Hispanics were less likely than whites to use steroids. Non-Hispanic blacks had a significant delay in initiation of steroid use. Age at start of steroid treatment decreased over time, and overall use increased.
Romitti, 2015[8]	Born 1986–2005; n = 707	Prevalence estimates per 10 000 boys, ages 5–9 y, were 1.93, 2.05, 2.04, and 1.51 for birth year categories 1991–1995, 1996–2000, 2001–2005, and 2006–2010, respectively. In 2010, prevalence of dystrophinopathy was 1.38 per 10 000 male individuals, ages 524 y. DMD was 3 times more prevalent than BMD. Non- Hispanic blacks had the lowest prevalence of dystrophinopathy across all ages as compared to non-Hispanic white and Hispanic.
Zhu, 2015[22]	Born 1982–2011; n = 918	Genitourinary issues are more common in those who are not ambulatory. Voiding dysfunction is the most common concern.
Conway, 2015[23]	Born 1982–2011; 3 groups: 857 overall; 765 oldest affected; 307 oldest affected at least 17 y of age	Most males with dystrophinopathy manifested with clinically reported behavioral problems, ADHD and depression. Older males showed higher rates of depression than behavioral problems and ADHD. Intervention rates varied by type of mental health concern. About 50% of dystrophinopathy patients experienced depression by age 29.
Kim, 2015[24]	Born 1982–2011; n = 477	Steroid use and duration has a complicated relationship with functional outcomes. Increased duration of steroid use was associated with up to 2 y of additional ambulation up until age 11.
James, 2015[8]	Born 1982–2006; n = 747	Corticosteroid usage was not associated with increased likelihood of fractures. Loss of ambulation was associated with fractures as boys using wheelchairs more often were likely to report having had a fracture. The most common fracture location was the femur.
Pandya, 2016[25]	Caregiver Interview survey; n = 296 caregivers	85% reported seeing a neuromuscular specialist, 71% a cardiologist, 54% a pulmonologist, 33% an orthopedist, 69% a physical therapist, 42% an occupational therapist, and 20% a speech therapist. Significantly higher proportion of nonambulatory males reported seeing a cardiologist, pulmonologist, or orthopedist.
Pandya, 2016[26]	Caregiver Interview survey; n = 362 caregivers	Caregiver reports of rehabilitative technology use differed across MD STAR*net* sites. Use of night splints varied from 37% to 73%, and use of standers varied from 3% to 22%.
Ciafaloni, 2016[27]	Born 1982–2009; n = 825	Earlier onset of symptoms was associated with earlier loss of ambulation (LOA); early signs and symptoms were identified as a risk factor for a more rapid progression of muscle weakness, as measured by age of LOA, after controlling for corticosteroid use, family history of dystrophinopathy, birth year, race/ethnicity, and MD STAR*net* site. There was a 10% reduction in the risk of loss of ambulation for every year of age before symptoms appear.
Lamb, 2016[28]	Born 1982–2011, with a growth record between ages 2 and 12; DMD only; n = 324	Ambulatory males with DMD who were treated with corticosteroid were significantly shorter and heavier (and thus had higher BMI) than their steroid-naïve counterparts with DMD and the general US pediatric male population. The 2 steroids used, prednisone and deflazacort, had slightly different effects on height and weight. For both prednisone and deflazacort, longer duration of use and higher dosages were associated with shorter stature. However, deflazacort was associated with lighter weight compared to prednisone.
Andrews, 2016[29]	DMD nonambulatory individuals who were at least 12 y of age between 2000–2010; n = 208	The monitoring of respiratory function and use of respiratory assistive devices appears to be less frequent than recommended by ATS. Fewer than 50% of nonambulatory individuals had the appropriate lung function tests (FVC, cough peak flow, perfusion) at the recommended testing interval (twice per year). Nearly 2 of 3 youths had an annual sleep test to monitor blood oxygen and CO_2 levels. Further details on evaluations by lung specialists and invasive respiratory procedures were discussed.
Soim, 2016[30]	Caregiver interview survey; n = 210 caregivers	More than 25% of boys with Duchenne had to repeat a grade (K-12). Approximately half of youth and caregivers reported the use of physical, speech, and/or occupational services at school; >90% of males with DMD attended general education classes. The majority of ambulatory and nonambulatory males with DMD used a variety of educational supports/accommodations (instructional assistant, resource room) in the school setting. Use of supports/accommodations increased with disability.
Frishman, 2017[31]	Family Quality of Life survey; n = 209 caregivers	Caregiver adaptation to a dystrophinopathy diagnosis and family quality of life were optimized by increased perceived control and supportive family resources.
Latimer, 2017[32]	Family Quality of Life survey; n = 209 caregivers	Cognitive deficits, constipation, and behavioral concerns were common conditions for both ambulatory and nonambulatory individuals. Depression/anxiety and kidney stones were more common among nonambulatory males.
Conway, 2017[33]	N/A	Based on clinician expertise, 71 ICF codes (24 second-, 41 third-, and 7 fourth-level) were identified for childhood dystrophinopathies. Of the second-level codes, 15 were successfully linked to MD STAR*net* surveillance data.

Article	Cohort and sample size	Key findings[a]
Kim, 2017[34]	Born 1982–2011; DMD only; n = 726	DMD patients who initiated corticosteroid treatment in early childhood had a higher risk of developing cardiomyopathy compared to cases who initiated treatment in late childhood. Patients with early childhood treatment had slightly decreased respiratory function compared with those who had late childhood treatment.
Gissy, 2017[35]	Born 1982–2011; DMD only; n = 463	Data on initiation of ambulation from MD STAR*net* were compared with data from other cohort and registry-based studies. Boys with DMD, on average, started walking later than boys with a typical developmental trajectory (17 mo as compared to 12 mo). This finding identified age at initiation of ambulation as a potential endpoint for very early therapeutic trials.

BMD, Becker muscular dystrophy; BMI, body mass index; CAM, complementary alternative medicine; CK, creatinine kinase; DMD, Duchenne muscular dystrophy; ICF, International Classification of Functioning, Disability and Health.

[a]Findings include all dystrophinopathies, unless DMD only is indicated.

Note: Cohorts are all males except for Imbornoni 2004. See Supplementary Table 1 for further details on MD STAR*net* affiliated surveys.