Spring 5-11-2018

Characterization of Individuals with Muscular Dystrophy from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet) Pilot in the United States

Bailey Hill

Follow this and additional works at: https://scholarworks.gsu.edu/iph_theses

Abstract

Characterization of Individuals with Muscular Dystrophy from the Muscular Dystrophy
Surveillance, Tracking, and Research Network (MD STAR*net*) pilot in the United States

By

Bailey Melissa Hill

23 April 2018

Introduction: Because of the variability in muscular dystrophy (MD) in terms of clinical manifestations, affected demographic, and health trajectories, it is important to study the distribution of characteristics by MD type; however, few U.S. population-based studies have examined the distributions of sociodemographic, socioeconomic, and clinical factors across MD types. MD STAR*net* is the only U.S. population-based surveillance system for MD. To assess the feasibility of expanding the original surveillance methodology to other forms of MD, MDS conducted a pilot study, which was carried out in four sites (Arizona, Colorado, Iowa, and 12 counties in Western New York).
Aims: We aim to describe the demographic, sociodemographic, and clinical characteristics of individuals within the MD STAR*net* pilot cohort by MD type.
Methods: Potential MD cases were identified through searches of clinical and administrative data sources using ICD-9-CM codes, ICD-10 codes, and prior MDS surveillance data. Data sources included medical records from inpatient and outpatient healthcare facilities, vital records, and hospital discharge data. Medical record abstraction of eligible cases was performed by trained abstractors. A total of 2,862 eligible MD cases who resided in an MDS site during the study period and had a health encounter were included in the pilot study.
Results: The MD STAR*net* pilot cohort were primarily male, white and non-Hispanic. Approximately half of DBMD and DM cases had public insurance, 30-35% had private insurance and 8-15% had both public and private. Most MD cases were not in congregate care or assisted living. 27.9% of CMD patients and 22.8% of DM patients were on NIPPV. EDMD, DM and LGMD patients had the most frequent use of pacemakers; heart transplants were most frequently documented in DD, EDMD and LGMD patients. The most common medications listed in the health records of MD patients were Lisinopril, Furosemide, Albuterol, Omeprazole, and Prednisone.

Characterization of Individuals with Muscular Dystrophy from the Muscular Dystrophy
Surveillance, Research and Tracking Network (MD STAR*net*) pilot in the United States

By

Bailey Melissa Hill

B.S, Presbyterian College

23 April 2018

A Thesis Submitted to the Graduate Faculty
of Georgia State University in Partial Fulfillment
of the
Requirements for the Degree

MASTER OF PUBLIC HEALTH

ATLANTA, GEORGIA
30303

APPROVAL PAGE

Characterization of Individuals with Muscular Dystrophy from the expanded pilot of the
Muscular Dystrophy Surveillance, Research and Tracking Network in the United States

by

Bailey Melissa Hill

Approved:

Richard Rothenberg, MD, MPH
Committee Chair

K. Tiffany Smith, MPH
Committee Member

Natalie Street, MGC
Committee Member

April 20, 2018

Author's Statement Page

In presenting this thesis as a partial fulfillment of the requirements for an advanced degree from Georgia State University, I agree that the Library of the University shall make it available for inspection and circulation in accordance with its regulations governing materials of this type. I agree that permission to quote from, to copy from, or to publish this thesis may be granted by the author or, in his/her absence, by the professor under whose direction it was written, or in his/her absence, by the Associate Dean, School of Public Health. Such quoting, copying, or publishing must be solely for scholarly purposes and will not involve potential financial gain. It is understood that any copying from or publication of this dissertation which involves potential financial gain will not be allowed without written permission of the author.

Bailey Melissa Hill

_____

Signature of Author

Contents

List of Tables

List of Figures

Chapter I: Introduction

Muscular dystrophy (MD) includes heterogeneous groups of genetic muscle diseases characterized by progressive muscle weakness and wasting. There are nine (9) major types of MD: Becker MD, Duchenne MD, Congenital MD, Distal MD, Emery-Dreiffus MD, Facioscapulohumeral MD, Limb-Girdle MD, Myotonic Dystrophy, and Oculopharyngeal MD. Because Duchenne MD and Becker MD represent a spectrum of severity and are caused by mutations of the same gene, they are referred to in the aggregate in this study. The types of MD are described in further detail in Chapter II. The types of muscular dystrophy differ widely in affected gene, age of onset, comorbidities and disease severity, clinical interventions needed, health trajectories, disease outcomes, geographic distribution, and survival [1-11]. Estimates of the crude prevalence of muscular dystrophies as a whole fall between 19.8 and 25.1/100,000 people [12].

Few population-based studies in the U.S. have examined the distributions of sociodemographic, socioeconomic, and clinical factors across muscular dystrophy types. Two studies have examined the risk of cancer and relative risks of other comorbidities for Myotonic Dystrophy patients in Utah using population-based research [3,13]. However, to my knowledge, there are no U.S. population-based studies of individuals diagnosed with muscular dystrophies.

To determine public health practices for targeted interventions and assess health needs, it is imperative that the number of people affected by muscular dystrophy, as well as the demographic and clinical characteristics of these individuals with different types of MD, be described. A description of the clinical status of persons with MD is needed to understand the scope of these diseases. Cross-tabulating clinical characteristics with MD type will help to identify areas of future research for these MD types.

The Muscular Dystrophy Surveillance, Tracking and Research Network (MD STAR*net*) is the only population-based surveillance system for MD in the U.S. and is maintained by the Centers for Disease Control and Prevention (CDC). From 2002-2011, MD STAR*net* conducted surveillance on Duchenne and Becker MD, using an active, multiple-sourced approach for case ascertainment. To assess the feasibility of expanding the methodology of Duchenne and Becker MD to the other forms of MD, MD STARnet funded a pilot study, which was carried out in four U.S. sites. This study will serve as an extension to a project currently in process that describes the methodology of the pilot of MD STAR*net* by describing the distribution of demographic, sociodemographic, and clinical characteristics of individuals within the MD STAR*net* pilot cohort by MD type. The MD STAR*net* pilot surveillance data were collected to assess the feasibility of extending the MD STAR*net* population-based surveillance protocol for Duchenne and Becker MD to other forms of muscular dystrophies. The MD STAR*net* pilot utilized a cross-sectional design; therefore, our analyses will provide a snapshot of the distribution of characteristics such as employment status, mobility status, medication use, and surgeries and procedures in a large population with muscular dystrophy. We will describe the demographics (race, sex, ethnicity, age) and sociodemographic factors of persons with MD (insurance, employment), and infer the clinical status of persons with MD by quantifying their mobility and use of supportive devices (mobility, cardiac interventions, PEG (percutaneous endoscopic gastrostomy), NIPPV (non-invasive positive pressure ventilation), Cough Assist, Tracheostomy, and medications).

Chapter II: Literature Review

2.1 Congenital Muscular Dystrophy

Congenital MD is a clinically and genetically heterogeneous type of MD. The major

subtypes of Congenital MD are collagen VI-related myopathies, laminin, alpha2-related

muscular dystrophy, the α-dystroglycan-related MDs, lamin A/C-related MD, and selenoprotein

N 1-related myopathy. Graziano et al. (2015) found that the most frequent subtypes of the

disease were alpha-dystroglycan glycosylation deficiency (40.18%)[14], while another study

supported collagen VI-related myopathy as the most common subtypes of Congenital MD [15,16].

These forms of Congenital MD vary in terms of survival, underlying genetic mechanism

and symptoms [17-19], and researchers have described a wide spectrum of system involvement and

prognosis for Congenital MD patients [20]. Many forms of Congenital MD feature mild symptoms

during infancy or at birth, while some forms are severe at birth and may be life-threatening in the

first few years of life. In particular, Muntoni and Voit (2004) note that while some forms of the

disease are severe in infants, others are more mild and survival may extend into adulthood [19].

Hyptonia, muscle weakness, delayed walking, and mental retardation are symptoms of many

forms of Congenital MD. Congenital MD patients typically do not have facial weakness or

ophthalmoplegia. Cardiomyopathy rarely occurs at birth in Congenital MD patients, though this

symptom may develop in the second decade. Night-time respiratory failure is a concern as the

disease progresses [21]. No studies have examined the health-care related cost of Congenital MD.

Because diagnostic and genetic confirmation capacities have only begun to evolve in the

past ten years for Congenital MD [21], epidemiologic estimates of the burden of the disease are

limited. Individual studies have reported the prevalence of Congenital MD as 0.563/100,000 [14],

13/100,000 and .77/100,000 [22]. In a systematic review, the pooled prevalence of Congenital MD in children was 0.82/100,000, while the pooled prevalence in adult populations was 0.99/100,000 [23].

2.2 Duchenne and Becker Muscular Dystrophy

Duchenne and Becker MD, X-linked disorders, almost exclusively affect males[24], though manifesting females have been described [25]. Duchenne and Becker MD are the most common types of MD among children [24]. The mean age of diagnosis for Duchenne and Becker MD patients is between four and five years of age [26-28]. Symptoms of Duchenne and Becker MD include delay and loss of motor function as well as muscle hypotonia, pain and weakness, cognitive delay, calf hypertrophy and cardiomyopathy and respiratory involvement [28-32]. An earlier onset of symptoms for Duchenne and Becker MD patients is associated with an accelerated loss of ambulation [33]. Studies have found that the mean age of ambulation loss is between 7 and 13 years[34] with wheel-chair use by 8-14 years of age [32]. Cardiomyopathy typically affects Duchenne MD patients between the ages of 14-15 [29-31]. Scoliosis and contractures may affect DMBD patients who use wheelchairs [32,35]. The median survival for Duchenne and Becker MD patients has been estimated at 24 years[36], with death occurring before or during the third decade [32].

A prior study conducted using MD STAR*net* data in 2010 found that the population-based prevalence of Duchenne and Becker MD was 1.38 /10,000 males from 5 to 24 years of age in six U.S. sites [37]. The pooled prevalence of Duchenne and Becker MD in males globally has been estimated at 4.78/100,000, and the incidence of Duchenne and Becker MD ranges from 10.7 to 27.8/100,000 people [38]. Landfeldt et al. (2017) calculated the total cost of Duchenne and

Becker MD for the patient and caregiver at 624,240 to 713,840 EUR. This study constructed financial models considering the 2015 value of the Great Britain pound.

2.3 Distal Muscular Dystrophy

Distal MD is a rare and progressive disease featuring muscle weakness and deterioration of extremities, including hands, feet and lower legs. Due to the rare and highly variable nature of Distal MD, the prevalence of the disease is difficult to quantify, and data are limited [39,40]. One cross-sectional study conducted in a muscle clinic in England noted that 0.9% of their MD population studied had Distal MD[41]. Another study conducted in Finland examined Tibial muscular dystrophy, a form of Distal MD, and found that 41 of their 60 patients were symptomatic [42]. Though originally identified in the Finnish populations [42], TMD has since been identified in Italian [43], Spanish [44], French[45], and Belgian [46] populations. The prevalence of some forms of Distal MD vary geographically [41]. Though most forms of Distal MD are autosomal dominant, there are a few subtypes that are autosomal recessive.

Because of the diversity of clinical characteristics, severity and age of onset for Distal MD, survival in these patients has not been described. Literature on Distal MD and the subtypes is limited; however, many forms of the disease have been identified. Muscle impairment and symptoms vary among these different forms. There is no evidence of cardiac or respiratory involvement in Laing Distal Myopathy, Miyoshi Myopathy, nor Tibial MD [40,42,47-49]. However, cardiac and mild respiratory issues affect Distal Nebulin Myopathy patients later in disease progression [50]. While both Miyoshi Myopathy and Tibial MD begin to manifest during the second or third decade of life [48,49], Laing Distal Myopathy features an early, yet variable, onset from 4 to 25 years of age [48,51], and Welander Distal Myopathy does not affect patients until the fourth or sixth decade of life.

2.4 Emery-Dreiffus Muscular Dystrophy

Emery-Dreiffus MD is characterized by a triad of clinical characteristics: contractures prior to significant muscle weakness; progressive, yet slow, wasting and weakness of the muscles with early involvement of the proximal muscle which may spread to the limb girdle areas; and defects in the cardiac conduction system [52].

Emery-Dreiffus MD is classified as (1) autosomal dominant, (2) autosomal recessive, and (3) X-linked recessive. The underlying genetics and clinical symptoms vary among these forms of the disease [53-56]. Cardiac involvement in the X-linked form of Emery-Dreiffus MD is more severe than in autosomal dominant [57]. Additionally, there may be cognitive impairment in the X-linked form, and the radiologic pattern of muscle involvement has not been established between X-linked and autosomal dominant Emery-Dreiffus MD [58].

Most patients are between 3-8 years of age at the onset of symptoms, but there is a great variability in the age at onset. Some patients may have symptoms prior to 2 years of age, while others may not show symptoms until adulthood [59]. Little information is available on the access to care for patients with Emery-Dreiffus MD, their survival rates, or healthcare-related costs. The pooled prevalence of Emery-Dreiffus MD in all age groups is 0.39/100,000 [23]. The prevalence of Emery-Dreiffus MD among children has only been quantified in one study, which found a prevalence of 0.22/100,000 [60].

2.5 Facioscapulohumeral Muscular Dystrophy

Facioscapulohumeral MD is the third most common type of MD [61]. There are two forms of Facioscapulohumeral MD (type 1 and type 2) that are genetically, but not clinically,

distinguishable [62]. Though symptoms of Facioscapulohumeral MD typically first appear in the second decade of life, there is variability in when symptoms present; some may begin at infancy or before the age of 10 [61,63,64]. Though Facioscapulohumeral MD is a genetic disorder and inherited from family members, de novo mutations have been reported [63,64]. The most widely cited prevalence of Facioscapulohumeral MD is 1/20,000 [65,66]. Researchers indicate that prevalence estimates for Facioscapulohumeral MD may vary geographically. More recently, the prevalence in Utah was estimated at 1/15,000, supporting the presence of a founder's effect, wherein a genetic mutation in one individual is passed along to future generations, creating a cluster of the disease. [67]. Population-based estimates of Facioscapulohumeral MD in the Netherlands are 12/100,000 [68]; in this same study, the incidence rate of Facioscapulohumeral MD was .3/100,000 person-years [68]. Italian studies have estimated Facioscapulohumeral MD prevalence at 4.6/100,000 people [69,70]. A systematic review found that the pooled prevalence of Facioscapulohumeral MD in all age groups is 3.95/100,000. The same systematic review calculated a pooled prevalence of 0.29/100,000 for children with Facioscapulohumeral MD [23], and the authors acknowledge the variability of prevalence estimates used to calculate the pooled measure.

Initial muscle impairment, particularly in face, back, shoulder, humeral, trunk and leg muscles [61,64] characterize Facioscapulohumeral MD. Progression of this disease is variable and slow [61]. Facial weakness is present in approximately 60% of Facioscapulohumeral MD patients, but the severity varies. In those Facioscapulohumeral MD patients who have facial weakness, 25% have mild facial weakness, which may obscure the diagnosis [64]. There is multisystem involvement in Facioscapulohumeral MD; pain and fatigue are common in Facioscapulohumeral MD patients [71-73]. One study documented pain in 88.6% of their sample at the time the study was

conducted [74], and another noted at least moderate pain in over half of Facioscapulohumeral MD patients. Pain also appears to impact quality of life (QoL) for Facioscapulohumeral MD patients [75]. There is some evidence of cardiac abnormalities for this type of MD, including incomplete right bundle branch block; however cardiomyopathy is not typically present in Facioscapulohumeral MD patients [64,76]. Respiration may also be affected in Facioscapulohumeral MD patients, and infrequently, hearing and vision loss may occur [61].

2.6 Limb-Girdle Muscular Dystrophy

Generally, Limb-Girdle MD affects the hip and shoulder girdle; however, there are several forms of Limb-Girdle MD, differentiated by the pattern of musculature involvement, age of onset, severity, and underlying genetics. In a systematic review, Mah et al. (2016) documented the pooled prevalence of Limb-Girdle MD as 1.63/100,000 when all age groups were considered. The pooled prevalence of Limb-Girdle MD in children was 0.48/100,000 [23]. As Mah et al. (2016) noted, there was heterogeneity in estimates of Limb-Girdle MD frequency in all age groups but not in the estimates of the frequency of Limb-Girdle MD in children [23]. Limb-Girdle MD has been documented globally, including in Denmark [77], India [78-81], Norway [82], Mexico [83], and Taiwan [84] among others.

The recessive forms of Limb-Girdle MD (LGMD2) are more common than the dominant forms (LGMD1)[83,84]; the cumulative prevalence of LGMD2 is 1/15,000 [85], while dominantly transmitted forms of Limb-Girdle MD may only account for 10% of cases [86]. Autosomal recessive forms of the disease are grouped into Calpainopathies, Dysferlinopathies, and Sarcoglycanopathies. Both Calpainopathies and Dysferlinopathies are slowly progressing and impact both genders in the second decade of life. Dysferlinopathies occur globally, have a distal or proximal onset beginning with gastrocnemius muscle impairment[78]. Calpainopathies are

characterized by proximal weakness in pelvic/shoulder girdle, joint and Achilles contractures, and hernias[78]. Sarcoglycanopathies have a childhood onset and often feature weakness of knee flexor [87,88]. Cardiomyopathy and severe respiratory impairment has been reported in patients with sarcoglycanopathies [89-91].

LGMD1B is considered a LMNA-related myopathy. Though LGMD1B has a later age of onset than other LMNA-related disease[92], such as Emery-Dreiffus MD, the lamnopathies are often considered a continuum of diseases as there is significant overlap in symptoms [93]. Because of the clinical and genetic variability of the disease, diagnosis can be challenging.

2.7 Myotonic Dystrophy

There are two forms of Myotonic Dystrophy, Myotonic Dystrophy Type 1 (DM1) and Myotonic Dystrophy Type 2 (DM2), which vary in terms of age of onset, survival, and severity. Literature suggests that DM2 is clinically similar to DM1 but may have more mild symptoms and is less frequent [94]. Both DM1 and DM2 involve multiple systems, including pulmonary, cardiac, endocrine, cognitive, sleep, and gastrointestinal dysfunction. Both DM1 and DM2 appear to be more common in Caucasians and essentially absent in other ethnicities. Researchers posit that this is due to a founder's effect of European origin. A study on an entirely Caucasian group in Italy found that the age-specific total prevalence for DM1 patients was 18.29/100,000 for the 41-50 years age group whereas the 61-70 years age group of DM2 patients had the highest prevalence at 2.23/100,000, standardizing for age based on European population standards [95]. In their systematic literature review, Theadom et al. (2014) noted that Myotonic Dystrophy is the most prevalent type of MD globally with prevalence estimates ranging from 0.5 to 18.1/100,000 people [12]. Mah et al. (2016) calculated the pooled prevalence of Myotonic Dystrophy in all age groups as 8.26 /100,000 and in children as 1.41/100,000 [23].

The mean and median ages at death have been estimated at 54 and 55 years for DM1 patients. However, 15% of the cohort used to obtain these estimates were congenital DM1 (cDM1) patients [96]. DM1 men have a higher mortality rate than DM1 women [97]. QoL and Health Related Quality of Life are often affected in patients with DM. These individuals have been shown to have lower scores on all SF-36 physical health subscales compared with normative data [98]. Studies have found that lower measures of physical health are associated with fatigue, muscular impairment severity, psychological distress, emotional stability, lower IQ, and not having worked within the preceding 12 months [98]. Both fatigue and the inability to do activities were reported as the most impactful symptoms for DM2 patients [99]. DM1 patients suffering from fatigue and daytime sleepiness have lower QoL levels [98,100].

2.8 Oculopharyngeal Muscular Dystrophy

The age at onset for Oculopharyngeal MD patients is in the fifth and sixth decade [101]. Oculopharyngeal MD is characterized by the late onset and slow progression of ptosis, dysphagia, and often proximal muscle weakness. In most cases ptosis or ptosis with dysphagia is the first symptom of Oculopharyngeal MD; however, in some cases dysphagia alone may be the first symptom [102]. Dysphagia may lead to malnutrition and aspiration pneumonia [101,103]. Other symptoms include weakness in axial and limb girdle muscles[104], external ophthalmoplegia [105], as well as impairment to pelvic girdle and proximal leg muscles [106]. Dysfunction of lower extremities influences HR-QoL for these patients [107].

The severity and age of onset of Oculopharyngeal MD do not appear to depend on the size of the GCNn triplet, but this is not proven [108-114]. Oculopharyngeal MD, though rare, has been reported globally, including France, Germany [110,115], the U.K [112], Thailand [116,117], Italy [111,118], Bulgarian Jews [119] and a Hispanic population in New Mexico [113,120]. A large cluster of

individuals with Oculopharyngeal MD has been documented in French-descendants in Quebec [121]. Estimates of the prevalence of Oculopharyngeal MD vary. Mazanec et al. (2013) cite studies that estimate the prevalence of Oculopharyngeal MD in Bukhara Jews in Israel, Quebec populations and French populations at 1/600, 1/1,000, and 1/200,000, respectively [122]. The estimated prevalence of Oculopharyngeal MD in the Czech Republic 1/285,700 [122], and in a Scottish population between 60 and 80 years of age, the prevalence of Oculopharyngeal MD has been estimated at 3.22/100 000 [114]. Though survival may not be impacted in Oculopharyngeal MD patients, QoL is reduced in comparison to controls [123].

Chapter III - Methods

3.1 MD STAR*net* pilot Cohort

Individuals with MD who resided in one of the four sites for any amount of time between January 1, 2007 until December 31, 2011 and had at least one health encounter were included in this surveillance. Health encounters may have occurred in neuromuscular clinics, hospitals, or emergency departments. Eligible MD types included Becker MD, Congenital MD (excluding congenital myopathies), Duchenne MD, Distal MD, Emery-Dreiffus MD, Facioscapulohumeral MD, Limb-Girdle MD, DM, Oculopharyngeal MD, other MD, and MD-not otherwise specified (MD-NOS). For the purpose of this study, the MD-NOS/Other category is the aggregate of cases defined as MD-NOS, which was selected as the case definition when the type of MD was not specified in the medical record, and 'other,' which was selected when the type of MD was specified in the record but there was not enough evidence to confirm the accuracy of the diagnosis. There were no age or gender limitations for inclusion.

3.2 Surveillance Methodology

The United States Congress amended the Public Health Service Act in 2001 to create the Muscular Dystrophy Community Assistance, Research, and Education Act (MD–CARE Act),, which directed federal agencies to conduct research into the muscular dystrophies. The MD-CARE Act directed CDC to conduct "epidemiological activities regarding Duchenne and other forms of muscular dystrophies, including collecting and analyzing information on the number, incidence, correlates, and symptoms of cases." Subsequently, the CDC funded the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*) to conduct population–based surveillance of the muscular dystrophies [124]. MD STAR*net* utilizes active record review with a multiple source approach.

From 2002-2011, MD STAR*net* conducted surveillance on Duchenne and Becker MD in the U.S. The methods of this surveillance program have been previously published (Mathews et al., 2010; Miller et al., 2006). Briefly, the DMBD surveillance can be segmented into four stages: identification of potential cases, case abstraction, clinical review and case definition and linkage of cases to administrative data. Trained abstractors identified individuals with ICD-9-CM code 359.1 in hospital discharge data and identified potential cases in neuromuscular clinics from cases lists. Sources for Duchenne and Becker MD surveillance included: neuromuscular clinics, hospitals, private physician records, birth defects surveillance systems, hospital discharge data, vital records (birth and death), and National Death Index searches. After a potential case was identified at a clinic source, a trained abstractor abstracted information from medical records. For each potential case, a portion of the information abstracted, including clinical and family history, was sent to a Clinical Review Committee (CRC), which consisted of a clinician from each MD STAR*net* site. Cases were reviewed on a monthly basis. The CRC members independently categorized potential cases by case definition: definite, probable, possible, asymptomatic, female, and not Duchenne and Becker MD. If case assignment was unanimous after initial review of the case, then the agreed upon case definition was used. If the CRC was not unanimous in assigning case definition, then the case was discussed on a monthly call to come to consensus on the case definition. If more information was needed to determine a case definition, the case was sent back to the site to gather additional information. Quality control measures were used to logic-check values and ensure data completeness [125,126].

3.3 MD STAR*net* Pilot Methods

The MD STAR*net* pilot was conducted in four MD STAR*net* sites: Arizona (AZ), Colorado (CO), Iowa (IA) and a 12 counties in western New York (wNY). AZ acted as an agent

of the Arizona Department of Health Services to conduct MD surveillance. The IRB at the University of Arizona reviewed, approved, and monitored MD STAR*net* activities in AZ as well as activities at healthcare facilities where records were accessed. CO, IA, and wNY operated through the legal authority for public health surveillance from their respective state health department. At each of the four aforementioned MD STAR*net* sites, a data manager, program manager, and one to three abstractors performed surveillance activities, with oversight and input from a principal investigator and a neuromuscular specialist. A surveillance protocol, considering potential analyses, was established collaboratively between the CDC and the sites prior to conducting surveillance activities.

The case-finding methodology for the MD STAR*net* pilot mirrored the case-finding methodology used by the MD STAR*net* for Duchenne and Becker MD surveillance. The MD STAR*net* pilot relied on case review from multiple case sources. Cases were identified in four ways: (1) ICD-9-CM codes [359.0, 359.1, 359.21] in medical records and administrative data; (2) ICD-10 codes [G71.0, G71.1] on death certificates; (3) cases from the Duchenne and Becker MD MD STAR*net* data that met criteria. The minimum criteria for case abstraction was a clinical diagnosis in the medical record.

Cases were ascertained from healthcare facilities where MD patients received care and administrative data sources. Clinics and health care facilities providing data included MDA/neuromuscular clinics, hospitals, rehabilitation or physical medicine clinics, and other specialty clinics. Data were not obtained from other outpatients facilities due to limited time and resources. Specialty clinics were those that provide genetic services or other outpatient services. Administrative sources included birth defects registries, healthcare administrative data (including

accounting records), state hospital discharge summaries, Medicaid claims (in CO), and vital records (state birth and death certificates).

Abstractors screened lists of ICD-9-CM and ICD-10 codes from healthcare sources and searched for ICD-9-CM and ICD-10 codes in administrative sources. If the abstractor identified an eligible case, additional information pertaining to the type of MD method of diagnosis, and eligibility criteria was abstracted. The method of diagnosis could be listed as clinical diagnosis, genetic diagnosis in self or genetic diagnosis in family. Subsequently, MD STAR*net* clinicians reviewed the abstracted data for cases in their own sites to evaluate MD type and method of diagnosis. If either the method of diagnosis or MD type were not clear, further review was executed by the CRC on a monthly basis. Using identifying and source data, abstractors determined if the eligible case was already included in MD STAR*net*'s Duchenne and Becker MD surveillance. If the case had been previously identified and had a more recent health encounter, then more recent information was abstracted and the records were linked. For each eligible case that had not been previously included in the MD STAR*net* Duchenne and Becker MD Surveillance, a full medical record abstraction was completed, which included core variables such as demographics.

Before surveillance field activities began, sites collaboratively decided on the protocol, the anticipated analyses, and the data variables needed. The MD STAR*net* Data Coordinating Center (DCC) developed software to manage the collection, storage, review, and pooling of data as well as to conduct quality control checks, in which all abstractors were trained. Training included detailed instructions, presentations on each MD, practice cases and scenarios, and additional training for variables/conditions that were inconsistent across sites. A manual to aid in the structured abstraction of information was created and given to each abstractor. From the

15

lexicon of language used in MD records, equivalent terminology was developed. Abstractor

reliability was, and a high agreement in abstraction results was reflected in the >90% Inter-rater

Reliability (IRR) calculated prior to data. Quarterly assessments of abstraction progress and data

quality were conducted to resolve database issues and provide targeted training.

3.4 Variables

Abstractors recorded the most recent information for time sensitive data from visits

between January 1, 2007 and December 31, 2011. Time-sensitive variables included mobility,

living situation, medication and vital status. Variables not dependent on time, such as race,

ethnicity, and family history, were abstracted regardless of when the information was recorded

between 2007 and 2011. Because of the epidemiological importance of race and ethnicity,

abstraction of this information was not restricted to prior to the December 31, 2011 endpoint.

The following demographic variables were included in this paper: type of MD (as

described below), sex (male/female), age at start of project (January 1, 2007), race

(white/Caucasian, black/African American, multiple/other, and unknown), and Hispanic

ethnicity (yes/no/missing). The following sociodemographic variables were included in this

paper: insurance status (private, public, both, uninsured/self-pay, other, not documented), living

situation (full-time in assisted living: yes/no), and employment (as described below). The

following clinical variables were included in this study: vital status (deceased/not deceased), age

at death, mobility (as described below), percutaneous endoscopic gastrostomy (PEG) (yes, not

documented), nasal intermittent positive pressure ventilation (NIPPV) (yes, not documented),

tracheostomy (yes, not documented), cough assist (yes, not documented), pacemaker (yes, not

documented), defibrillator (yes, not documented), and cardiac transplant (yes, not documented).

The count of medications at the most recent visit and the most frequently used medications at the most recent health encounter are also described.

Individuals who were American Indian/Alaska Native, Asian, multiple races, Native Hawaiian/Pacific Islander or other were included in the multiple/other category. Hispanic ethnicity, regardless of race, referred to persons of Cuban, Mexican, South or Central American, or other Spanish culture or origin. Age at the start of the study was calculated using date of birth (DOB) and January 1, 2007. Participants who were born during the study had a start age of 0. The ages used to stratify mobility and employment were calculated using DOB and the date at which the variables were recorded in the medical records.

Vital status was listed as deceased if documentation of death was available in the form of a death certificate, medical record, or a newspaper obituary. For deceased cases, date of death was recorded and the age at death was calculated using the DOB. If a case died after the conclusion of the study period (12/31/2011), they were considered living.

Individuals with an MD type of Duchenne MD or Becker MD who were female were reclassified as DBMD manifesting females. Male Duchenne MD and male Becker MD cases were combined into one category, Duchenne and Becker MD. For the purposes of this study, MD NOS and 'Other' were combined into the category MD NOS/Other.

Employment status was included as seven dichotomous variables: younger than school age, student, working for pay, disabled, retired, unemployed, and not documented. For each individual case, more than one employment status was recorded where appropriate. Employment status was stratified by the age at which employment status was recorded, with the exception of younger than school age and not documented. Employment status was reported for the following

forms of MD: Duchenne and Becker MD, Facioscapulohumeral MD, Limb-Girdle MD, DM, Oculopharyngeal MD and MD NOS/Other.

Mobility status reflected the patient's mobility at the most recent health encounter prior to December 31, 2011. If a patient was able to ambulate with or without devices, such as walkers, canes, or crutches, mobility status was 'ambulatory'. If a patient used a wheel-chair or stroller part-time, even if only for long distance, mobility status was 'ambulatory with device support'. If a patient used a full-time manual or power wheel-chair, a full-time scooter, a full-time unknown device, or was bedridden, mobility status was 'non-ambulatory'. When the patient's mobility did not conform to these categories or was not documented, then mobility status was 'other' or 'not documented'.

Clinical variables were included as 'yes' if they were present. An affirmative response for NIPPV included the use of CPAP or BiPAP. The most recent medications were abstracted from the cases' most recent health encounter. A count of the medications for each individual was calculated from the Medications variable. Therapeutic class was assigned for the most frequently used medications.

When information on a variable was not available in the medical record of an individual or in an administrative data set, 'not documented' or 'unknown' was indicated in the data set. Missing data were excluded from analyses.

3. 5 Statistical Analyses

Statistical Analyses were conducted in SAS 9.4, (SAS Institute, Cary NC). Means and standard deviations as well as median and interquartile ranges were reported for continuous variables. Frequencies and proportions were reported for categorical variables. Due to the rare nature of the muscular dystrophies, frequencies under 10 were not reported for demographic

variables in order to protect the privacy of subjects. Consequently, denominators for estimates

for the total sample were adjusted according to the reportable groups of MDs. In Tables 1-7,

excluded forms of MD are indicated for each variable.

Chapter IV: Results

4.1 Demographics

A cohort of 2,862 eligible cases was included in this study. Table 1 describes the mean age by MD type and provides the frequency and percent for each form of MD. The most frequent types of MD were Myotonic Dystrophy, Duchenne and Becker MD, and Facioscapulohumeral MD, which accounted for 33%, 25.5% and 9.7% of cases, respectively. The mean age at the start of the study was 15.5 (12.3) for Duchenne and Becker cases, while the mean age at the start of the study for manifesting females was 31.3 (19.6). The mean ages at the start of the study for Distal MD, Facioscapulohumeral MD, Limb-Girdle MD, and Myotonic Dystrophy were 43.9 (12.6), 43.6 (20.0), 38.5 (21.8), and 38.6 (18.3). In contrast, the mean age at the start of the study was lower for Congenital MD cases ($\bar{X}$=13.2) and Emery-Dreiffus cases ($\bar{X}$=23.2). Oculopharyngeal MD cases were the oldest with a mean age at the beginning of the study period of 65.7 (9.8).

Demographic and sociodemographic variables, including gender, race, Hispanic ethnicity, most recent insurance status and living situation, are described in Table 2. All demographic variables were not reported for Emery-Dreiffus MD or Distal MD cases due to the small number of cases. For those cases for whom demographics were reported, 36.2% were female and 63.7% were male as evidenced in Table 2. Table 2 further shows that 79.9% of the MD STAR*net* pilot cohort, excluding Facioscapulohumeral MD, Emery-Dreiffus MD, Distal MD cases, were Caucasian or white, 3.0% were black or African American, and 7.6% were in the Multiple/Other category. For 9.6% of cases, race was unknown. For Myotonic Dystrophy cases, 85.3% were white or Caucasian, and 62.6% were not Hispanic. Similarly, 78.5% of Duchenne and Becker MD cases were white or Caucasian, and 67.6% were not Hispanic. Thirty

four percent of Oculopharyngeal MD cases were Hispanic while only 26.1% were not Hispanic. Overall, 13.8% of cases were Hispanic, 59.5% were not Hispanic, and the Hispanic ethnicity was not known for 26.7% of the sample.

4.2 Sociodemographic

Frequencies and percentages for insurance status were not reported in Table 2 for individuals with Congenital MD, Distal MD, Emery-Dreiffus MD, Duchenne and Becker MD manifesting females, Facioscapulohumeral MD, Limb-Girdle MD, Oculopharyngeal MD and those classified as MD NOS/Other due to small sample sizes. 32.4% of individuals with Myotonic Dystrophy and males with Duchenne and Becker MD were only insured privately, 48.8% had only public insurance, and 11.6% had both public and private insurance. 2.7% of this group of cases were uninsured or paid for medical costs out-of-pocket. Insurance status was not documented for 4.5% of Duchenne and Becker MD and Myotonic Dystrophy cases together. A description of the living situation was reported for Congenital MD, Myotonic Dystrophy, Oculopharyngeal MD and MD NOS/Other in Table 2; small cell sizes limited the analysis of other types of MD. Most cases were not in congregate care or assisted living (85.6%). Though over 80% of Myotonic Dystrophy, Oculopharyngeal MD and MD NOS/Other each were not in congregate care or assisted living, between 8 and 13% of these groups were not living independently.

All Congenital MD, Distal MD, Emery-Dreiffus MD cases as well as all Duchenne and Becker MD manifesting females were excluded from analysis of employment status as there were not enough cases to describe patterns of employment stratified by age. Of note, it was possible for multiple employment status and student status entries to be made; therefore, the quantification of employment status for these MD types does not represent mutually exclusive

classification. The percentage and frequency of those who were younger than school age as well as the descriptive statistics for those who were students for each type of MD are provided in Table 3. As evidenced in Table 3, there were no Facioscapulohumeral MD, Limb-Girdle MD, or Oculopharyngeal MD cases younger than school age. For Duchenne and Becker MD and Myotonic Dystrophy cases, 2.9% and 2.7% of were younger than school age, respectively. While 46.2% of Duchenne and Becker MD cases who were under 5 years old were students, there were not enough Facioscapulohumeral MD, Limb Girdle MD or Myotonic Dystrophy cases in the same age group who were students to report exact values. The majority of Duchenne and Becker MD(98.3%), Facioscapulohumeral MD (96.9%), and Limb-Girdle (95.4%) cases between the ages of 5 and 18 were students whereas a smaller percentage of Myotonic Dystrophy cases in the same age group were students (89.8%). Considering those older than 18 but younger than 35, 41.4% of Duchenne and Becker MD and 19.2% of Myotonic Dystrophy cases were students. There were no Oculopharyngeal MD cases under the age of 35 who were students.

Table 4 describes employment status for each type of MD stratified by the age at which the employment status was recorded. While only 13.5% of Duchenne and Becker cases between 18 and 35 were working for pay, 32.3% between 35 and 65 were working for pay. In contrast a larger percentage of Facioscapulohumeral MD (47.9%), Limb-Girdle MD (49%) and Myotonic Dystrophy (38.3%) cases between 18 and 35 were working for pay than Facioscapulohumeral MD (44.6%), Limb-Girdle MD (40.5%), and Myotonic Dystrophy (25.4%) cases between 35 and 65 years of age. While 17.8% of Duchenne and Becker cases between 18 and 35 years of age were disabled or unable to work, there were a larger percentage of those from 35 to 65 years of age who were disabled (49.2%). Duchenne and Becker cases from 35 to 65 years of age had the highest percentage of those who were disabled or unable to work, followed by Myotonic

Dystrophy cases in the same age group (45.1%). A higher percentage of Oculopharyngeal MD cases who were between 35 and 65 years of age were disabled compared to Oculopharyngeal MD cases over the age of 65. Sixty-four percent of Oculopharyngeal MD cases over 65 years-old were retired, and there were Duchenne and Becker cases over the age of 65 who were retired.

4.3 Clinical Variables

The frequency and proportion of MD cases who are ambulatory, ambulatory with device support, and non-ambulatory are stratified by the age which mobility status was recorded and reported by MD type in Table 5. The percentage of Congenital MD cases under 10 years of age who are ambulatory and the percentage of those who are non-ambulatory were equivalent (37.5%). For Congenital MD cases who are 18 to 35 years of age, 47.8% were ambulatory and 39.1% were non-ambulatory. There were few cases with Congenital MD who were older than 35. Most Duchenne and Becker MD under the age of 10 were ambulatory (59.4%), and 15.6% were ambulatory with device support. Though only 20.6% of Duchenne and Becker MD cases under the age of 10 were non-ambulatory, 67.7% from 10 to 18 years of age were non-ambulatory, and 78.5% between 18 and 35 years-old were non-ambulatory. No Distal MD cases were under 18 years-old. Most (64.3%) of Distal MD cases from 35 to 65 years-old were ambulatory. For Distal MD cases in this same age group, 14.3% were ambulatory with support, and 21.4% were non-ambulatory. The percentage of ambulatory Emery-Dreiffus cases decreased as age increased, and there were no Emery-Dreiffus case who were ambulatory with device support. There were 3 Duchenne and Becker manifesting females between the ages of 18 and 35 who were non-ambulatory, representing 60% of cases in this age group.

Though 94.4% of Limb-Girdle MD cases under 10 years of age in the MD STAR*net* pilot were ambulatory and no cases in this age group were non-ambulatory, only 40% of case over 65

were ambulatory and 45% were non-ambulatory. For Facioscapulohumeral MD cases, 74.5%

between 18 and 35 years of age were ambulatory. However, only 65% of Facioscapulohumeral

MD cases between 35 and 65 were ambulatory. Comparing Facioscapulohumeral MD cases from

35 to 65 years of age and those who are 65 years and older, the percentage of ambulatory

Facioscapulohumeral MD cases did not change greatly. Most Myotonic Dystrophy cases from 10

to 18 years of age (90.2%) and from 18 to 35 years of age (88.8%) were ambulatory. However,

76.3% and 66.2% of Myotonic Dystrophy cases from 35-65 years and over 65 years were

ambulatory, respectively. Eighty-five percent of Oculopharyngeal MD cases from 35 to 65 years

of age were ambulatory, while only 68% of Oculopharyngeal MD cases over the age of 65 were

ambulatory.

The frequency and proportion of deceased cases for each type of MD are provided in

Table 6, and the descriptive values for the age at death are provided in Table 1. The highest

proportion of deceased cases were those with Oculopharyngeal MD (21.0%), and

Oculopharyngeal MD cases had the highest average age at death ($\bar{X}$= 77.0). In contrast, a small

proportion of Distal MD, Duchenne and Becker MD manifesting females, and

Facioscapulohumeral MD were deceased. For Distal MD and Duchenne and Becker MD

manifesting females, this low proportion may be due to the small number of cases ascertained

and included in the cohort. Congenital MD cases had the youngest average age of death

($\bar{X}$=12.1). Male Duchenne and Becker MD cases, not surprisingly, had a young average age at

death as well ($\bar{X}$=25.5).

The frequency of PEG in Congenital MD, Distal MD, Duchenne and Becker MD,

Duchenne and Becker MD manifesting females, Emery-Dreiffus MD, Limb-Girdle MD and MD

NOS/Other are provided in Table 6. Approximately 21% of Congenital MD cases had a PEG

while no Distal MD cases received PEGs. Additionally, 9.3% of Duchenne and Becker MD males required a PEG. NIPPV was reported for individuals with all forms of MD except for Oculopharyngeal MD in Table 6. In total, 21.5% of these cases had been on NIPPV, and NIPPV was not documented in the records of the other 2133 cases. 27.9% of Congenital MD cases, 32.6% of DMBD males, and 22.8% of Myotonic Dystrophy case had used some form of NIPPV.

The frequency of cases who had ever had a tracheostomy or cough assist for Duchenne and Becker MD males and manifesting females as well as individuals in the MD NOS group is reported in Table 6. Overall, 9.1% cases had a tracheostomy documented in their records, and 16% of cases had the use of cough assist documented in their records. Individuals in the MD NOS/Other group had tracheostomies (7.54%) more frequently than they used cough assist (0.75%).

The use of cardiac devices and transplants are reported for individuals with Congenital MD, Distal MD, EDMD, Limb-Girdle MD and Myotonic Dystrophy as well as those in the MD NOS/Other group in Table 6. Pacemakers were noted in the records of 7.1% of cases while only 2.6% required defibrillators. Heart transplants were required in only 10 MD cases. The use of pacemakers was documented for only 1 Congenital MD patient whereas 4 of 22 Emery-Dreiffus MD cases had pacemakers. Pacemakers were documented for 9.9% of Myotonic Dystrophy cases. No Distal MD cases had pacemakers, and a small percentage of Limb-Girdle MD and MD NOS/Other cases had pacemakers. Defibrillators were documented in 3.82% Myotonic Dystrophy cases. No Congenital MD or Distal MD cases had defibrillators, and only 1 Emery-Dreiffus MD case had documented defibrillator use. Overall, there were 10 heart transplants documented in the 1726 cases for which this variable was reported (0.6%). Two of 17 Distal MD cases and 2/22 Emery-Dreiffus MD cases required heart transplants. No heart transplants were

documented for Congenital MD cases. Table 6 provides the frequencies and percentages of cases who had heart transplants for each MD type.

. Descriptive statistics for medication counts are provided in Table 7. As a whole, MD cases in the MD STAR*net* pilot cohort had an average of 4.41 (4.47) medications listed in their medical record at their most recent health encounter. Oculopharyngeal MD cases had the highest average number of medications listed at their most recent health encounter, while Emery-Dreiffus MD cases had the lowest average of medications.

Table 8 described the frequency and percentage of MD cases who were taking frequently documented medications. Lisinopril was most frequently used by Distal MD (23.5%) and Duchenne and Becker MD (21.7%) cases. Approximately 9% of Oculopharyngeal MD cases were on Furosemide, and 6.9% of Limb Girdle cases were on Furosemide. The highest percentage of cases using Albuterol were Duchenne and Becker Manifesting Females (29.4%) and Congenital MD (14.0%) cases. Nearly 7% of Facioscapulohumeral MD cases and 7.8% of Duchenne and Becker cases were taking Albuterol at their most recent health encounter. The same percentage of Myotonic Dystrophy and Oculopharyngeal MD cases (9.2%) were taking Omeprazole. Duchenne and Becker MD cases were the most frequent users of Prednisone; 19.8% of Duchenne and Becker MD cases had Prednisone documented in their record at the most recent health encounter.

Chapter V: Discussion

5.1 Demographics

Race and Hispanic Ethnicity

There is some evidence of racial and ethnic differences in MD. Though Congenital MD is present in many races and ethnicities [16,127], 76.74% of Congenital MD cases in the MD STAR*net* pilot cohort were white, while only 13.95% were categorized 'Multiple /Other'. Less than 10 cases of Congenital MD were black or African American. Unfortunately, we were unable to report Hispanic ethnicity for Congenital MD cases due to small cell sizes. Similarly, race and ethnicity could not be reported for cases of Distal MD. Literature does indicate that Distal MD primarily affects individuals of western European descent [42], and Distal MD has not yet been documented in Hispanic populations.

Prior studies using MD STAR*net* Duchenne and Becker MD Surveillance data have found some ethnic differences in the prevalence of Duchenne and Becker MD. Romitti et al. (2015) found that DMBD was more common in Hispanic individuals than in black, non-Hispanic individuals [128]. In the MD STAR*net* pilot surveillance data, most Duchenne and Becker MD cases were white or Caucasian (78.53%), and the majority of Duchenne and Becker MD cases were not Hispanic (67.59%), which reflects the low diversity in these surveillance sites.

In a U.S-based study of the symptom burden of Facioscapulohumeral MD cases, most Facioscapulohumeral MD cases were white and non-Hispanic [129]. Though we could not report the distribution of race for Facioscapulohumeral MD cases due to small cell sizes, it was found that only 7.91% of Facioscapulohumeral MD cases were of Hispanic ethnicity. The majority of these cases (57.19%) were not Hispanic. In terms of the influence of ethnicity, Facioscapulohumeral MD has also been documented in Turkish cases [130]; thus further study, with

larger sample sizes, is needed to adequately compare the distribution of race for Facioscapulohumeral MD cases in the MD STAR*net* pilot cohort comparatively with other literature.

As evidenced in Table 1, most Limb-Girdle MD cases (77.69%), Myotonic Dystrophy cases (85.26%) and Oculopharyngeal MD cases (63.3%) were white or Caucasian. Though Myotonic Dystrophy and Limb-Girdle MD cases were also primarily non-Hispanic, there were a higher percentage of Hispanic Oculopharyngeal MD cases than non-Hispanic Oculopharyngeal MD cases. Literature indicates that both DM1 and DM2 appear to be more common in Caucasians and essentially absent in other ethnicities, but the ethnic and racial distribution of Limb-Girdle MD and Oculopharyngeal MD cases are more diverse in the literature. A severe, childhood onset form of Limb-Girdle MD has been found in Hispanic populations in Puerto Rico [131], and Oculopharyngeal MD has been described in a Hispanic Population in New Mexico [113,120]. The racial distribution of Emery-Dreiffus MD is not well described and no literature has described Emery-Dreiffus MD in Hispanic populations. As aforementioned, Distal MD is most common in areas in Western Europe; however, as a result of the small number of cases of Emery-Dreiffus MD and Distal MD, race and Hispanic ethnicity were not reported. As a whole for the MDs with reportable race and ethnicities, most were white (79.88%) and non-Hispanic (54.49%).

5.2 Sociodemographic

Insurance Status

For Duchenne and Becker MD cases and Myotonic Dystrophy cases in the MD STAR*net* pilot cohort, a similar pattern of insurance status was observed. Nearly 50% of cases were publicly insured, between 30-35% had private insurance, and 8-15% were both publicly and

privately insured. The percentage of Duchenne and Becker MD and Myotonic Dystrophy cases who were uninsured or paid for medical expenses out of pocket was small (2-3%). The percentage of individuals who had insurance in the MD STAR*net* cohort was larger compared to the percent with insurance in the 2014 study conducted by Larkindale et al. [132]. Using data from commercial insurance databases, Medicare claims, and family surveys, Larkindale et al. (2014) noted that 51% and 70% of Duchenne MD and Myotonic Dystrophy cases, respectively, either had private insurance or coverage via Medicare [132].

Larkindale et al. (2014) also estimated a high annual cost for individual Myotonic Dystrophy and Duchenne MD patients ($32,236.00 and $50,952, respectively) and a high annual cost at a national level in the U.S. for Myotonic Dystrophy and Duchenne MD patients ($448 million and $787 million, respectively) [132]. Because the cost of MD related medical expenses are high, insurance is incredibly significant to this population as costs of MD related medical expenses is incredibly high. Further, in a study using self-reported data from 1,057 male Duchenne and Becker MD patients, researchers determined that insurance status was a significant predictor of longer wheelchair-free survival [133].

To my knowledge, insurance coverage for patients with Congenital MD, Distal MD, Emery-Dreiffus MD, Limb-Girdle MD, or Oculopharyngeal MD have not been described. Due to small sample sizes we were not able to describe the insurance status of these patients as well as Facioscapulohumeral MD patients.

Independence and Assisted Living

This analysis of the MD STAR*net* cohort revealed that most Congenital MD, Myotonic Dystrophy, Oculopharyngeal MD and MD NOS/other cases were not in congregate care or assisted living A description of the living situation of MD patients, including whether the patient

is in congregate or assisted living, is absent in the literature for many forms of MD. However, independence has been assessed through qualitative studies and by measuring Activities of Daily Living (ADL).

Yamaguchi et al. (2013) conducted a qualitative study in which Duchenne and Becker MD patients in Japan were interviewed to ascertain their reasons for pursuing independent living. The researchers found that Duchenne and Becker MD patients emphasized choice, retaining autonomy, and improving social inclusion as the primary reasons for pursuing independent living [134] . In another qualitative study, the use of invasive home mechanical ventilation facilitated independent living in Duchenne and Becker MD patients [135]. This study did not describe the demographics of these patients. Other researchers have found that over 30% of Duchenne MD patients are independent in self-care, but total assistance for self-care is required between 3% and 7% of Duchenne MD patients [136]. Unfortunately, due to small cell sizes, the results of independent living for Duchenne and Becker MD cases could not be reported.

In a study examining Myotonic Dystrophy patients in combination with proximal MD and Myopathia distalis tarda hereditaria, researchers found that over half of patients relied on others for activities of daily living [137]. Further, Natterlund (2001) found that dependence on others for Myotonic Dystrophy patients increased over a 5 year period [137]. Similar to the deterioration in Myotonic Dystrophy patients, there appears a reduction in ADL scores overtime for Facioscapulohumeral MD and Limb-Girdle MD patients [138,139]. Though other publications have documented a reduction in ADL over time for Myotonic Dystrophy, Limb-Girdle MD and Facioscapulohumeral MD patients overtime, most of the MD STAR*net* cohort were not in congregate care or assisted living. This suggests that while daily activities and mobility may be reduced in individuals with MD, they are still able to live independently.

Future iterations of MD STAR*net* surveillance may collect a larger cohort of Facioscapulohumeral MD, Distal MD, Limb-Girdle MD, and Emery-Dreiffus MD patients which would enable a description of independent living for these individuals. Additionally, future studies with a larger number of cases may allow for an age-stratified analysis of living situation and analyses that examine the relationship between living situation, other clinical interventions and health outcomes for MD cases.

Education

There were no Oculopharyngeal MD, Facioscapulohumeral MD, or Limb-Girdle MD cases who were younger than school age. It is likely that there were no Oculopharyngeal MD cases who were younger than school age or students because the typical onset of this MD is later than the ages for which we reported education status. It is also not surprising that a small percentage of Duchenne and Becker cases and Myotonic Dystrophy cases are younger than school age as Duchenne and Becker MD affects children and there is a congenital form of Myotonic Dystrophy. A smaller percentage of Myotonic Dystrophy cases between 18-35 years of age in the MD STAR*net* cohort students compared to Duchenne and Becker MD, Facioscapulohumeral MD, and Limb-Girdle cases of the same age group. Further a lower percentage of Myotonic cases compared to Duchenne and Becker MD cases between 18 and 35 years of age were students. Though very little is known regarding the employment/education of the forms of MD, one study did report that 90% of Emery-Dreiffus patients who were employed had jobs that related to their education, supporting the significance of education for MD patients [140]. In the MD STAR*net* study cell sizes were too small to describe the employment and student status for Congenital MD, Distal MD, Emery-Dreiffus MD, and Duchenne and Becker MD manifesting females. Though studies have described educational attainment in patients with

Myotonic Dystrophy Type 1, Facioscapulohumeral MD, and Emery-Dreiffus MD, little has been

published on education in individuals with Oculopharyngeal MD, Limb-Girdle MD, Duchenne

and Becker MD, Distal MD and Congenital MD [141-143].

Employment

Almost one third of Duchenne and Becker MD cases between 35 and 65 were working

for pay, and there were Duchenne and Becker MD cases who were over the age of 65 and retired

in the MD STAR*net* cohort. These cases who are 35 and over are likely representative of the

Becker MD cases. Other studies have supported that 73% of Becker MD patients had an

employment history. Further, some Becker MD patients in other studies have reported that they

ceased work due to physical disability [144]. The MD STAR*net* cohort supports that burden of

disability in these cases as nearly half of the Duchenne and Becker MD cases between 65 and 35

years of age were disabled or unable to work

The percentage of cases working for pay decreased with age for Facioscapulohumeral

MD, LGMD, and Myotonic Dystrophy cases; however, for Duchenne and Becker MD cases,

there was an increase in those working for pay between the 18 to <35 and 35 to <65 age groups.

This result may be due to a shift in the make-up of the Duchenne and Becker MD group to a

higher percentage of Becker cases.

Though Duchenne and Becker cases from 35 to 65 years of age represented the highest

percentage of cases disabled or unable to work, a higher percentage of Myotonic Dystrophy

cases were disabled or unable to work compared to Limb Girdle cases and Facioscapulohumeral

MD cases in the 35 to <65 age group, suggesting that the symptoms of Myotonic Dystrophy may

lead to more disability in third through sixth decades of life compared to Facioscapulohumeral

MD and Limb-Girdle patients. Interestingly, a higher percentage of Oculopharyngeal MD cases

who were between 35 and 65 years of age were disabled compared to Oculopharyngeal MD cases over the age of 65. It may be either that severely affected Oculopharyngeal MD cases do not survive into the sixth decade, thus making it appear as though disability may decrease with age for Oculopharyngeal MD cases, or that employment status was more frequently recorded as 'retired' as opposed to disabled/unable to work for older cases.

Employment trends in Duchenne MD patients are not well described as these patients have historically not survived past their second or third decade of life. As the life expectancy for Duchenne MD patients grows, researchers have emphasized the importance of transition into adulthood for Duchenne MD patients, including education and social activities, for QoL [145]. In another study, 70% of Facioscapulohumeral MD patients were employed compared to 48% of Myotonic Dystrophy [146]. Similarly, in the MD STAR*net* pilot cohort, a higher percentage of Facioscapulohumeral MD patients who were over the age of 18 were employed compared to Myotonic Dystrophy patients who were over the age of 18. A U.S.-based registry study found that approximately half of adult Myotonic Dystrophy and Facioscapulohumeral MD patients reported that their disease negatively impacted their employment through a variety of mechanisms, including earlier retirement, the need for disability and job accommodations [147], which was supported by the results of the MD STAR*net* pilot as the percentage of those who were disabled or unable to work increased as age increased for Myotonic Dystrophy and Facioscapulohumeral MD case. Future studies may compare the retirement ages of Facioscapulohumeral MD and Myotonic Dystrophy cases in the MD STAR*net* pilot to normative data. Additionally, because QoL and symptom burden are related to employment status for MD patients [98,99,148], characterizing and describing employment patterns for these individuals may

help to stratify MDs by risk of reduced QoL as a result of disrupted or decreased employment, thus identifying areas for intervention and support.

5.3 Clinical Characteristics

Respiratory Devices

    NIPPV

Diminished expiratory muscle strength can lead to pulmonary impairment and ventilator insufficiency in MD patients [149]; however, MDs differ in the degree and pattern of respiratory involvement. NIPPV may prevent hypoventilation and atelectasis which may slow the progression of a restrictive respiratory pattern in some forms of MD [150]. In the MD STAR*net* pilot cohort, NIPPV was most documented for the highest percentage of Duchenne and Becker MD cases, and nearly 28% of Congenital MD cases had NIPPV documented in their records. Though a smaller percentage of Limb Girdle MD and Myotonic Dystrophy cases comparatively required NIPPV, approximately 20% of these MD cases did have this respiratory intervention documented in their medical records. Of note, 9% of Facioscapulohumeral MD cases required NIPPV.

In the MD STAR*net* pilot, Congenital MD cases required NIPPV frequently. Though Congenital MD patients appear to have impairment to non-voluntary, inspiratory muscles while expiratory muscles are relatively unaffected [151], only case reports have described the use of NIPPV in Congenital MD patients [152]. Consequently, it is surprising that such a large percentage of Congenital MD cases in the MD STARnet pilot required NIPV. The percentage of Myotonic Dystrophy cases requiring NIPPV in the MD STARnet pilot cohort (22.8%) was highly consistent with result from other studies that determined between 25% [153] and 28% of Myotonic Dystrophy patients need NIV [154].

NIPPV were required infrequently for Emery Dreiffus MD and Distal MD cases in the MD STAR*net* pilot cohort as only 2 cases for both MDs were confirmed to have used NIPPV. Other studies support the infrequency of respiratory involvement in Distal and Emery Dreiffus MD. In a German study involving patients with a different forms of Distal MD, there was impairment to respiration in all patients, and no patient required NIPPV [149]. Respiratory failure in Emery-Dreiffus MD cases may result from either weakness in the respiratory muscles or chest deformities [140], and some researchers have suggested that non-invasive ventilation may benefit Emery-Dreiffus MD patients at risk for ventilator insufficiency [155]. However, the use of ventilator devices are not well described for Emery-Dreiffus MD in the literature.

Though 9% of the Facioscapulohumeral MD cases in the MD STAR*net* pilot coort required NIPPV, other studies indicate that respiratory involvement is uncommon in Facioscapulohumeral MD patients, and the need for NIPPV is infrequent [156]. Other researchers have found that only 1% of Facioscapulohumeral MD patients needed ventilator support [157]. However, Wohlgemuth et al. (20117) showed that respiratory insufficiency in Facioscapulohumeral MD patients is related to the progression of the disease and degree of muscle impairment. They found no abnormalities in pulmonary function for ambulatory Facioscapulohumeral MD patients, and these researchers did support the presence of respiratory insufficiency in 1/3 of Facioscapulohumeral MD patients who were in wheelchairs [158]. Similar to Facioscapulohumeral MD patients, the degree of respiratory involvement for Limb-Girdle MD patients may be related to ambulatory status; Forced Vital Capacity (FVC) for non-ambulatory Limb-Girdle MD is lower than FVC patients who are ambulatory [159]. In this same study, the percentage of Limb-Girdle MD patients who required NIPPV (3/43) was lower than the percentage requiring NIPPV in the MD STAR*net* pilot cohort (17.3%) [159]. Future analyses may

cross tabulate and examine the relationship between the use of NIPPV and ambulatory status for the MDs.

Cough Assist

The use of assisted cough devices was described only for Duchenne and Becker MD males and manifesting females. Approximately one fourth of Duchenne and Becker MD males had used Cough Assist devices, and one manifesting female used Cough Assist devices in the MD STAR*net* pilot cohort. Pneumonia, acute respiratory failure and upper-respiratory infections due to the retention of fluids subsequent to ineffective coughing may lead to intubation for Duchenne MD patients. Assisted Cough devices are recommended in order to improve airway clearance and reduce the risk of infection for these patients [160]. The use of cough assistive devices had not been described for manifesting females; the use of this respiratory intervention likely speaks to the severity of symptoms for the manifesting female in this case.

Tracheostomy

Non-invasive ventilation (NIV) has been identified as an alternative to tracheostomy [161]. Tracheostomies, a more traditional approach to manage pulmonary involvement in MD patients, have risks including that it may decrease cough efficiency, provoke secretions, lead to trachea aspiration and elevate the frequency of respiratory infections [162]. There is limited contemporary research on tracheostomy in Myotonic Dystrophy patients. [163,164]. In the MD STAR*net* pilot cohort, only 10% of Duchenne and Becker MD males had tracheostomies and only one Duchenne and Becker MD manifesting female (5.88%) had a tracheostomy whereas nearly 1/3 of Duchenne and Becker MD males in the MD STAR*net* pilot cohort had the use of some form of NIPPV listed in their record.

Cardiac Devices and Interventions

Pacemakers and defibrillators

Research indicates that Emery-Dreiffus MD, Limb-Girdle MD, and Myotonic Dystrophy Type 1 frequently require pacemaker implantation [165]. In keeping with the literature, pacemakers were most frequently documented in Emery-Dreiffus MD (4 of 22), Myotonic Dystrophy (93 of 943), and Limb-Girdle MD (10 of 260) patients in the MD STAR*net* pilot. Additionally, defibrillator use was most frequently documented in Emery-Dreiffus MD (4.55% or 1/22) and Myotonic Dystrophy (3.82% or 36 of 943). Though there is a bevy of information on pacemaker and defibrillator treatment in Myotonic Dystrophy patients [166-173], research has only begun to classify cardiac issues and pacemaker and defibrillator use in Emery-Dreiffus MD and Limb-Girdle MD patients [165,174] and most of this research is limited to case reports and series [175].

Between 3-22% of Myotonic Dystrophy patients require antiarrhythmic devices, such as pacemaker or cardioverter defibrillator [176]. As pacemakers were documented in 9.86% of Myotonic Dystrophy patients and defibrillator use in 3.82% of Myotonic Dystrophy patients, the estimates of antiarrhythmic devices are consistent with the literature. Research indicates that the burden of sudden death is higher in those who have pacemakers. Due to this increased burden of sudden death and VT/VF in Myotonic Dystrophy patients with pacemakers, Bhakta et al. (2011) suggest that ICDs may be the preferred device for implantation [177]; however, these authors also indicate that antiarrhythmic devices may not always improve the outcome, QoL, or the course of disease for patients, especially for those with severe impairment and high risk of non-sudden death [177].

Permeant pacing has been used in Emery-Dreiffus MD and Limb-Girdle MD patients for AV block, atrial paralysis bradycardia, atrial standstill and atrial fibrillation [30,178,179], and pacemakers and ICDs have been used in Emery-Dreiffus MD patients to avoid sudden death

[180,181]. Most Emery-Dreiffus MD patients requiring cardiac devices are between 20-40 years of age [174,182], and studies have indicated that over 50% of Emery-Dreiffus MD patients require pacemaker implantations [183]. However, in this analysis, 4 of 22 individuals with Emery-Dreiffus MD, or 18.18%, had pacemakers documented in his or her record and only 1 patient (4.55%) had a defibrillator documented in his or her record. Because of the small number of Emery-Dreiffus MD patients in the MD STAR*net* pilot data and because of the lack of consistency with the literature, this measurement may not capture the true picture of defibrillator and pacemaker use in this group of MD patients.

Cardiac involvement is frequent in some forms of Limb-Girdle MD, primarily due to changes in the LMNA gene [184]. Though studies have noted that patients with laminopathies frequently require pacemakers or ICDs after 30 years of age [184], the frequency of the patients with Limb-Girdle MD who need pacemakers has not been described, though studies have noted that pacemaker implantation may precede heart transplants in these patients [185].

In this analysis, a pacemaker was only documented in the record of one of 86 Congenital MD patients (1.16%), and no individuals with Congenital MD had defibrillators. To our knowledge, only one case report has noted the use of a pacemaker in a child with Congenital MD [186], supporting the infrequency of pacemaker and defibrillator use in this group of MD patients. Similarly, there was no evidence of defibrillators or pacemakers in Distal MD patients in the MD STAR*net* pilot data, and only one case report has documented the use of a pacemaker in a Distal MD patient [187].

Heart Transplants

MD patients often develop cardiomyopathy, necessitating cardiac transplantation [188]. In the MD STAR*net* pilot data, heart transplantation was documented most frequently for

individuals with Distal MD (2/17), Emery-Dreiffus MD (2/22), and Limb-Girdle MD (4/260). Of note, no researchers have documented, described, or quantified the frequency of heart transplants in Distal MD patients.

Case reports and series have documented cardiac transplantation in these patients [189,190], and one study notes that 6% of the individuals with Emery-Dreiffus MD that they studied required heart transplants [183]. Though 9.09% of Emery-Dreiffus MD patients in the MD STAR*net* pilot cohort had heart transplants recorded in their medical records, the number of Emery-Dreiffus MD cases ascertained for this surveillance dataset is small. Further studies examining a larger number of Emery-Dreiffus MD patients would be needed to assess the frequency of heart transplants in this population as transplantation is the best therapy for cardiomyopathy in Emery-Dreiffus MD patients. However, there are very few studies on the efficacy and outcomes of cardiac transplant in these patients. Despite the limitations in the body of literature, evidence suggests cardiac transplant may be life-saving in these patients [191]. In the single long-term study examining outcomes of heart transplant in Emery-Dreiffus MD patients, the researchers found that long term outcomes did not differ for Emery-Dreiffus MD and non-Emery-Dreiffus MD patients [192].

Similarly, cardiac involvement, frequently resulting in the need for a heart transplant, is characteristic of other LMNA-related myopathies, including forms of Limb-Girdle MD [92,193]. The mean age of heart transplantation for Limb-Girdle MD was found to be 46 years [185], and there is not an increase of postoperative complications in Limb-Girdle MD patients who receive HTs compared to other HT patients [185,188]. The frequency of heart transplants in Limb-Girdle MD is not described in the literature.

To our knowledge no publications report the frequency of heart transplants for

Congenital MD patients, though one case report did document the transplant of a heart from a

CDM patients [194]; consequently, it is not surprising that no Congenital MD patients had heart

transplants. Further, in keeping with the literature, heart transplants were infrequent in the

Myotonic Dystrophy patients. Despite the involvement of the heart in DM, this group of MD

patients are infrequently eligible for heart transplants because of the perioperative risk [195].

Medications

Lisinopril, an angiotensin converting enzyme inhibitor (ACE-I), has replaced Digoxin as

the favored treatment for cardiomyopathy in Duchenne MD patients though some also use

losartan, an angiotensin II receptor blocker [196]. The use of Lisinopril for other MD patients has

not been described. However, in the MD STAR*net* cohort, a higher percentage of Distal MD

cases used Liniopril than Duchenne and Becker MD cases. Due to the small number of Distal

MD cases (N=17), this result may be imprecise. Oculopharyngeal MD and Limb Girdle MD

cases most frequently used Furosemide. Furosemide is a diuretic used in the treatment of heart

failure, and may amplify neuromuscular blockade during anesthesia [197]. Due to the cardiac

involvement of Limb-Girdle MD, it is not surprising that approximately 7% of these cases were

on Furosemide; however, there is no evidence of cardiac involvement in Oculopharyngeal MD

patients. The intended use of Furosemide in Oculopharyngeal MD patients may therefore be

different than it is for Limb Girdle MD patients. No Congenital MD, Distal MD, Duchenne and

Becker MD manifesting females, or Emery-Dreiffus MD patients used furosemide.

Albuterol is a beta2-adrenergic agonist. Nearly 30% of Duchenne and Becker

Manifesting Females in the MD STAR*net* pilot cohort were on Albuterol. Albuterol was also

frequently documented in the medical records of Congenital MD, Facioscapulohumeral MD, and

Duchenne and Becker cases at their most recent health encounters. In Facioscapulohumeral MD patients, Albuterol, in combination with strength training, was safe, though there was not a significant impact on muscle strength and volume [198]. Albuterol does not change pain, fatigue or functional status for Facioscapulohumeral MD patients [199]. Treatment with Albuterol does not change manual muscle testing scores for Facioscapulohumeral MD patients, the drug does appear to increase lean body mass as well as handgrip strength in Facioscapulohumeral MD patients, which suggests that the drug does have an anabolic effect [200,201]. A similar increase in lean body mass after short-term treatment with Albuterol has been described for Duchenne and Becker MD patients [202]. However, because of inconsistent results between a pilot trial and further analyses, it is unclear whether Albuterol improves function in Duchenne and Becker MD patients [202,203].

Omeprazole is a proton pump inhibitor that is commonly used to treat Gastroesophageal reflux disease (GERD) [204,205]. The percentage of Myotonic Dystrophy and Oculopharyngeal MD cases on Omeprazole were equal in the MD STAR*net* pilot cohort. This suggests that GERD may be a burdensome symptom for both these forms of MD. Researchers found that 24% of DM1 and 31% of DM2 patients have GERD [206], and medications for gastroesophageal reflux are used in 22.5% of DM1 and 18.9% of DM2 patients [207]. A small percentage of Duchenne and Becker MD cases were prescribed Omeprazole. Consistent with this modest percentage, Pane et al. (2006) found that while GERD may be a concern for some Duchenne and Becker MD patients, it affects them infrequently [208]. Further, though other studies have found GERD to be a comorbidity in 18.1% of Facioscapulohumeral MD patients studied [206], less than 6% of the Facioscapulohumeral MD case in the MD STAR*ner* pilot cohort were on Omeprazole.

Almost 20% of Duchenne and Becker MD cases had Prednisone documented in their record at the most recent health encounter. The use of prednisone in DMBD males has been previously described in studies using MD STARnet data [209,210]. As Prednisone has been shown to improve muscle and strength, this finding is not surprising [211].

5.4 Limitations

Though the cross-sectional design of this study allows for a preliminary characterization of the population studied, there are limitations that arise as a result of surveillance methods. Cross-sectional study design does not enable us to study rate of progression for the MDs. Further, those patients who have a more rapid progression of the disease are likely to require healthcare more frequently than those with a slower progression of the disease in the same period. Thus, this pilot dataset may have more complete data for cases more severely affected by MD or with faster progressing forms of the disease. Additionally, less complete information may be available for cases who resided in an MD STAR*net* site but received care elsewhere. For examples, cases who lived near to a state border in one of the four MD *STARnet* sites may have traveled to larger neuromuscular clinic in another state, and this information would not be included in the pilot dataset. In comparison with patients who lived in the geographic areas for the entire study period, those who moved out of the areas in the first year of the study or into a geographic area in the concluding year of the study may have less complete information. Because of delays in diagnosis are common for many forms of MD, it is likely that there are individuals who have MD who have yet to be diagnosed in these sites.

Using medical records as a source of data means that some data is missing or incomplete. Some demographic and sociodemographic information in the MD STAR*net* pilot data is incomplete, including income level, marital status, level of education, and type of occupation. As

a result of the incomplete data, this study provides only a preliminary and fragmented characterization of the MD STAR*net* pilot cohort.

The most recent medications a patient took at their last health encounter during the study period were recorded as a free text variable and included vitamins, supplements, and over-the-counter medications. The number of medications, and measures of central tendency and dispersion, include these over-the-counter medications and may distort the assessment of symptomatology. Further, we did not capture the history of medications. No information regarding the patients' compliance, dosage, or intended use for each drug was recorded. Consequently, the characterization of medications does not capture the full scope of the medicinal management for these diseases. Longitudinal data would be needed to assess the progression of medications used in concordance with the progression of symptoms. Future data collection will feature focused collection of longitudinal data about prescription drugs for individuals with MD.

In aggregating information for the classification of mobility status, important nuances may have been obscured. For instance, patients who were bedridden as well as patients who used a wheelchair full-time were classified as non-ambulatory. There are likely important quality of life and health-related differences in patients who are bedridden compared to those who use a device full-time. However, owing to the small number of cases originally classified as 'bedridden' it was not possible to cross-tabulate this individual mobility status with the type of MD. Further, this variable, like employment, was stratified by the age of the patient when the mobility status was recorded, but this may not reflect the age at which the mobility impairment began.

The small number of cases that were ascertained for Distal MD (N=17), Emery-Dreiffus MD (N=22), and Duchenne and Becker MD manifesting females (N=17) precluded reporting

many sociodemographic and demographic variables for these groups. Though we have provided

a preliminary characterization of a U.S. group with muscular dystrophy, the forms of MD extend

beyond the nine forms included in this study. Further, since the catchments from which cases

were ascertained were not chosen randomly or to be nationally representative, the findings of this

study are not generalizable to the entire U.S. population.

5.5 Implications

Though these limitations are numerous, they highlight the unique challenge of conducting

surveillance in populations with rare diseases. The pilot dataset for the MD STAR*net* pilot is the

only U.S., population-based active surveillance that exists for MD patients, and thus represents a

cautious beginning The robust methodology for identifying and classifying cases of MD,

including active case ascertainment, case review from a group of clinicians, and utilization of

both medical records and administrative data, is a strength of the surveillance network. This

study provides an important description of the various forms of MD and enhances the

understanding of demographic and clinical characteristics of MD patients, which may help in

identifying future research.

Currently MD STAR*net* is collecting data at six U.S. sites and have improved data

collection through lessons learned. With more data and larger cohorts, more detailed clinical and

public health questions may be answered. Future data collection, which may include survey data,

may seek to measure age at diagnosis and diagnostic delays for each MD Type. Future research

may also examine the relationship between QoL and demographic/sociodemographic variables

for patients with some MD types. Additional areas of interest include the presence of

comorbidities and causes of death. Future studies using the MD STAR*net* pilot data will seek to

establish the minimum treated prevalence for the MDs in these six sites and compare the clinical

interventions these patients receive to current recommendations

This analysis not only describes the only population-based cohort of individuals with

many forms of MD, but also informs future iterations of the MD STAR*net* pilot surveillance data

collection, which would serve as the basis for studies examining the epidemiology of the MDs

and site-specific prevalence estimates, studies on the disease progression of the MD types,

analyses of healthcare utilizations and costs as well as studies focusing on disparities in care for

these patients. Further, using future data, the MD STAR*net* pilot cohort may facilitate an analysis

of the factors that influence health outcomes for MD patients. Population-based surveillance for

the major forms of MD is needed to establish racial and ethnic patterns in the U.S. The MD

STAR*net* pilot is currently conducting surveillance in six sites; analyses using current data may

enable a demographic analysis. Consequently, these results serve as the basis for future studies

that aim to identify areas for targeted interventions, lower morbidity, and describe factors that

influence health-outcomes for MD patients.

5.6 Conclusions

Characterization of the MD population is important to assessing public health needs. MD

STAR*net* (MDS) is the only U.S. population-based surveillance system for MD. From 2011-

2014, the MD STARnet expanded surveillance to nine MDs to test the feasibility of identifying

individuals with childhood and adult-onset MDs. Basic demographic and clinical information

was collected in the pilot which enabled us to characterize this population. Using multiple

clinical and administrative data sources, the study showed it was feasible to conduct surveillance

for other MDs. Lessons learned from the pilot have informed current methods in MD STARnet.

This study provides an important description of the various forms of MD and enhances the

understanding of demographic and clinical characteristics of MD patients, which may help in

identifying future research.

Appendix

Figure 1: Frequency of each type of MD in the MD STAR*net* pilot Cohort
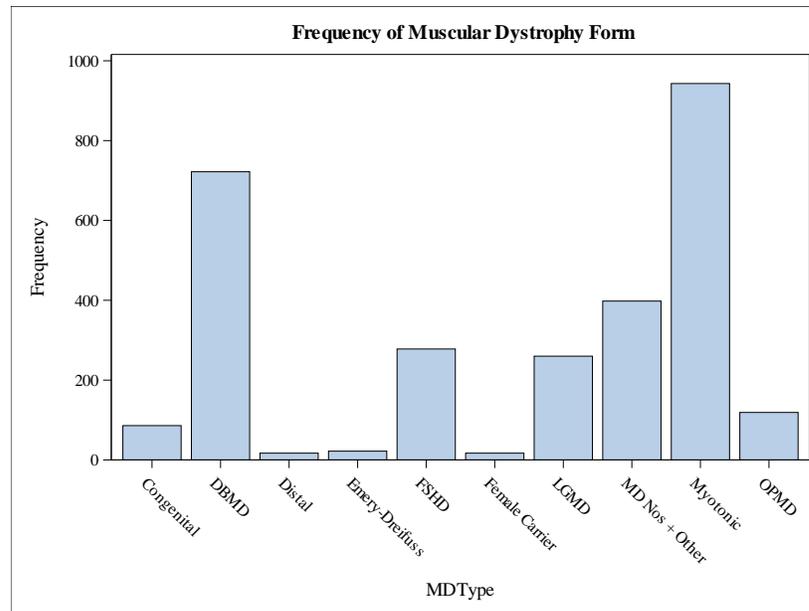
Figure 1 provides the frequencies of individuals with each form of eligible MD who were included in the cohort of cases used for this analysis.

Table 1: Mean Ages and Case Counts

Variables		Total		Muscular Dystrophy Type																	
				Congenital		DBMD Male		Manifesting Female		Distal		Emery-Dreifuss		FSHD		LGMD		Myotonic		OPMD		MD NOS + Other	
Frequency	N/%	2862		86	3.0	722	25.2	17	0.6	17	0.6	22	0.8	278	9.7	260	9.1	943	33.0	119	4.2	398	13.9
Age at 1/1/2007	Mean/SD	34.6	22.1	13.2	14.3	15.5	12.3	31.3	19.6	43.9	12.6	23.2	14.7	43.6	20.0	38.5	21.8	38.6	18.3	65.7	9.8	46.9	20.5
Age at Death	Mean /SD	51.6	22.2	12.2	7.5	25.5	11.8	44.2	-	73.9	-	53.2	14.9	65.6	8.5	67.0	15.9	53.6	16.3	77.0	8.7	67.0	20.6

Caption: Frequencies for the number of cases of each type of MD are included in Table 1. Percentages represent the proportion of the total MD STARnet pilot cohort. The mean age at the start of the study and the mean age at death are provided. Cases who were born during the study period have a study start age of 0. 2 Myotonic Dystrophy cases were excluded from the analysis of age due to incorrect data.

Table 2: Demographic Variables by Muscular Dystrophy Type

Variables		Congenital		DBMD Males		Manifesting Female		FSHD		LGMD		Myotonic		OPMD		MD NOS + Other		Total	
		Muscular Dystrophy Type																		
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Gender	Female	41	47.7	0	0.0	17	0.0	117	42.1	129	49.6	470	49.8	65	54.6	187	47.0	1026	36.3
	Male	45	52.3	722	0.0	0	0.0	161	57.9	131	50.4	473	50.2	54	45.4	211	53.0	1797	63.7
Race	White/Caucasian	66	76.7	567	78.5	11	64.7	*		202	77.7	804	85.3	75	63.0	308	77.4	2033	79.9
	Black/African American	<10	-	19	2.6	0	0.0	*		14	5.4	23	2.4	0	0.0	16	4.0	75	3.0
	Multiple /Other	12	14.0	83	11.5	<10	-	*		16	6.2	44	4.7	13	10.9	22	5.5	193	7.6
	Unknown	<10	-	53	7.3	<10	-	*		28	10.8	72	7.6	31	26.1	52	13.1	244	9.6
Hispanic Ethnicity	Yes	*		147	20.4	*		22	7.9	30	11.5	78	8.3	41	34.5	58	14.6	376	13.8
	No	*		488	67.6	*		159	57.2	143	55.0	590	62.6	31	26.1	207	52.0	1618	59.5
	Unknown	*		87	12.1	*		97	34.9	87	33.5	275	29.2	47	39.5	133	33.4	726	26.7
Insurance (most recent)	Private	*		210	29.1	*		*		*		329	34.9	*		*		539	32.4
	Public	*		351	48.6	*		*		*		462	49.0	*		*		813	48.8
	Both	*		111	15.4	*		*		*		82	8.7	*		*		193	11.6
	Uninsured / Self-pay	*		23	3.2	*		*		*		22	2.3	*		*		45	2.7
	Not documented	*		27	3.7	*		*		*		48	5.1	*		*		75	4.5
Full-time in Assisted living	Yes	<10	-	*		*		*		*		97	10.3	10	8.4	51	12.8	162	10.5
	No	81	94.2	*		*		*		*		813	86.2	98	82.4	332	83.4	1324	85.6
	Not documented	<10	-	*		*		*		*		33	3.5	11	9.3	15	3.8	60	3.9

*Caption: Frequencies and percentages of demographic variables are provided for each type of MD, where possible. Note that the distribution of gender, race, Hispanic ethnicity, most recent insurance status, and living situation were not reportable for Emery-Dreiffus MD or Distal MD due to small sample sizes. Where * is indicated in the table, the variable was no reportable for the form of MD.*

Table 3: Students and Younger than School Age by Muscular Dystrophy Type

Variables	Age	Muscular Dystrophy Type												Total	
		DBMD Males		FSHD		LGMD		Myotonic		OPMD		MD NOS + Other			
		n	%	n	%	n	%	n	%	n	%	n	%	n	%
Younger than school age		21	2.9	0	0.00	0	0.0	25	2.7	0	0.00	*		46	2.0
Student	0 to <5	18	46.2	<10	-	<10	-	<10	-	0	0	0	0.0	27	35.5
	5 to <18	293	98.3	31	96.9	41	95.4	79	89.8	0	0	23	82.1	467	95.5
	18 to <35	86	41.4	<10	-	<10	-	32	19.2	0	0	<10	-	144	26.6

*The frequency and percentage of Duchenne and Becker MD, Facioscapulohumeral MD, Limb-Girdle MD, DM, Oculopharyngeal MD and MD NOS/Other cases who too young to be in school are provided. The frequency and percentage of those cases who are under 35 years of age and are students are stratified by age for the same MD types. These variables, Younger than school age and Student, were not reportable for Congenital MD, Distal MD, Emery-Dreiffus MD, and Duchenne and Becker MD manifesting females. Where a variable is not reportable * is indicated.*

Table 4: Employment Status by Muscular Dystrophy Type

| Variables | Age | Muscular Dystrophy Type | | | | | | | | | | | | | Total | |
| | | DBMD Males | | FSHD | | LGMD | | Myotonic | | OPMD | | MD NOS + Other | | | |
		n	%	n	%	n	%	n	%	n	%	n	%	n	%
Working for Pay	18 to <35	28	13.46	23	47.92	25	49.02	64	38.3	0	0.0	21	31.34	161	29.8
	35 to <65	21	32.3	62	44.6	49	40.5	144	25.4	12	28.6	37	18.69	325	28.7
	65+	<10	-	<10	-	<10	-	<10	-	<10	-	<10	-	18	5.1
Disabled or Unable to Work	18 to <35	37	17.8	<10	-	<10	-	30	18.0	0	0.0	15	22.4	93	17.2
	35 to <65	32	49.2	39	28.1	41	33.9	256	45.1	11	26.2	84	42.4	463	40.9
	65+	<10	-	<10	-	<10	-	19	26.4	<10	-	10	9.7	45	12.9
Unemployed	18 to <35	19	9.1	<10	-	<10	-	23	13.8	0	0.0	14	20.9	68	12.6
	35 to <65	<10	-	16	11.5	15	12.4	76	13.4	<10	-	34	17.2	154	13.6
	65+	0	0.0	<10	-	<10	-	<10	-	<10	-	<10	-	17	4.9
Retired	35 to <65	<10	-	11	7.9	<10	-	46	8.1	<10	-	20	10.1	92	8.1
	65+	<10	-	30	53.6	30	75.0	44	61.1	48	64.0	67	65.1	222	63.4
Not documented		153	21.2	28	10.1	22	8.5	82	8.7	23	19.3	60	15.1	368	13.5

The employment status of Duchenne and Becker MD, Facioscapulohumeral MD, Limb-Girdle MD, DM, Oculopharyngeal MD and MD NOS/Other cases are reported as frequencies and percentages. Employment status is stratified by the age at which the employment status was recorded. In describing those who are working for pay, disabled or unable to work, or unemployed only cases whose employment status was recorded when they were 18 years of age or older and younger than 65 were considered. The frequency and percentage of retired cases is limited to those whose employment status was recorded when they were 35 years or older. Employment status was not reportable for Congenital MD, Distal MD, Emery-Dreiffus MD, and Duchenne and Becker MD manifesting females due to small case numbers

Table 5: Mobility Status by Muscular Dystrophy Type

Muscular Dystrophy	Mobility Status	Age									
		0 to <10		10 to <18		18 to <35		35 to <65		65+	
		n	%	n	%	n	%	n	%	n	%
Congenital	Ambulatory	12	37.5	5	20.8	11	47.8	3	60.0	1	50.0
	Ambulatory with Device Support	4	12.5	5	20.8	2	8.7	1	20.0	0	0.0
	Non-Ambulatory	12	37.5	14	58.3	9	39.1	1	20.0	1	50.0
DBMD Males	Ambulatory	107	59.4	40	17.7	43	18.5	19	31.7	1	20.0
	Ambulatory with Device Support	28	15.6	32	14.2	4	1.7	5	8.3	1	20.0
	Non-Ambulatory	37	20.6	153	67.7	182	78.5	35	58.3	3	60.0
Manifesting Females	Ambulatory	1	0.0	1	50.0	2	40.0	2	57.1	2	100.0
	Ambulatory with Device Support	0	0.0	1	50.0	0	0.0	1	14.3	0	0.0
	Non-Ambulatory	0	0.0	0	0.0	3	60.0	1	14.3	0	0.0
Distal	Ambulatory	0	0.0	0	0.0	1	100.0	9	64.3	1	50.0
	Ambulatory with Device Support	0	0.0	0	0.0	0	0.0	2	14.3	1	50.0
	Non-Ambulatory	0	0.0	0	0.0	0	0.0	3	21.4	0	0.0
EDMD	Ambulatory	1	100.0	5	83.3	5	62.5	4	57.1	0	0.0
	Ambulatory with Device Support	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Non-Ambulatory	0	0.0	1	16.7	2	25.0	3	42.9	0	0.0
FSHD	Ambulatory	6	85.7	24	92.3	35	74.5	91	65.0	37	64.9
	Ambulatory with Device Support	1	14.3	0	0.0	7	14.9	11	7.9	12	21.1
	Non-Ambulatory	0	0.0	1	3.9	3	6.4	33	23.6	7	12.3
LGMD	Ambulatory	17	94.4	23	79.3	30	57.7	62	51.5	16	40.0
	Ambulatory with Device Support	1	5.6	2	6.9	8	15.4	12	9.9	4	10.0
	Non-Ambulatory	0	0.0	4	13.8	14	26.9	43	35.5	18	45.0
Myotonic	Ambulatory	40	70.2	55	90.2	158	88.8	425	76.3	49	66.2
	Ambulatory with Device Support	1	1.8	1	1.6	5	2.8	49	8.8	10	13.5
	Non-Ambulatory	3	5.3	3	4.9	6	3.4	58	10.4	12	16.2
OPMD	Ambulatory	0	0.0	0	0.0	0	0.0	36	85.7	51	68.0
	Ambulatory with Device Support	0	0.0	0	0.0	0	0.0	3	7.1	4	5.3
	Non-Ambulatory	0	0.0	0	0.0	0	0.0	1	2.4	12	16.0
MD NOS +Other	Ambulatory	6	75.0	15	71.4	46	64.8	104	53.1	46	46.5
	Ambulatory with Device Support	0	0.0	1	4.8	4	5.6	15	7.7	12	12.1
	Non-Ambulatory	1	12.5	5	23.8	18	25.4	56	28.6	32	32.3
	Other	18	5.9	0	0.0	2	0.3	8	0.7	2	0.6
	Not Documented	8	2.6	4	1.0	17	2.8	52	4.5	21	5.9

Mobility status is reported as the frequency and percentage for each type of MD and is stratified by the age at which the mobility status was recorded. Patients who do not require device assistance to walk are classified as 'Ambulatory'. Those who require part-time device support are classified as 'Ambulatory with Device Support,' and patients who use a device, such as a scooter or wheelchair, full-time or who are bedridden are classified as 'Non-ambulatory'.

Table 6: Clinical Interventions by Muscular Dystrophy Type

Variables		Congenital		Distal		DBMD Males		Manifesting Females		EDMD		FSHD		LGMD		Myotonic		OPMD		MD NOS + Other		Total	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Vital Status	Deceased	9	10.5	1	5.9	82	11.4	1	5.9	2	9.1	21	7.6	29	11.2	161	17.1	25	21.0	80	20.1	411	14.4
PEG	Yes	18	20.9	0	0.0	67	9.3	1	5.9	1	4.6	+		10	3.9	+		+		35	8.8	132	8.7
	Not doc.	68	79.1	17	100.0	653	90.7	16	94.1	21	95.5	+		250	96.2	+		+		363	91.2	1388	91.3
NIPPV(CPAP/BIPAP)	Yes	24	27.9	2	11.8	235	32.6	2	11.8	2	9.1	25	9.0	45	17.3	215	22.8	+		58	14.6	608	21.5
	Not doc.	62	72.1	15	88.2	485	67.4	15	88.2	20	90.9	253	91.0	215	82.7	728	77.2	+		340	85.4	2133	78.5
Tracheostomy	Yes	+		+		72	10.0	1	5.9	+		+		+		+		+		30	7.5	103	9.1
	Not doc.	+		+		648	90.0	16	94.1	+		+		+		+		+		368	92.5	1032	90.9
Cough Assist	Yes	+		+		178	24.7	1	5.9	+		+		+		+		+		3	0.8	182	16.0
	Not doc.	+		+		542	75.3	16	94.1	+		+		+		+		+		395	99.3	953	84.0
Pacemaker	Yes	1	1.2	0	0.0	+		+		4	18.2	+		10	3.9	93	9.9	+		15	3.8	123	7.1
	Not doc.	85	98.8	17	100.0	+		+		18	81.8	+		250	96.2	850	90.1	+		383	96.2	1603	92.9
Defibrillator	Yes	0	0.0	0	0.0	+		+		1	4.6	+		3	1.2	36	3.8	+		5	1.3	45	2.6
	Not doc.	86	100.0	17	100.0	+		+		21	95.5	+		257	98.9	907	96.2	+		393	98.7	1681	97.4
Cardiac Transplant	Yes	0	0.0	2	11.8	+		+		2	9.1	+		4	1.5	1	0.1	+		1	0.3	10	0.6
	Not doc.	86	100.0	15	88.2	+		+		20	90.9	+		256	98.5	942	99.9	+		397	99.8	1716	99.4

The frequency and percentage of cases who had the use of the clinical interventions considered listed in their medical record were provided for each MD type. The percentage and frequency of those who are deceased are also provided for each type of MD. Clinical variables are only reported for MD types where future iterations of the MD STAR*net* pilot *will collect data. Thus, where a variable was not reported, + is indicated.*

Table 7: Mean and Median Medication Count at Most Recent Health Encounter

Variable	Muscular Dystrophy Type										Total	
	Congenital		Distal		DBMD		Manifesting Female		Emery-Dreifuss		FSHD	
Medications	Mean	*STD*	Mean	*STD*	Mean	*STD*	Mean	*STD*	Mean	*STD*	Mean	*STD*
	3.6	*4.1*	4.1	*3.1*	4.4	*4.5*	5.3	*5.2*	2.8	*2.4*	4.0	*4.3*

LGMD		Myotonic		OPMD		MD NOS + Other		Total	
Mean	*STD*	Mean	*STD*	Mean	*STD*	Mean	*STD*	Mean	*STD*
4.1	*4.4*	4.2	*4.3*	5.9	*4.4*	5.3	*5.0*	4.4	*4.5*

Means and standard deviations are provided for the number of medications recorded in the medical records of cases at their last health encounter for each MD type.

54

Table 8: Distribution of the Most Frequently Documented Medications

Medication	Muscular Dystrophy Type																			
	Congenital		Distal		DBMD Male		Manifesting Female		EDMD		FSHD		LGMD		Myotonic		OPMD		MD NOS + Other	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Lisinopril	4	4.7	4	23.5	157	21.7	2	11.8	2	9.1	39	14.0	36	13.8	64	6.8	17	14.3	49	12.3
Albuterol	12	14.0	0	0.0	56	7.8	5	29.4	1	4.5	19	6.8	13	5.0	75	8.0	9	7.6	37	9.3
Omeprazole	1	1.2	1	5.9	38	5.3	0	0.0	1	4.5	16	5.8	20	7.7	87	9.2	11	9.2	33	8.3
Furosemide	0	0.0	0	0.0	40	5.5	0	0.0	0	0.0	13	4.7	18	6.9	51	5.4	11	9.2	45	11.3
Prednisone	0	0.0	1	5.9	143	19.8	1	5.9	0	0.0	4	1.4	4	1.5	8	0.8	3	2.5	12	3.0

The most frequently recorded medications recorded in the medical record of cases at their most recent health encounter are provided. For each medication, the frequency and percentage of cases using the medication by MD Type are provided.

References

1.   Brais B. Oculopharyngeal muscular dystrophy: a late-onset polyalanine disease. Cytogenetic and Genome Research 2003;100:252-60.
2.   Mercuri E, Muntoni F. Muscular dystrophies. The Lancet;381:845-60.
3.   Johnson NE, Abbott D, Cannon-Albright LA. Relative risks for comorbidities associated with myotonic dystrophy: A population-based analysis. Muscle & Nerve 2015;52:659-61.
4.   Smith AE, McMullen K, Jensen MP, Carter GT, Molton IR. Symptom burden in persons with myotonic and facioscapulohumeral muscular dystrophy. Am J Phys Med Rehabil 2014;93:387-95.
5.   Cheuk DK, Wong V, Wraige E, et al. Surgery for scoliosis in Duchenne muscular dystrophy. The Cochrane database of systematic reviews 2007:Cd005375.
6.   Acosta-Mérida MA, Marchena-Gómez J, Afonso-Déniz JM. Utility of surgical myotomy in the dysphagia due to oculopharyngeal dystrophy. Revista Espanola de Enfermedades Digestivas 2016;108:843-4.
7.   Becher MW, Morrison L, Davis LE, et al. Oculopharyngeal muscular dystrophy in hispanic new mexicans. JAMA 2001;286:2437-40.
8.   Fishman FG, Goldstein EM, Peljovich AE. Surgical treatment of upper extremity contractures in Emery–Dreifuss muscular dystrophy. Journal of Pediatric Orthopaedics B 2017;26:32-5.
9.   Falsaperla R, Praticò AD, Ruggieri M, et al. Congenital muscular dystrophy: from muscle to brain. Italian Journal of Pediatrics 2016;42:78.
10.   Blumen SC, Nisipeanu P, Sadeh M, Asherov A, Tomé FMS, Korczyn AD. Clinical features of oculopharyngeal muscular dystrophy among Bukhara Jews. Neuromuscular Disorders 1993;3:575-7.
11.   Mathieu J, De Braekeleer M, Prévost C. Genealogical reconstruction of myotonic dystrophy in the Saguenay-Lac-Saint- Jean area (Quebec, Canada). Neurology 1990;40:839-.
12.   Theadom A, Rodrigues M, Roxburgh R, et al. Prevalence of muscular dystrophies: a systematic literature review. Neuroepidemiology 2014;43:259-68.
13.   Abbott D, Johnson NE, Cannon-Albright LA. A population-based survey of risk for cancer in individuals diagnosed with myotonic dystrophy. Muscle and Nerve 2016;54:783-5.
14.   Graziano A, Bianco F, D'Amico A, et al. Prevalence of congenital muscular dystrophy in Italy: a population study. Neurology 2015;84:904-11.
15.   Okada M, Kawahara G, Noguchi S, et al. Primary collagen VI deficiency is the second most common congenital muscular dystrophy in Japan. Neurology 2007;69:1035-42.
16.   Peat RA, Smith JM, Compton AG, et al. Diagnosis and etiology of congenital muscular dystrophy. Neurology 2008;71:312-21.
17.   Sframeli M, Sarkozy A, Bertoli M, et al. Congenital muscular dystrophies in the UK population: Clinical and molecular spectrum of a large cohort diagnosed over a 12-year period. Neuromuscular Disorders 2017;27:793-803.
18.   Lisi MT, Cohn RD. Congenital muscular dystrophies: new aspects of an expanding group of disorders. Biochimica et Biophysica Acta 2007;1772:159-72.
19.   Muntoni F, Voit T. The congenital muscular dystrophies in 2004: a century of exciting progress. Neuromuscular Disorders 2004;14:635-49.
20.   Mercuri E, Muntoni F. The ever-expanding spectrum of congenital muscular dystrophies. Annals of Neurology 2012;72:9-17.
21.   Bertini E, D'Amico A, Gualandi F, Petrini S. Congenital muscular dystrophies: a brief review. Seminars in Pediatric Neurology 2011;18:277-88.

22.   Norwood FLM, Harling C, Chinnery PF, Eagle M, Bushby K, Straub V. Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. Brain 2009;132:3175-86.

23.   Mah JK, Korngut L, Fiest KM, et al. A Systematic Review and Meta-analysis on the Epidemiology of the Muscular Dystrophies. Canadian Journal of Neurological Sciences 2016;43:163-77.

24.   Emery AEH. The muscular dystrophies. Bmj 1998;317:991-5.

25.   Giliberto F, Radic CP, Luce L, Ferreiro V, de Brasi C, Szijan I. Symptomatic female carriers of Duchenne muscular dystrophy (DMD): genetic and clinical characterization. Journal of the Neurological Sciences 2014;336:36-41.

26.   Davidson ZE, Ryan MM, Kornberg AJ, et al. Observations of body mass index in Duchenne muscular dystrophy: a longitudinal study. European Journal of Clinical Nutrition 2014;68:892-7.

27.   Magri F, Govoni A, D'Angelo MG, et al. Genotype and phenotype characterization in a large dystrophinopathic cohort with extended follow-up. Journal of Neurology 2011;258:1610-23.

28.   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). Journal of Pediatrics 2009;155:380-5.

29.   Viollet L, Thrush PT, Flanigan KM, Mendell JR, Allen HD. Effects of angiotensin-converting enzyme inhibitors and/or beta blockers on the cardiomyopathy in Duchenne muscular dystrophy. American Journal of Cardiology 2012;110:98-102.

30.   Allen HD, Thrush PT, Hoffman TM, Flanigan KM, Mendell JR. Cardiac management in neuromuscular diseases. Physical Medicine & Rehabilitation Clinics of North America 2012;23:855-68.

31.   Hor KN, Wansapura J, Markham LW, et al. Circumferential strain analysis identifies strata of cardiomyopathy in Duchenne muscular dystrophy: a cardiac magnetic resonance tagging study. Journal of the American College of Cardiology 2009;53:1204-10.

32.   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.

33.   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 STARnet. J Pediatr Rehabil Med 2016;9:5-11.

34.   Wong BL, Christopher C. Corticosteroids in Duchenne muscular dystrophy: a reappraisal. Journal of Child Neurology 2002;17:183-90.

35.   Shapiro F, Zurakowski D, Bui T, Darras BT. Progression of spinal deformity in wheelchair-dependent patients with Duchenne muscular dystrophy who are not treated with steroids: coronal plane (scoliosis) and sagittal plane (kyphosis, lordosis) deformity. Bone & Joint Journal 2014;96-B:100-5.

36.   Rall S, Grimm T. Survival in Duchenne muscular dystrophy. Acta Myologica 2012;31:117-20.

37.   Romitti PA, Zhu Y, Puzhankara S, et al. Prevalence of Duchenne and Becker muscular dystrophies in the United States. Pediatrics 2015;135:513-21.

38.   Mah JK, Korngut L, Dykeman J, Day L, Pringsheim T, Jette N. A systematic review and meta-analysis on the epidemiology of Duchenne and Becker muscular dystrophy. Neuromuscular Disorders 2014;24:482-91.

39.   Udd B. Genetics and pathogenesis of distal muscular dystrophies. Advances in Experimental Medicine & Biology 2009;652:23-38.

40.   Udd B. Molecular biology of distal muscular dystrophies--sarcomeric proteins on top. Biochimica et Biophysica Acta 2007;1772:145-58.

41.   Norwood FLM, Harling C, Chinnery PF, Eagle M, Bushby K, Straub V. Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. Brain : a journal of neurology 2009;132:3175-86.

42.   Udd B, Partanen J, Halonen P, et al. Tibial muscular dystrophy: Late adult-onset distal myopathy in 66 finnish patients. Archives of Neurology 1993;50:604-8.
43.   Pollazzon M, Suominen T, Penttila S, et al. The first Italian family with tibial muscular dystrophy caused by a novel titin mutation. Journal of Neurology 2010;257:575-9.
44.   Pardal-Fernandez JM, Jerez-Garcia P, Rallo-Gutierrez B, Puentes-Gil JM, Godes-Medrano B, Marco-Giner J. Tibial muscular dystrophy with late adult onset in a Spanish family. Electromyography & Clinical Neurophysiology 2005;45:285-90.
45.   de Seze J, Udd B, Haravuori H, et al. The first European family with tibial muscular dystrophy outside the Finnish population. Neurology 1998;51:1746-8.
46.   Van den Bergh PYK, Bouquiaux O, Verellen C, et al. Tibial muscular dystrophy in a Belgian family. Annals of Neurology 2003;54:248-51.
47.   Van den Bergh PY, Martin JJ, Lecouvet F, Udd B, Schmedding E. Laing early-onset distal myopathy in a Belgian family. Acta Neurologica Belgica 2014;114:253-6.
48.   Malicdan MC, Nonaka I. Distal myopathies a review: highlights on distal myopathies with rimmed vacuoles. Neurology India 2008;56:314-24.
49.   Linssen WH, de Voogt WG, Krahn M, et al. Long-term follow-up study on patients with Miyoshi phenotype of distal muscular dystrophy. European Journal of Neurology 2013;20:968-74.
50.   Wallgren-Pettersson C, Lehtokari VL, Kalimo H, et al. Distal myopathy caused by homozygous missense mutations in the nebulin gene. Brain 2007;130:1465-76.
51.   Lamont PJ, Udd B, Mastaglia FL, et al. Laing early onset distal myopathy: slow myosin defect with variable abnormalities on muscle biopsy. Journal of Neurology, Neurosurgery & Psychiatry 2006;77:208-15.
52.   Emery AE. Emery-Dreifuss muscular dystrophy - a 40 year retrospective. Neuromuscular Disorders 2000;10:228-32.
53.   Felice KJ, Schwartz RC, Brown CA, Leicher CR, Grunnet ML. Autosomal dominant Emery-Dreifuss dystrophy due to mutations in rod domain of the lamin A/C gene. Neurology 2000;55:275-80.
54.   Raffaele Di Barletta M, Ricci E, Galluzzi G, et al. Different mutations in the LMNA gene cause autosomal dominant and autosomal recessive Emery-Dreifuss muscular dystrophy. American Journal of Human Genetics 2000;66:1407-12.
55.   Hayashi YK. X-linked form of Emery-Dreifuss muscular dystrophy. Acta Myologica 2005;24:98-103.
56.   Jimenez-Escrig A, Gobernado I, Garcia-Villanueva M, Sanchez-Herranz A. Autosomal recessive Emery-Dreifuss muscular dystrophy caused by a novel mutation (R225Q) in the lamin A/C gene identified by exome sequencing. Muscle & Nerve 2012;45:605-10.
57.   Goncu K, Guzel R, Guler-Uysal F. Emery-Dreifuss muscular dystrophy in the evaluation of decreased spinal mobility and joint contractures. Clinical Rheumatology 2003;22:456-60.
58.   Diaz-Manera J, Alejaldre A, Gonzalez L, et al. Muscle imaging in muscle dystrophies produced by mutations in the EMD and LMNA genes. Neuromuscular Disorders 2016;26:33-40.
59.   Bonne G, Mercuri E, Muchir A, et al. Clinical and molecular genetic spectrum of autosomal dominant Emery-Dreifuss muscular dystrophy due to mutations of the lamin A/C gene. Annals of Neurology 2000;48:170-80.
60.   Chung B, Wong V, Ip P. Prevalence of Neuromuscular Diseases in Chinese Children: A Study in Southern China. Journal of Child Neurology 2003;18:217-9.
61.   Tawil R, Kissel JT, Heatwole C, et al. Evidence-based guideline summary: Evaluation, diagnosis, and management of facioscapulohumeral muscular dystrophy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. Neurology 2015;85:357-64.

62.	de Greef JC, Lemmers RJ, Camano P, et al. Clinical features of facioscapulohumeral muscular dystrophy 2. Neurology 2010;75:1548-54.
63.	Nikolic A, Ricci G, Sera F, et al. Clinical expression of facioscapulohumeral muscular dystrophy in carriers of 1-3 D4Z4 reduced alleles: experience of the FSHD Italian National Registry. BMJ Open 2016;6:e007798.
64.	Mul K, Lassche S, Voermans NC, Padberg GW, Horlings CG, van Engelen BG. What's in a name? The clinical features of facioscapulohumeral muscular dystrophy. Practical Neurology 2016;16:201-7.
65.	Schipper K, Bakker M, Abma T. Fatigue in facioscapulohumeral muscular dystrophy: a qualitative study of people's experiences. Disability & Rehabilitation 2017;39:1840-6.
66.	Tawil R, Van Der Maarel SM. Facioscapulohumeral muscular dystrophy. Muscle & Nerve 2006;34:1-15.
67.	Flanigan KM, Coffeen CM, Sexton L, Stauffer D, Brunner S, Leppert MF. Genetic characterization of a large, historically significant Utah kindred with facioscapulohumeral dystrophy. Neuromuscular Disorders 2001;11:525-9.
68.	Deenen JC, Arnts H, van der Maarel SM, et al. Population-based incidence and prevalence of facioscapulohumeral dystrophy. Neurology 2014;83:1056-9.
69.	Mostacciuolo ML, Pastorello E, Vazza G, et al. Facioscapulohumeral muscular dystrophy: epidemiological and molecular study in a north-east Italian population sample. Clinical Genetics 2009;75:550-5.
70.	Sposito R, Pasquali L, Galluzzi F, et al. Facioscapulohumeral muscular dystrophy type 1A in northwestern Tuscany: a molecular genetics-based epidemiological and genotype-phenotype study. Genetic Testing 2005;9:30-6.
71.	Dorgham M, Kodivalasa M, Vasu T. A rare case of facioscapulohumeral syndrome (FSHS) presenting with chronic wide spread pain. British Journal of Pain 2017;11 (2 Supplement 1):81-2.
72.	Miro J, Gertz KJ, Carter GT, Jensen MP. Pain location and intensity impacts function in persons with myotonic dystrophy type 1 and facioscapulohumeral dystrophy with chronic pain. Muscle & Nerve 2014;49:900-5.
73.	Della Marca G, Frusciante R, Vollono C, et al. Pain and the alpha-sleep anomaly: a mechanism of sleep disruption in facioscapulohumeral muscular dystrophy. Pain Medicine 2013;14:487-97.
74.	Moris G, Wood L, FernaNdez-Torron R, et al. Chronic pain has a strong impact on quality of life in facioscapulohumeral muscular dystrophy. Muscle & Nerve 2017;20:20.
75.	Padua L, Aprile I, Frusciante R, et al. Quality of life and pain in patients with facioscapulohumeral muscular dystrophy. Muscle & Nerve 2009;40:200-5.
76.	Labombarda F, Maurice M, Simon JP, et al. Cardiac Abnormalities in Type 1 Facioscapulohumeral Muscular Dystrophy. Journal of Clinical Neuromuscular Disease 2017;18:199-206.
77.	Sveen ML, Schwartz M, Vissing J. High prevalence and phenotype-genotype correlations of limb girdle muscular dystrophy type 2I in Denmark. Annals of Neurology 2006;59:808-15.
78.	Khadilkar SV, Faldu HD, Patil SB, Singh R. Limb-girdle Muscular Dystrophies in India: A Review. Annals of Indian Academy of Neurology 2017;20:87-95.
79.	Khadilkar SV, Chaudhari CR, Dastur RS, Gaitonde PS, Yadav JG. Limb-girdle muscular dystrophy in the Agarwals: Utility of founder mutations in CAPN3 gene. Annals of Indian Academy of Neurology 2016;19:108-11.
80.	Khadilkar SV, Singh RK. Limb girdle muscular dystrophies in India. Neurology India 2008;56:281-8.
81.	Khadilkar SV, Singh RK, Agarwal P, Krahn M, Levy N. Twenty-two year follow-up of an Indian family with dysferlinopathy-clinical, immunocytochemical, western blotting and genetic features. Neurology India 2008;56:388-90.

82.   Stensland E, Lindal S, Jonsrud C, et al. Prevalence, mutation spectrum and phenotypic variability in Norwegian patients with Limb Girdle Muscular Dystrophy 2I. Neuromuscular Disorders 2011;21:41-6.
83.   Pantoja-Melendez CA, Miranda-Duarte A, Roque-Ramirez B, Zenteno JC. Epidemiological and Molecular Characterization of a Mexican Population Isolate with High Prevalence of Limb-Girdle Muscular Dystrophy Type 2A Due to a Novel Calpain-3 Mutation. PLoS ONE [Electronic Resource] 2017;12:e0170280.
84.   Liang WC, Chou PC, Hung CC, et al. Probable high prevalence of limb-girdle muscular dystrophy type 2D in Taiwan. Journal of the Neurological Sciences 2016;362:304-8.
85.   Nigro V. Molecular bases of autosomal recessive limb-girdle muscular dystrophies. Acta Myologica 2003;22:35-42.
86.   Mustafa E, Khandaker MAH, Rashid MM, Ghose SK, Chowdhury MK. Sarcoglycanopathy - A rare case report and literature review. Journal of Medicine (Bangladesh) 2014;15:77-9.
87.   Kirschner J, Lochmuller H. Sarcoglycanopathies. Handbook of Clinical Neurology 2011;101:41-6.
88.   Meena AK, Sreenivas D, Sundaram C, et al. Sarcoglycanopathies: a clinico-pathological study. Neurology India 2007;55:117-21.
89.   Schade van Westrum SM, Dekker LR, de Voogt WG, et al. Cardiac involvement in Dutch patients with sarcoglycanopathy: a cross-sectional cohort and follow-up study. Muscle Nerve 2014;50:909-13.
90.   Fanin M, Melacini P, Boito C, Pegoraro E, Angelini C. LGMD2E patients risk developing dilated cardiomyopathy. Neuromuscular disorders : NMD 2003;13:303-9.
91.   Fayssoil A, Ogna A, Chaffaut C, et al. Natural History of Cardiac and Respiratory Involvement, Prognosis and Predictive Factors for Long-Term Survival in Adult Patients with Limb Girdle Muscular Dystrophies Type 2C and 2D. PLoS ONE [Electronic Resource] 2016;11:e0153095.
92.   Maggi L, D'Amico A, Pini A, et al. LMNA-associated myopathies: the Italian experience in a large cohort of patients. Neurology 2014;83:1634-44.
93.   Maggi L, Carboni N, Bernasconi P. Skeletal muscle laminopathies: A review of clinical and molecular features. Cells 2016;5 (3) (no pagination).
94.   Turner C, Hilton-Jones D. Myotonic dystrophy: diagnosis, management and new therapies. Current Opinion in Neurology 2014;27:599-606.
95.   Vanacore N, Rastelli E, Antonini G, et al. An Age-Standardized Prevalence Estimate and a Sex and Age Distribution of Myotonic Dystrophy Types 1 and 2 in the Rome Province, Italy. Neuroepidemiology 2016;46:191-7.
96.   Groh WJ, Groh MR, Shen C, Monckton DG, Bodkin CL, Pascuzzi RM. Survival and CTG repeat expansion in adults with myotonic dystrophy type 1. Muscle Nerve 2011;43:648-51.
97.   Dogan C, De Antonio M, Hamroun D, et al. Gender as a modifying factor influencing myotonic dystrophy type 1 phenotype severity and mortality: A nationwide multiple databases cross-sectional observational study. PLoS ONE 2016;11 (2) (no pagination).
98.   Laberge L, Mathieu J, Auclair J, Gagnon E, Noreau L, Gagnon C. Clinical, psychosocial, and central correlates of quality of life in myotonic dystrophy type 1 patients. Eur Neurol 2013;70:308-15.
99.   Heatwole C, Johnson N, Bode R, et al. Patient-Reported Impact of Symptoms in Myotonic Dystrophy Type 2 (PRISM-2). Neurology 2015;85:2136-46.
100.   Laberge L, Dauvilliers Y, Bégin P, Richer L, Jean S, Mathieu J. Fatigue and daytime sleepiness in patients with myotonic dystrophy type 1: To lump or split? Neuromuscul Disord 2009;19:397-402.
101.   Christopher K, Horkan C, Patterson RB, Yodice PC. Oculopharyngeal muscular dystrophy complicating airway management. Chest 2001;120:2101-3.
102.   Tondo M, Gamez J, Gutierrez-Rivas E, Medel-Jimenez R, Martorell L. Genotype and phenotype study of 34 Spanish patients diagnosed with oculopharyngeal muscular dystrophy. Journal of Neurology 2012;259:1546-52.

103.   Youssof S, Romero-Clark C, Warner T, Plowman E. Dysphagia-related quality of life in oculopharyngeal muscular dystrophy: Psychometric properties of the SWAL-QOL instrument. Muscle & Nerve 2017;56:28-35.

104.   Van Der Sluijs BM, Hoefsloot LH, Padberg GW, Van Der Maarel SM, Van Engelen BG. Oculopharyngeal muscular dystrophy with limb girdle weakness as major complaint. Journal of Neurology 2003;250:1307-12.

105.   van der Sluijs BM, Raz V, Lammens M, van den Heuvel LP, Voermans NC, van Engelen BG. Intranuclear Aggregates Precede Clinical Onset in Oculopharyngeal Muscular Dystrophy. Journal of neuromuscular diseases 2016;3:101-9.

106.   van der Sluijs BM, Lassche S, Knuiman GJ, et al. Involvement of pelvic girdle and proximal leg muscles in early oculopharyngeal muscular dystrophy. Neuromuscular Disorders 2017;27:1099-105.

107.   Youssof S. The relationship between physical symptoms and health-related quality of life in oculopharyngeal muscular dystrophy. Muscle & Nerve 2016;53:694-9.

108.   Shan J, Chen B, Lin P, et al. Oculopharyngeal muscular dystrophy: phenotypic and genotypic studies in a Chinese population. NeuroMolecular Medicine 2014;16:782-6.

109.   Robinson DO, Hammans SR, Read SP, Sillibourne J. Oculopharyngeal muscular dystrophy (OPMD): analysis of the PABPN1 gene expansion sequence in 86 patients reveals 13 different expansion types and further evidence for unequal recombination as the mutational mechanism. Human Genetics 2005;116:267-71.

110.   Muller T, Deschauer M, Kolbe-Fehr F, Zierz S. Genetic heterogeneity in 30 German patients with oculopharyngeal muscular dystrophy. Journal of Neurology 2006;253:892-5.

111.   Mirabella M, Silvestri G, de Rosa G, et al. GCG genetic expansions in Italian patients with oculopharyngeal muscular dystrophy. Neurology 2000;54:608-14.

112.   Hill ME, Creed GA, McMullan TF, et al. Oculopharyngeal muscular dystrophy: phenotypic and genotypic studies in a UK population. Brain 2001;124:522-6.

113.   Becher MW, Morrison L, Davis LE, et al. Oculopharyngeal muscular dystrophy in Hispanic New Mexicans. JAMA 2001;286:2437-40.

114.   Agarwal PK, Mansfield DC, Mechan D, et al. Delayed diagnosis of oculopharyngeal muscular dystrophy in Scotland. British Journal of Ophthalmology 2012;96:281-3.

115.   Bumm K, Zenker M, Bozzato A. Oculopharyngeal muscular dystrophy as a rare differential diagnosis for unexplained dysphagia: a case report. Cases journal 2009;2:94.

116.   Pulkes T, Papsing C, Busabaratana M, Dejthevaporn C, Witoonpanich R. Mutation and haplotype analysis of oculopharyngeal muscular dystrophy in Thai patients. Journal of Clinical Neuroscience 2011;18:674-7.

117.   Witoonpanich R, Phankhian S, Sura T, Lertrit P, Phudhichareonrat S. Oculopharyngodistal myopathy in a Thai family. Journal of the Medical Association of Thailand 2004;87:1518-21.

118.   Tremolizzo L, Galbussera A, Tagliabue E, et al. An apparently sporadic case of oculopharyngeal muscular dystrophy: the first Italian report.[Erratum appears in Neurol Sci. 2008 Sep;29(4):291 Note: Curto, N [added]]. Neurological Sciences 2007;28:339-41.

119.   Blumen SC, Kesler A, Dabby R, et al. Oculopharyngeal muscular dystrophy among Bulgarian Jews: a new cluster? Israel Medical Association Journal: Imaj 2013;15:748-52.

120.   Tung JD, Oh SR, Gruber AB, et al. The man who could not see what he could not eat. Survey of Ophthalmology 2011;56:461-5.

121.   Codere F, Brais B, Rouleau G, Lafontaine E. Oculopharyngeal muscular dystrophy: What's new? Orbit 2001;20:259-66.

122.   Mazanec R, Seeman P, Seemanova E. Oculopharyngeal muscular dystrophy in the population of the Czech republic. [Czech]. Ceska a Slovenska Neurologie a Neurochirurgie 2013;76:717-22.

123.   Palmer PM, Neel AT, Sprouls G, Morrison L. Swallow characteristics in patients with oculopharyngeal muscular dystrophy. Journal of Speech Language & Hearing Research 2010;53:1567-78.
124.   H.R. 717 (107th): MD-CARE Act. 2001. (Accessed October 17, 2017, at https://www.govtrack.us/congress/bills/107/hr717)
125.   Miller LA, Romitti PA, Cunniff C, et al. The muscular Dystrophy Surveillance Tracking and Research Network (MD STARnet): surveillance methodology. Birth Defects Research 2006;76:793-7.
126.   Mathews KD, Cunniff C, Kantamneni JR, et al. Muscular Dystrophy Surveillance Tracking and Research Network (MD STARnet): case definition in surveillance for childhood-onset Duchenne/Becker muscular dystrophy. Journal of Child Neurology 2010;25:1098-102.
127.   Falsaperla R, Pratico AD, Ruggieri M, et al. Congenital muscular dystrophy: from muscle to brain. Italian Journal of Pediatrics 2016;42:78.
128.   Romitti PA, Zhu Y, Puzhankara S, et al. Prevalence of Duchenne and Becker muscular dystrophies in the United States.[Erratum appears in Pediatrics. 2015 May;135(5):945; PMID: 25934896]. Pediatrics 2015;135:513-21.
129.   Smith AE, McMullen K, Jensen MP, Carter GT, Molton IR. Symptom Burden in Persons with Myotonie and Facioscapulohumeral Muscular Dystrophy. American Journal of Physical Medicine & Rehabilitation 2014;93:387-95.
130.   Thomas NS, Wiseman K, Spurlock G, MacDonald M, Ustek D, Upadhyaya M. A large patient study confirming that facioscapulohumeral muscular dystrophy (FSHD) disease expression is almost exclusively associated with an FSHD locus located on a 4qA-defined 4qter subtelomere. Journal of Medical Genetics 2007;44:215-8.
131.   Al-Zaidy SA, Malik V, Kneile K, et al. A slowly progressive form of limb-girdle muscular dystrophy type 2C associated with founder mutation in the SGCG gene in Puerto Rican Hispanics. Molecular Genetics & Genomic Medicine 2015;3:92-8.
132.   Larkindale J, Yang W, Hogan PF, et al. Cost of illness for neuromuscular diseases in the United States. Muscle & Nerve 2014;49:431-8.
133.   Wang RT, Silverstein Fadlon CA, Ulm JW, et al. Online self-report data for duchenne muscular dystrophy confirms natural history and can be used to assess for therapeutic benefits. PLoS currents 2014;6:17.
134.   Yamaguchi M, Suzuki M. Independent living with Duchenne muscular dystrophy and home mechanical ventilation in areas of Japan with insufficient national welfare services. International Journal of Qualitative Studies on Health and Well-being 2013;8:20914.
135.   Dreyer PS, Steffensen BF, Pedersen BD. Life with home mechanical ventilation for young men with Duchenne muscular dystrophy. Journal of Advanced Nursing 2010;66:753-62.
136.   Nguyen TH, Thi HB, Thuy LTT, et al. Study of functional independence of patients with Duchene muscular dystrophy. Annals of Translational Medicine Conference: 12th Asia Pacific Conference on Human Genetics 2017;5.
137.   Nätterlund B. Living with Muscular Dystrophy: Illness Experience, Activities of Daily Living, Coping, Quality of Life and Rehabilitation. Scandinavian Journal of Occupational Therapy 2001;8:157.
138.   Stubgen JP, Stipp A. Facioscapulohumeral muscular dystrophy: a prospective study of weakness and functional impairment. Journal of Neurology 2010;257:1457-64.
139.   Stubgen JP. Limb girdle muscular dystrophy: an interval study of weakness and functional impairment. Journal of Clinical Neuromuscular Disease 2008;9:333-40.
140.   Madej-Pilarczyk A, Kochanski A. Emery-Dreifuss muscular dystrophy: the most recognizable laminopathy. Folia Neuropathologica 2016;54:1-8.
141.   Minis M-A, Engels J, Akkermans R, et al. Employment status of patients with neuromuscular diseases in relation to personal factors, fatigue and health status. Journal of Rehabilitation Medicine 2010;42:60 - 5.

142.   Laberge L, Mathieu J, Auclair J, Gagnon E, Noreau L, Gagnon C. Clinical, psychosocial, and central correlates of quality of life in myotonic dystrophy type 1 patients. European neurology 2013;70:308-15.

143.   Madej-Pilarczyk A. Professional activity of Emery-Dreifuss muscular dystrophy patients in Poland. International Journal of Occupational Medicine and Environmental Health 2014;27:270-7.

144.   Mori-Yoshimura M, Mizuno Y, Yoshida S, et al. Social involvement issues in patients with Becker muscular dystrophy: A questionnaire survey of subjects from a patient registry. Brain & Development 2017;29:29.

145.   Lue YJ, Chen SS, Lu YM. Quality of life of patients with Duchenne muscular dystrophy: from adolescence to young men. Disability & Rehabilitation 2017;39:1408-13.

146.   Minis MA, Kalkman JS, Akkermans RP, et al. Employment status of patients with neuromuscular diseases in relation to personal factors, fatigue and health status: a secondary analysis. Journal of Rehabilitation Medicine 2010;42:60-5.

147.   Hilbert JE, Kissel JT, Luebbe EA, et al. If you build a rare disease registry, will they enroll and will they use it? Methods and data from the National Registry of Myotonic Dystrophy (DM) and Facioscapulohumeral Muscular Dystrophy (FSHD). Contemporary Clinical Trials 2012;33:302-11.

148.   Rakocevic-Stojanovic V, Peric S, Madzarevic R, et al. Significant impact of behavioral and cognitive impairment on quality of life in patients with myotonic dystrophy type 1. Clinical Neurology & Neurosurgery 2014;126:76-81.

149.   Kraya T, Schmidt B, Muller T, Hanisch F. Impairment of respiratory function in late-onset distal myopathy due to MATR3 Mutation. Muscle & Nerve 2015;51:916-8.

150.   Annunziata A, Fiorentino G, Esquinas A. Effect on lung function of mouthpiece ventilation in Steinert disease. A case report. Acta Myol 2017;36:33-5.

151.   Khirani S, Dabaj I, Amaddeo A, Ramirez A, Quijano-Roy S, Fauroux B. The value of respiratory muscle testing in a child with congenital muscular dystrophy. Respirology Case Reports 2014;2:95-8.

152.   Crescimanno G, Marrone O. Successful treatment of atelectasis with Dornase alpha in a patient with congenital muscular dystrophy. Revista Portuguesa de Pneumologia 2014;20:42-5.

153.   Pincherle A, Patruno V, Raimondi P, et al. Sleep breathing disorders in 40 Italian patients with Myotonic dystrophy type 1. Neuromuscul Disord 2012;22:219-24.

154.   Bianchi MLE, Losurdo A, Di Blasi C, et al. Prevalence and clinical correlates of sleep disordered breathing in myotonic dystrophy types 1 and 2. Sleep and Breathing 2013:1-11.

155.   Zaim S, Bach J, Michaels J. Sudden death in an Emery-Dreifuss muscular dystrophy patient with an implantable defibrillator. American Journal of Physical Medicine & Rehabilitation 2008;87:325-9.

156.   Della Marca G, Frusciante R, Dittoni S, et al. Sleep disordered breathing in facioscapulohumeral muscular dystrophy. Journal of the Neurological Sciences 2009;285:54-8.

157.   Wohlgemuth M, van der Kooi EL, van Kesteren RG, van der Maarel SM, Padberg GW. Ventilatory support in facioscapulohumeral muscular dystrophy. Neurology 2004;63:176-8.

158.   Wohlgemuth M, Horlings CGC, van der Kooi EL, et al. Respiratory function in facioscapulohumeral muscular dystrophy 1. Neuromuscular Disorders 2017;27:526-30.

159.   Mori-Yoshimura M, Segawa K, Minami N, et al. Cardiopulmonary dysfunction in patients with limb-girdle muscular dystrophy 2A. Muscle & Nerve 2017;55:465-9.

160.   LoMauro A, D'Angelo MG, Aliverti A. Assessment and management of respiratory function in patients with Duchenne muscular dystrophy: current and emerging options. Therapeutics & Clinical Risk Management 2015;11:1475-88.

161.   Pinto T, Chatwin M, Banfi P, Winck JC, Nicolini A. Mouthpiece ventilation and complementary techniques in patients with neuromuscular disease: A brief clinical review and update. Chronic Respiratory Disease 2017;14:187-93.

162.   Nugent A, Smith IE, Shneerson JM. Domicilliary-assisted ventilation in patients with myotonic dystrophy. Chest 2002;121:459-64.

163.   Ilce Z, Celayir S, Tekand GT, Murat NS, Erdogan E, Yeker D. Tracheostomy in childhood: 20 years experience from a pediatric surgery clinic. Pediatr Int 2002;44:306-9.
164.   Ahmadian JL, Heller SL, Nishida T, Altman KW. Myotonic dystrophy type 1 (DM1) presenting with laryngeal stridor and vocal fold paresis. Muscle & Nerve 2002;25:616-8.
165.   Groh WJ. Arrhythmias in the muscular dystrophies. Heart Rhythm 2012;9:1890-5.
166.   Wahbi K, Meune C, Porcher R, et al. Electrophysiological study with prophylactic pacing and survival in adults with myotonic dystrophy and conduction system disease. JAMA 2012;307:1292-301.
167.   Wahbi K, Babuty D, Probst V, et al. Incidence and predictors of sudden death, major conduction defects and sustained ventricular tachyarrhythmias in 1388 patients with myotonic dystrophy type 1. European heart journal 2017;38:751-8.
168.   Laurent V, Pellieux S, Corcia P, et al. Mortality in myotonic dystrophy patients in the area of prophylactic pacing devices. International journal of cardiology 2011;150:54-8.
169.   Bhakta D, Shen C, Kron J, Epstein AE, Pascuzzi RM, Groh WJ. Pacemaker and implantable cardioverter-defibrillator use in a US myotonic dystrophy type 1 population. Journal of cardiovascular electrophysiology 2011;22:1369-75.
170.   Finsterer J, Stollberger C, Keller H. Arrhythmia-related workup in hereditary myopathies. Journal of electrocardiology 2012;45:376-84.
171.   Nigro G, Papa AA, Politano L. The heart and cardiac pacing in Steinert disease. Acta myologica : myopathies and cardiomyopathies : official journal of the Mediterranean Society of Myology 2012;31:110-6.
172.   Nigro G, Russo V, Politano L, et al. Does Bachmann's bundle pacing prevent atrial fibrillation in myotonic dystrophy type 1 patients? A 12 months follow-up study. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2010;12:1219-23.
173.   Nigro G, Russo V, Vergara P, et al. Optimal site for atrial lead implantation in myotonic dystrophy patients: the role of Bachmann's Bundle stimulation. Pacing and clinical electrophysiology : PACE 2008;31:1463-6.
174.   Steckiewicz R, Stolarz P, Swieton E, et al. Cardiac pacing in 21 patients with Emery-Dreifuss muscular dystrophy: a single-centre study with a 39-year follow-up. Kardiologia Polska 2016;74:576-83.
175.   Golzio PG, Chiribiri A, Gaita F. 'Unexpected' sudden death avoided by implantable cardioverter–defibrillator in Emery–Dreifuss patient. EP Europace 2007;9:1158-60.
176.   Laurent V, Pellieux S, Corcia P, et al. Mortality in myotonic dystrophy patients in the area of prophylactic pacing devices. Int J Cardiol 2011;150:54-8.
177.   Bhakta D, Shen C, Kron J, Epstein AE, Pascuzzi RM, Groh WJ. Pacemaker and implantable cardioverter-defibrillator use in a US myotonic dystrophy type 1 population. J Cardiovasc Electrophysiol 2011;22:1369-75.
178.   Hong JS, Ki CS, Kim JW, et al. Cardiac dysrhythmias,cardiomyopathy and muscular dystrophy in patients with Emery-Dreifuss muscular dystrophy and limb-girdle muscular dystrophy type 1B. Journal of Korean Medical Science 2005;20:283-90.
179.   Hickey RM, Cullen JD, Sachs GM. An overview of cardiac management in neuromuscular disease. Open Cardiovascular Medicine Journal 2016;10:82-8.
180.   Nigro G, Russo V, Ventriglia VM, et al. Early onset of cardiomyopathy and primary prevention of sudden death in X-linked Emery-Dreifuss muscular dystrophy. Neuromuscular Disorders 2010;20:174-7.
181.   Golzio PG, Chiribiri A, Gaita F. 'Unexpected' sudden death avoided by implantable cardioverter defibrillator in Emery Dreifuss patient. Europace 2007;9:1158-60.
182.   Sanna T, Dello Russo A, Toniolo D, et al. Cardiac features of Emery-Dreifuss muscular dystrophy caused by lamin A/C gene mutations. European Heart Journal 2003;24:2227-36.

183.   Boriani G, Gallina M, Merlini L, et al. Clinical relevance of atrial fibrillation/flutter, stroke, pacemaker implant, and heart failure in Emery-Dreifuss muscular dystrophy: a long-term longitudinal study. Stroke 2003;34:901-8.

184.   Nigro G, Carboni N, Marchel M, et al. Cardiac involvement in laminopathies-short invited review. Family Medicine and Primary Care Review 2015;17:327-9.

185.   Ambrosi P, Mouly-Bandini A, Attarian S, Habib G. Heart transplantation in 7 patients from a single family with limb-girdle muscular dystrophy caused by lamin A/C mutation. International Journal of Cardiology 2009;137:e75-6.

186.   Ellesoe SG, Reimers JI, Andersen HO. Normalisation of left ventricular systolic function after change from VVI pacing to biventricular pacing in a child with congenital complete atrioventricular block, long-QT syndrome, and congenital muscular dystrophy: a 10-year follow-up. Cardiology in the Young 2014;24:520-3.

187.   Nalini A, Gayathri N, Richard P, Cobo AM, Urtizberea JA. New mutation of the desmin gene identified in an extended Indian pedigree presenting with distal myopathy and cardiac disease. Neurology India 2013;61:622-6.

188.   Wu RS, Gupta S, Brown RN, et al. Clinical outcomes after cardiac transplantation in muscular dystrophy patients. Journal of Heart & Lung Transplantation 2010;29:432-8.

189.   Blagova O, Nedostup A, Shumakov D, Poptsov V, Shestak A, Zaklyasminskaya E. Dilated cardiomyopathy with severe arrhythmias in Emery-Dreifuss muscular dystrophy: from ablation to heart transplantation. Journal of Atrial Fibrillation 2016;9:1468.

190.   San Roman I, Navarro M, Martinez F, et al. Unclassifiable arrhythmic cardiomyopathy associated with Emery-Dreifuss caused by a mutation in FHL1. Clinical Genetics 2016;90:171-6.

191.   Dell'Amore A, Botta L, Martin Suarez S, et al. Heart transplantation in patients with Emery-Dreifuss muscular dystrophy: case reports. Transplantation Proceedings 2007;39:3538-40.

192.   Kracht J, Gay AJ, Nafeh-Bizet C, et al. Long-term outcomes after heart transplantation for Emery-Dreifuss muscular dystrophy. Archives of Cardiovascular Diseases Supplements 2013;5 (1):26.

193.   Volpi L, Ricci G, Passino C, et al. Prevalent cardiac phenotype resulting in heart transplantation in a novel LMNA gene duplication. Neuromuscular Disorders 2010;20:512-6.

194.   Plonka C, Wearden PD, Morell VO, Miller SA, Webber SA, Feingold B. Successful heart transplantation from a donor with Ullrich congenital muscular dystrophy. American Journal of Transplantation 2013;13:1915-7.

195.   Conraads VM, Beckers PJ, Vorlat A, Vrints CJ. Importance of physical rehabilitation before and after cardiac transplantation in a patient with myotonic dystrophy: a case report. Archives of Physical Medicine & Rehabilitation 2002;83:724-6.

196.   Allen HD, Flanigan KM, Thrush PT, et al. A randomized, double-blind trial of lisinopril and losartan for the treatment of cardiomyopathy in duchenne muscular dystrophy.[Erratum appears in PLoS Curr. 2015;7. pii: ecurrents.md.995441cf82fd58a29c6e4fdd5cd36b89. doi: 10.1371/currents.md.995441cf82fd58a29c6e4fdd5cd36b89; PMID: 25821645]. PLoS currents 2013;5:12.

197.   Romero A, Joshi GP. Neuromuscular disease and anesthesia. Muscle and Nerve 2013;48:451-60.

198.   van der Kooi EL, Vogels OJ, van Asseldonk RJ, et al. Strength training and albuterol in facioscapulohumeral muscular dystrophy. Neurology 2004;63:702-8.

199.   van der Kooi EL, Kalkman JS, Lindeman E, et al. Effects of training and albuterol on pain and fatigue in facioscapulohumeral muscular dystrophy. Journal of Neurology 2007;254:931-40.

200.   Kissel JT, McDermott MP, Mendell JR, et al. Randomized, double-blind, placebo-controlled trial of albuterol in facioscapulohumeral dystrophy. Neurology 2001;57:1434-40.

201.   Rose MR, Tawil R. Drug treatment for facioscapulohumeral muscular dystrophy. Cochrane Database of Systematic Reviews 2004:CD002276.

202.   Skura CL, Fowler EG, Wetzel GT, Graves M, Spencer MJ. Albuterol increases lean body mass in ambulatory boys with Duchenne or Becker muscular dystrophy. Neurology 2008;70:137-43.
203.   Fowler EG, Graves MC, Wetzel GT, Spencer MJ. Pilot trial of albuterol in Duchenne and Becker muscular dystrophy. Neurology 2004;62:1006-8.
204.   Henry SM. Discerning differences: Gastroesophageal reflux and gastroesophageal reflux disease in infants. Advances in Neonatal Care 2004;4:235-47.
205.   Khatwa UA, Dy FJ. Pulmonary Manifestations of Neuromuscular Diseases. Indian Journal of Pediatrics 2015;82:841-51.
206.   Fitzgerald BP, Conn KM, Smith J, et al. Medication adherence in patients with myotonic dystrophy and facioscapulohumeral muscular dystrophy. Journal of Neurology 2016;263:2528-37.
207.   Hilbert JE, Barohn RJ, Clemens PR, et al. High frequency of gastrointestinal manifestations in myotonic dystrophy type 1 and type 2. Neurology 2017;89:1348-54.
208.   Pane M, Vasta I, Messina S, et al. Feeding problems and weight gain in Duchenne muscular dystrophy. European Journal of Paediatric Neurology 2006;10:231-6.
209.   Matthews DJ, James KA, Miller LA, et al. Use of corticosteroids in a population-based cohort of boys with duchenne and becker muscular dystrophy. Journal of Child Neurology 2010;25:1319-24.
210.   Matthews E, Brassington R, Kuntzer T, Jichi F, Manzur AY. Corticosteroids for the treatment of Duchenne muscular dystrophy. Cochrane Database of Systematic Reviews 2016:CD003725.
211.   Tsao CY. Muscle disease. Pediatrics in Review 2014;35:49-60.