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

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

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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

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

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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. Estimates of the crude prevalence of muscular dystrophies as a whole fall between 19.8 and 25.1/100,000 people.

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. 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 STARnet) 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 STARnet 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 STARnet by describing the distribution of demographic, sociodemographic, and clinical characteristics of individuals within the MD STARnet pilot cohort by MD type. The MD STARnet pilot surveillance data were collected to assess the feasibility of extending the MD STARnet population-based surveillance protocol for Duchenne and Becker MD to other forms of muscular dystrophies. The MD STARnet 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 \( \alpha \)-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. 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.

2.2 Duchenne and Becker Muscular Dystrophy

Duchenne and Becker MD, X-linked disorders, almost exclusively affect males, though manifesting females have been described. Duchenne and Becker MD are the most common types of MD among children. The mean age of diagnosis for Duchenne and Becker MD patients is between four and five years of age. 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. An earlier onset of symptoms for Duchenne and Becker MD patients is associated with an accelerated loss of ambulation. Studies have found that the mean age of ambulation loss is between 7 and 13 years with wheel-chair use by 8-14 years of age. Cardiomyopathy typically affects Duchenne MD patients between the ages of 14-15. Scoliosis and contractures may affect DMBD patients who use wheelchairs. The median survival for Duchenne and Becker MD patients has been estimated at 24 years, with death occurring before or during the third decade.

A prior study conducted using MD STARnet 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. 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. 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 MD41. 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, French45, 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.  

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. Cardiac involvement in the X-linked form of Emery-Dreiffus MD is more severe than in autosomal dominant. 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.

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. 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. The prevalence of Emery-Dreiffus MD among children has only been quantified in one study, which found a prevalence of 0.22/100,000.

2.5 Facioscapulohumeral Muscular Dystrophy

Facioscapulohumeral MD is the third most common type of MD. There are two forms of Facioscapulohumeral MD (type 1 and type 2) that are genetically, but not clinically,
distinguishable. 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. Though Facioscapulohumeral MD is a genetic disorder and inherited from family members, de novo mutations have been reported. The most widely cited prevalence of Facioscapulohumeral MD is 1/20,000. 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.

Population-based estimates of Facioscapulohumeral MD in the Netherlands are 12/100,000; in this same study, the incidence rate of Facioscapulohumeral MD was .3/100,000 person-years. Italian studies have estimated Facioscapulohumeral MD prevalence at 4.6/100,000 people. 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, 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 characterize Facioscapulohumeral MD. Progression of this disease is variable and slow. 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. There is multisystem involvement in Facioscapulohumeral MD; pain and fatigue are common in Facioscapulohumeral MD patients. One study documented pain in 88.6% of their sample at the time the study was
conducted\textsuperscript{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\textsuperscript{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\textsuperscript{64,76}. Respiration may also be affected in Facioscapulohumeral MD patients, and infrequently, hearing and vision loss may occur\textsuperscript{61}.

\section*{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\textsuperscript{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\textsuperscript{23}. Limb-Girdle MD has been documented globally, including in Denmark\textsuperscript{77}, India\textsuperscript{78-81}, Norway\textsuperscript{82}, Mexico\textsuperscript{83}, and Taiwan\textsuperscript{84} among others.

The recessive forms of Limb-Girdle MD (LGMD2) are more common than the dominant forms (LGMD1)\textsuperscript{83,84}; the cumulative prevalence of LGMD2 is 1/15,000\textsuperscript{85}, while dominantly transmitted forms of Limb-Girdle MD may only account for 10\% of cases\textsuperscript{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\textsuperscript{78}. Calpainopathies are
characterized by proximal weakness in pelvic/shoulder girdle, joint and Achilles contractures, and hernias. Sarcoglycanopathies have a childhood onset and often feature weakness of knee flexor. Cardiomyopathy and severe respiratory impairment has been reported in patients with sarcoglycanopathies.

LGMD1B is considered a LMNA-related myopathy. Though LGMD1B has a later age of onset than other LMNA-related disease, such as Emery-Dreiffus MD, the lamnopathies are often considered a continuum of diseases as there is significant overlap in symptoms. 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. 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. 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. 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.
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. DM1 men have a higher mortality rate than DM1 women. 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. 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. Both fatigue and the inability to do activities were reported as the most impactful symptoms for DM2 patients. DM1 patients suffering from fatigue and daytime sleepiness have lower QoL levels.

### 2.8 Oculopharyngeal Muscular Dystrophy

The age at onset for Oculopharyngeal MD patients is in the fifth and sixth decade. 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. Dysphagia may lead to malnutrition and aspiration pneumonia. Other symptoms include weakness in axial and limb girdle muscles, external ophthalmoplegia, as well as impairment to pelvic girdle and proximal leg muscles. Dysfunction of lower extremities influences HR-QoL for these patients.

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. Oculopharyngeal MD, though rare, has been reported globally, including France, Germany, the U.K, Thailand, Italy, Bulgarian Jews, and a Hispanic population in New Mexico. 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 STARnet 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 STARnet) to conduct population–based surveillance of the muscular dystrophies. MD STARnet utilizes active record review with a multiple source approach.
From 2002-2011, MD STARnet 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 STARnet 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.\textsuperscript{125,126}

3.3 MD STARnet Pilot Methods

The MD STARnet pilot was conducted in four MD STARnet 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 STARnet 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 STARnet 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 STARnet pilot mirrored the case-finding methodology used by the MD STARnet for Duchenne and Becker MD surveillance. The MD STARnet 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 STARnet 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 STARnet 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 STARnet’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 STARnet 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 STARnet 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
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 STARnet 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 STARnet 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 STARnet 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 STARnet 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 STARnet 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 STARnet 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 STARnet 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\textsuperscript{131}, and Oculopharyngeal MD has been described in a Hispanic Population in New Mexico\textsuperscript{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 STARnet 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 STARnet 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 STARnet 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. In another qualitative study, the use of invasive home mechanical ventilation facilitated independent living in Duchenne and Becker MD patients. 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. 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. Further, Natterlund (2001) found that dependence on others for Myotonic Dystrophy patients increased over a 5 year period. Similar to the deterioration in Myotonic Dystrophy patients, there appears a reduction in ADL scores overtime for Facioscapulohumeral MD and Limb-Girdle MD patients. 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 STARnet 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 STARnet 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 STARnet 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 STARnet 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 \textsuperscript{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\textit{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\textsuperscript{144}. The MD STAR\textit{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. 
In another study, 70% of Facioscapulohumeral MD patients were employed compared to 48% of
Myotonic Dystrophy. Similarly, in the MD STARnet 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,
which was supported by the results of the MD STARnet 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 STARnet pilot to normative
data. Additionally, because QoL and symptom burden are related to employment status for MD
patients, 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 STARnet 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 STARnet 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\(^{154}\) of Myotonic Dystrophy patients need NIV.
NIPPV were required infrequently for Emery Dreiffus MD and Distal MD cases in the MD STARnet 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. Respiratory failure in Emery-Dreiffus MD cases may result from either weakness in the respiratory muscles or chest deformities, and some researchers have suggested that non-invasive ventilation may benefit Emery-Dreiffus MD patients at risk for ventilator insufficiency. 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 STARnet pilot cohort required NIPPV, other studies indicate that respiratory involvement is uncommon in Facioscapulohumeral MD patients, and the need for NIPPV is infrequent. Other researchers have found that only 1% of Facioscapulohumeral MD patients needed ventilator support. However, Wohlgemuth et al. (2011) 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. 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. 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 STARnet pilot cohort (17.3%). 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 STARnet 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. 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. 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. There is limited contemporary research on tracheostomy in Myotonic Dystrophy patients. In the MD STARnet 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 STARnet 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\textsuperscript{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\textit{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\textsuperscript{166-173}, research has only begun to classify cardiac issues and pacemaker and defibrillator use in Emery-Dreiffus MD and Limb-Girdle MD patients\textsuperscript{165,174} and most of this research is limited to case reports and series\textsuperscript{175}.

Between 3-22\% of Myotonic Dystrophy patients require antiarrhythmic devices, such as pacemaker or cardioverter defibrillator\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{30,178,179}, and pacemakers and ICDs have been used in Emery-Dreiffus MD patients to avoid sudden death.
Most Emery-Dreiffus MD patients requiring cardiac devices are between 20-40 years of age \cite{174,182}, and studies have indicated that over 50% of Emery-Dreiffus MD patients require pacemaker implantations \cite{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 STARnet 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 \cite{184}. Though studies have noted that patients with laminopathies frequently require pacemakers or ICDs after 30 years of age \cite{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 \cite{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 \cite{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 STARnet pilot data, and only one case report has documented the use of a pacemaker in a Distal MD patient \cite{187}.

Heart Transplants

MD patients often develop cardiomyopathy, necessitating cardiac transplantation \cite{188}. In the MD STARnet 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 STARnet 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 STARnet cohort, a higher percentage of Distal MD cases used Linopril 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 STARnet 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. Albuterol does not change pain, fatigue or functional status for Facioscapulohumeral MD patients. 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. A similar increase in lean body mass after short-term treatment with Albuterol has been described for Duchenne and Becker MD patients. 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.

Omeprazole is a proton pump inhibitor that is commonly used to treat Gastroesophageal reflux disease (GERD). The percentage of Myotonic Dystrophy and Oculopharyngeal MD cases on Omeprazole were equal in the MD STARnet 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, and medications for gastroesophageal reflux are used in 22.5% of DM1 and 18.9% of DM2 patients. 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. Further, though other studies have found GERD to be a comorbidity in 18.1% of Facioscapulohumeral MD patients studied, less than 6% of the Facioscapulohumeral MD case in the MD STARner 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. As Prednisone has been shown to improve muscle and strength, this finding is not surprising.

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 STARnet site but received care elsewhere. For examples, cases who live 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 STARnet 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 STARnet 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 STARnet 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 STARnet 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 STARnet 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 STARnet 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 STARnet 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 STARnet 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 STARnet (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 STARnet 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**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total</th>
<th>Muscular Dystrophy Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Congenital</td>
</tr>
<tr>
<td>Frequency</td>
<td>N/%</td>
<td>2862</td>
</tr>
<tr>
<td>Age at 1/1/2007 Mean/SD</td>
<td>34.6</td>
<td>22.1</td>
</tr>
<tr>
<td>Age at Death Mean/SD</td>
<td>51.6</td>
<td>22.2</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Variables</th>
<th>Muscular Dystrophy Type</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Congenital</td>
<td>DBMD Males</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>45</td>
</tr>
<tr>
<td>Race</td>
<td>White/Caucasian</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Black/African American</td>
<td>&lt;10 -</td>
</tr>
<tr>
<td></td>
<td>Multiple /Other</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>&lt;10 -</td>
</tr>
<tr>
<td>Hispanic Ethnicity</td>
<td>Yes</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>*</td>
</tr>
<tr>
<td>Insurance (most recent)</td>
<td>Private</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>Public</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>Uninsured / Self-pay</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>Not documented</td>
<td>*</td>
</tr>
<tr>
<td>Full-time in Assisted living</td>
<td>Yes</td>
<td>&lt;10 -</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Not documented</td>
<td>&lt;10 -</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variables</th>
<th>Age</th>
<th>DBMD Males</th>
<th>FSHD</th>
<th>LGMD</th>
<th>Myotonic</th>
<th>OPMD</th>
<th>MD NOS + Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Younger than school age</td>
<td>0 to &lt;5</td>
<td>18</td>
<td>46.2</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5 to &lt;18</td>
<td>293</td>
<td>98.3</td>
<td>31</td>
<td>96.9</td>
<td>79</td>
<td>89.8</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>18 to &lt;35</td>
<td>86</td>
<td>41.4</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>32</td>
<td>19.2</td>
<td>0</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variables</th>
<th>Age</th>
<th>DBMD Males</th>
<th>FSHD</th>
<th>LGMD</th>
<th>Myotonic</th>
<th>OPMD</th>
<th>MD NOS + Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Working for Pay</td>
<td>18 to &lt;35</td>
<td>28</td>
<td>13.46</td>
<td>23</td>
<td>47.92</td>
<td>25</td>
<td>49.02</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>35 to &lt;65</td>
<td>21</td>
<td>32.3</td>
<td>62</td>
<td>44.6</td>
<td>49</td>
<td>40.5</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>65+</td>
<td>&lt;10</td>
<td>-</td>
<td>&lt;10</td>
<td>-</td>
<td>&lt;10</td>
<td>-</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Disabled or Unable</td>
<td>18 to &lt;35</td>
<td>37</td>
<td>17.8</td>
<td>&lt;10</td>
<td>-</td>
<td>&lt;10</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>to Work</td>
<td>35 to &lt;65</td>
<td>32</td>
<td>49.2</td>
<td>39</td>
<td>28.1</td>
<td>41</td>
<td>33.9</td>
<td>256</td>
</tr>
<tr>
<td></td>
<td>65+</td>
<td>&lt;10</td>
<td>-</td>
<td>&lt;10</td>
<td>-</td>
<td>&lt;10</td>
<td>-</td>
<td>19</td>
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<tr>
<td>Unemployed</td>
<td>18 to &lt;35</td>
<td>19</td>
<td>9.1</td>
<td>&lt;10</td>
<td>-</td>
<td>&lt;10</td>
<td>-</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>35 to &lt;65</td>
<td>&lt;10</td>
<td>-</td>
<td>16</td>
<td>11.5</td>
<td>15</td>
<td>12.4</td>
<td>76</td>
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<tr>
<td></td>
<td>65+</td>
<td>0</td>
<td>0.0</td>
<td>&lt;10</td>
<td>-</td>
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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

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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

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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 STARnet 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

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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.
Table 8: Distribution of the Most Frequently Documented Medications

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

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

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.


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.


