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HEALTHCARE AND HUMAN SERVICES POLICY, RESEARCH, AND CONSULTING — WITH REAL-WORLD PERSPECTIVE.

Cost of Amyotrophic Lateral Sclerosis, Muscular Dystrophy, and Spinal Muscular Atrophy in the United States

Final Report

Prepared for: **Muscular Dystrophy Association**

Submitted by: **The Lewin Group, Inc.**

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Abbreviations

Abbreviation	Name
ALS	Amyotrophic Lateral Sclerosis
BMD	Becker Muscular Dystrophy
CMD	Congenital Muscular Dystrophy
DMD	Duchenne Muscular Dystrophy
HPMD	Hereditary Progressive Muscular Dystrophy
LGMD	Limb-girdle Muscular Dystrophy
MD	Muscular Dystrophy
MDA	Muscular Dystrophy Association
MMD	Myotonic Muscular Dystrophy
SMA	Spinal Muscular Atrophy
SMA1	Spinal Muscular Atrophy Type 1
SMA2	Spinal Muscular Atrophy Type 2
SMA3	Spinal Muscular Atrophy Type 3
SMA4	Spinal Muscular Atrophy Type 4
SMA Early Onset	Spinal Muscular Atrophy Early Childhood Onset
SMA Other	Other Types of Spinal Muscular Atrophy

Executive Summary

Amyotrophic lateral sclerosis (ALS), **muscular dystrophy (MD),** and **spinal muscular atrophy (SMA)** are among the more common neuromuscular diseases. Such severe diseases result in significant costs to families with one or more affected individual(s), through direct medical costs, through non-medical costs (e.g., modifications to houses and vehicles to accommodate the affected individual) and through loss of household income through reduced employment of both the affected individual and of family caregivers.

As part of its initiative to understand the economic burden of several neuromuscular diseases, the Muscular Dystrophy Association (MDA) commissioned The Lewin Group to estimate the economic impact on the United States in 2010 of ALS, two major forms of MD, and SMA. To date, there have been limited data on the medical costs associated with these diseases, and literature on the non-medical and loss of productivity costs of these diseases is even less well-established.

This study aims to estimate the direct, indirect, and, ultimately, the total national economic burden associated with these diseases in 2010.

We used commercial and Medicare claims data to estimate the direct medical costs associated with several key neuromuscular diseases. Primary data, collected from a cost-of-illness survey developed as part of this research, were used to estimate the non-medical costs to families and the indirect economic impact of these diseases.

The methodology used in the analysis of loss of productivity was based on the "human capital" approach. This approach assesses the labor market earnings lost from illness or injury, as measured by income forgone because of morbidity or mortality, and the earnings loss of household members as they direct efforts toward the care of the affected person in the household and away from the labor market. Household income loss was used to calculate the value of indirect costs in the U.S. in 2010 due to having one or more family members affected by these diseases.

Total economic cost of a disease was calculated as the multiplication of prevalence of the disease with total per-capita annual cost. Based on a literature search, we conducted the calculations using a range of published prevalence estimates that we characterized as low, moderate, and high.

Using the moderate prevalence estimate, we estimated that the total economic cost of **amyotrophic lateral sclerosis (ALS), Duchenne muscular dystrophy (DMD), myotonic muscular dystrophy (MMD), and spinal muscular atrophy (SMA)** was approximately $3.2 billion dollars in 2010. We also estimated that the total national burden is in the range of $1.2-$4.8 billion (using the low and high prevalence estimates respectively).

When using the moderate prevalence estimates, among the diseases studied, ALS is associated with the highest national economic burden ($1.03 billion), followed by SMA ($957 million), DMD ($791 million), and MMD ($450 million). It should be noted that due to low sample sizes of the populations, there is a large margin of error for the estimate for SMA.

Of the total economic burden of $3.2 billion (moderate estimate) from all four diseases, $1.63 billion (51%) is due to medical costs associated with these diseases, $835 million (26%) is due to non-medical costs, and $753 million (23%) is due to loss of productivity.

Exhibit ES-1 shows the high, moderate, and low estimates of total national economic burden by disease.

Exhibit ES-1: National Economic Burden by Disease (In Millions of US Dollars) In 2010

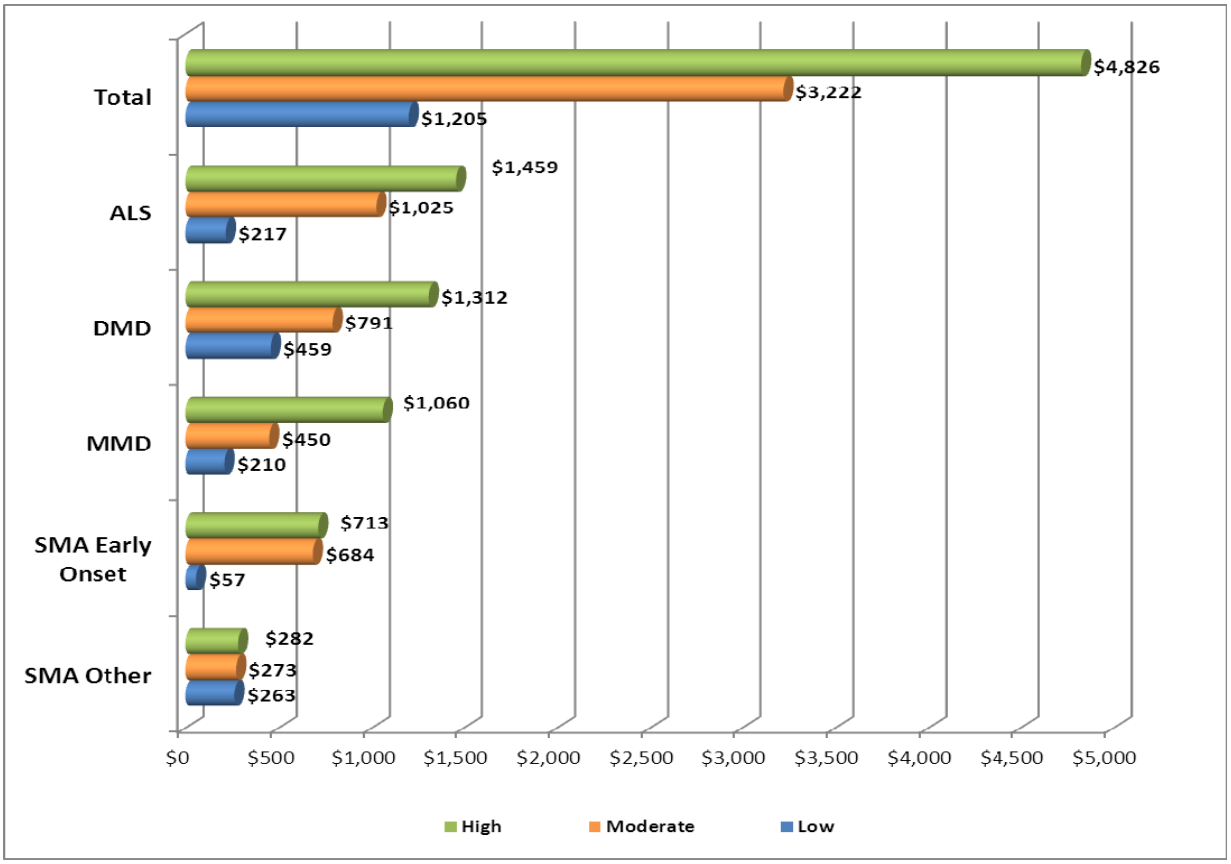
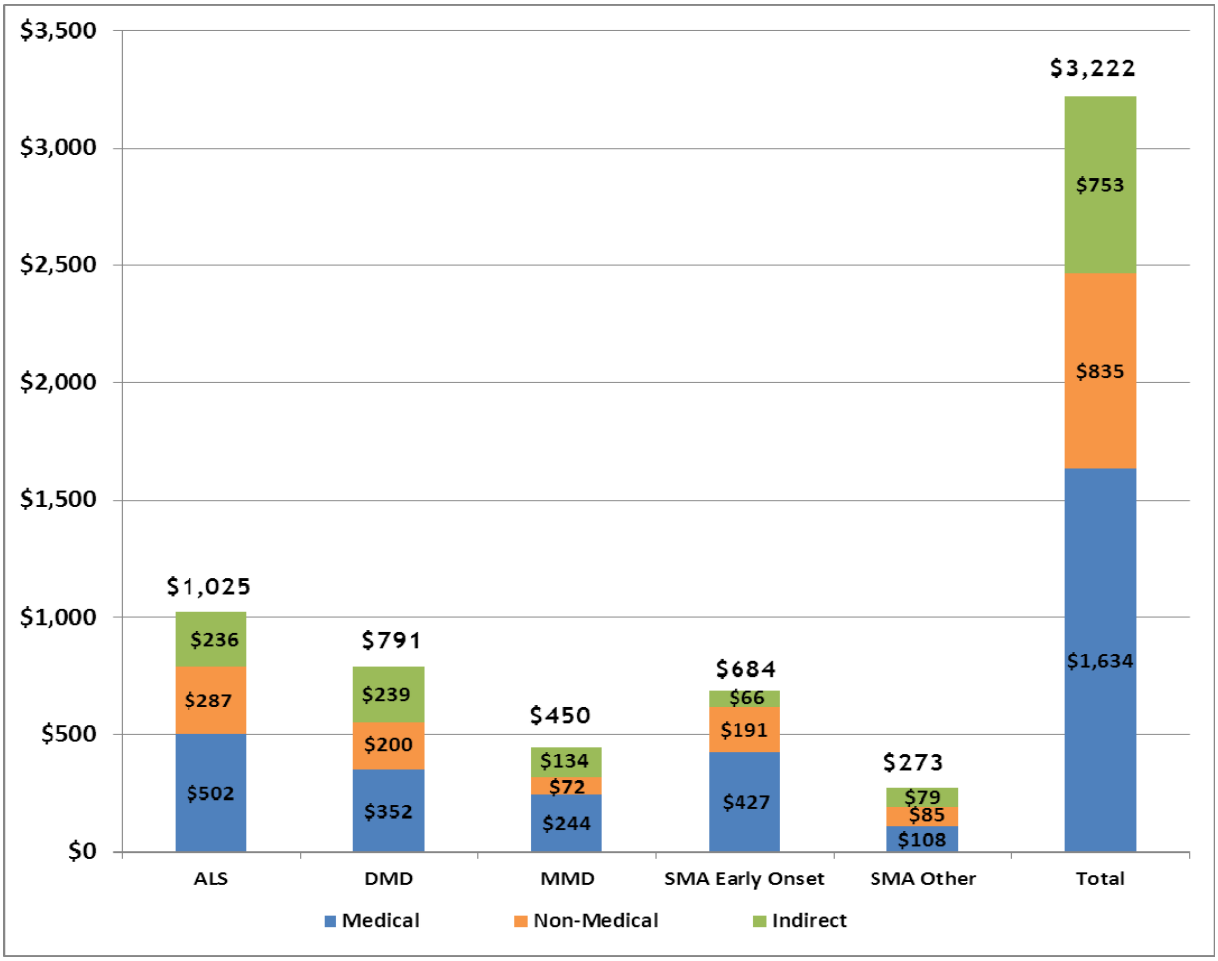


Exhibit ES-2 shows the total medical, non-medical, and productivity costs by disease based on the costs projected from the moderate prevalence estimates (as shown in Exhibit I).

Exhibit ES-2: National Economic Burden by Disease and Type of Cost (In Millions of US Dollars and Based on Moderate Prevalence Estimates) In 2010



1. Background

As part of its initiative to understand the economic burden of several neuromuscular diseases, the Muscular Dystrophy Association (MDA) commissioned The Lewin Group to estimate the economic impact on the United States in 2010 of **amyotrophic lateral sclerosis (ALS),** two major forms of **muscular dystrophy: Duchenne muscular dystrophy (DMD) and myotonic dystrophy (MMD), early-childhood onset spinal muscular atrophy (SMA diagnosed in patients under age 3)** and **other SMA**.

To date, there have been limited data on the medical, non-medical (e.g., home/car modifications, paid personal care attendants, etc.), and indirect productivity costs associated with these diseases. It has been recognized in the cost-of-illness research that there is a need to identify and estimate the indirect economic burden to patients diagnosed with muscle disease and to their caregivers.[1] Although rare, these diseases have been shown to generate significant financial impact to the patient, to the family, and, ultimately, to society through third-party payer costs and taxes.[2-6]

This study aimed to provide a comprehensive analysis of the total societal cost associated with several key types of neuromuscular diseases. Specifically, we posed the following research questions:

1. What is the direct medical cost associated with the diseases for affected individuals that are covered by private and public health insurance plans?
2. What are the non-medical costs (e.g., home and motor vehicle modification, professional caregiving, etc.) associated with these diseases?
3. What is the indirect family income loss (due to reduced labor market participation, reduced work performance, etc.) associated with these diseases?

We answered the first research question by using existing health plan administrative data (claims data) from a large commercial insurance plan in the U.S. and data from Medicare Standard Analytical Files (SAFs) 5% sample for the following diseases:

Amyotrophic lateral sclerosis (ALS): ICD-9 codes 335.20, 335.21, and 335.22

Congenital muscular dystrophy (CMD): ICD-9 code 359.0

Hereditary progressive muscular dystrophy (HPMD): ICD9 code 359.1, which includes, among other muscular dystrophies:

- **Duchenne muscular dystrophy (DMD)**
- **Becker muscular dystrophy (BMD)**
- **Limb-girdle muscular dystrophy (LGMD)**

Myotonic muscular dystrophy (MMD): ICD9 code 359.21

Spinal muscular atrophy (SMA): ICD9 codes 335.0, 335.10, 335.11 and 335.19

- **SMA — early-onset (diagnosis before or at age 3)**
- **SMA — other (diagnosis after age 3)**

In order to capture the total family burden and answer the second and third research questions, we designed and implemented a cost-of-illness survey, with input from an expert advisory committee. The survey focused on **ALS**, **DMD** (a subset of **HPMD), MMD**, **SMA Early Onset**, and **SMA Other**.

Information captured from these different data sources, coupled with an estimate of the disease prevalence, enabled us to estimate the total national economic burden associated with these diseases in the United States in 2010.

The study protocol and survey instrument were reviewed and approved by the New England Institutional Review Board.

1.1 Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS), also known as **Lou Gehrig's disease**, is a progressive and ultimately fatal degenerative disease affecting both upper and lower motor neurons in the brain and spinal cord. ALS may occur in people throughout their lives, but predominantly manifests in people between 40 and 75 years of age. ALS is characterized by a progressive loss of voluntary motor activity (including speech, swallowing and respiratory function), muscle weakness, cramping, spasticity, brisk reflexes, emotional liability, and fasciculation.[7] ALS first affects legs, arms and/or throat and mouth muscles but ultimately affects all voluntary muscles, resulting in paralysis. It usually progresses rapidly with an average survival time of 2 to 5 years [4], with significant variability between patients.

ALS affects thousands of people throughout the world, with country-specific prevalence ranging from 1.1 [8] to 7.4 [9] individuals per 100,000 populations. ALS has a crude incidence rate of between 0.3 and 2.6 cases per 100,000 (averaging 1.75/100, 000 worldwide) and its incidence is increasing in many countries, due mainly to increases in longevity and improved diagnosis in developed countries.[4] According to the National Institute of Neurological Disorders and Stroke, approximately 20,000 Americans have ALS, and an estimated 5,000 people in the United States are diagnosed with the disease each year.[10]

With no known cure, treatment of ALS focuses on supportive care, such as physical, speech and occupational therapy, symptomatic treatment, mobility aids, and nursing support.[11] Percutaneous endoscopic gastrostomy (PEG) to support nutrition and bi-level intermittent positive pressure (Bipap) ventilation to support respiratory function are also used, and in later stage disease the use of mechanical ventilation, delivered via an indwelling tracheostomy tube and requiring trans-tracheal suctioning of airway secretions may be considered.[12, 13] Riluzole has been shown to have modest effects on survival (as opposed to functional gains) and is currently the only drug approved for the treatment of ALS.[14]

1.2 Muscular Dystrophy (MD)

Muscular dystrophy (MD) is a group of inherited disorders that involve progressive skeletal muscle weakness and loss of muscle. Some forms of muscular dystrophy also affect the heart. Signs and symptoms vary with the different types of MD. The disease onset is variable depending on the specific type, and there is often a delay between onset of disease symptoms and the time of

definitive diagnosis.[15] In this study we focus on two of the most common muscular dystrophies: Duchenne muscular dystrophy (DMD) and myotonic muscular dystrophy (MMD).

In calculating the medical costs of these diseases, we had to approximate the costs based on ICD-9 codes used to classify the diseases in medical records. Accordingly, we calculated the medical costs for MMD, congenital muscular dystrophy (CMD, a muscular dystrophy likely to have similar costs to DMD), both of which have unique ICD-9 codes; and the costs for "hereditary progressive muscular dystrophy", an ICD-9 diagnosis code that includes DMD and several other less severe dystrophies.

Exhibit 1-1 describes the general disease onset, symptoms, and disease progression for the muscular dystrophies.

Exhibit 1-1: Description of Types of Muscular Dystrophy Featured in this Study

Disease	Onset	Symptoms	Progression
CMD [16, 17]	At or near birth	Generalized muscle weakness with possible joint stiffness or looseness. Depending on the type, CMD may involve spinal curvature, respiratory insufficiency, mental retardation or learning disabilities, eye defects, or seizures.	Varies with type; many are slowly progressive; some shorten life span
DMD (classified as a form of HPMD by ICD-9) [18, 19]	Early childhood - about 2 to 6 years. Average diagnosis at 5 years of age	Generalized weakness and muscle atrophy first affecting the muscles of the hips, pelvic area, thighs, and shoulders. Calves often are enlarged. DMD eventually affects all voluntary muscles, as well as involuntary muscles such as the heart and muscles associated with respiration.	Loss of ambulation between ages 7 and 13 years and death may occur in the teens or 20s, survival increasing with improved medical management [20]
BMD (classified as a form of HPMD by ICD-9) [19, 21]	Later onset than DMD, usually in adolescence or adulthood	Generalized weakness and muscle atrophy first affecting the muscles of the hips, pelvic area, thighs and shoulders. Calves often are enlarged. BMD is similar to DMD but often less severe. The heart can be seriously affected.	Disease progresses slowly and with variability but can affect all voluntary muscles. Most patients with BMD survive well into mid-to-late adulthood
LGMD (classified as a form of HPMD by ICD-9) [22, 23]	Childhood to adulthood	Weakness and atrophy first affecting the muscles around the shoulders and hips (limb girdles).	Usually progresses slowly with cardiopulmonary complications often occurring in later stages of some forms of the disease
MMD [24, 25]	Congenital form appears at birth. More common form may begin in teen or adult years	Generalized weakness and muscle atrophy first affecting the face, lower legs, forearms, hands, and neck, with delayed relaxation of muscles after contraction. Other symptoms can emerge in the gastrointestinal system, vision, heart or respiratory systems. Learning disabilities occur in some cases. Congenital MMD is the most severe form of MMD.	Progression is slow, sometimes spanning 50 to 60 years

According to the Society for Neuroscience, an estimated 55,000 people in the United States had MD in 2006.[26] Orphanet, which has aggregated data in the literature to provide the best estimate of prevalence of rare diseases, states that DMD is found in approximately 5 out of every 100,000 people, predominantly affecting males.[27] MMD affects 4.5 individuals per 100,000.[27]

There are no known cures for any of the muscular dystrophies, but corticosteroids have been shown to slow the progression of DMD and some other dystrophies.[28] Medications are used to treat the cardiac complications of several forms, and treatments for some symptoms specific to particular dystrophies, such as myotonia in MMD, are available.[29] As with ALS, much of the treatment of MD patients is supportive in nature, with patient survival increasing in response to cardiac and respiratory monitoring and treatment, rather than a disease specific treatment. Patients may also use physical and occupational therapy, mobility aids, and nursing support.[11]

1.3 Spinal Muscular Atrophy (SMA)

Spinal muscular atrophy (SMA) is a neuromuscular disorder that leads to progressive muscle weakness and atrophy. SMA is generally divided into sub-categories termed SMA1, 2 and 3 based on disease onset and severity, with SMA1 being the earliest onset and most severe. There is no exact marker to categorize these sub-categories, and they are not well-distinguished by ICD-9 code. Accordingly, this study defines "early-childhood onset" as SMA diagnosed before or at age 3, irrespective of what the patient or medical record says with respect to subtype.

Exhibit 1-2 describes the general disease onset, symptoms, and disease progression for different types of SMA.

Exhibit 1-2: Description of Types of Spinal Muscular Atrophy Featured in this Study

Disease	Onset	Symptoms	Progression
SMA type 1 [30]	Before birth to 6 months	Generalized muscle weakness, weak cry, difficulty swallowing as well as sucking, and breathing distress. Cannot sit without support.	Can progress very rapidly with early childhood death
SMA type 2 [30]	6 to 18 months	Weakness is most severe in muscles closest to the center of the body, such as those of the shoulders, hips, thighs, and upper back. Respiratory muscles also can be involved. Spinal curvature often develops.	Usually progresses slowly, and survival into adulthood is common if respiratory status is closely monitored
SMA type 3 [30]	After 18 months	Weakness is most severe in muscles closest to the center of the body, such as those of the shoulders, hips, thighs, and upper back. Respiratory muscle weakness and spinal curvature sometimes develop.	Disease progresses slowly, with walking ability usually maintained until at least adolescence. Wheelchair often required later in life. Life span usually not affected

It is estimated that 9,000 people in the United States have SMA, and one in every 10,000 children born is affected by the disease. One in 50 people (approximately 6 million Americans) are carriers of the SMA gene.[31]

Later onset SMA is generally less severe than early onset SMA (SMA1 patients frequently die in early childhood due to respiratory failure), but there are no specific treatments for any form. Depending on severity of symptoms, SMA patients may use critical care services, ventilatory support, orthopedic surgery, physical therapy and/or nutritive support to manage the disease, and often use assistive devices to aid movement.

2. Methods

2.1 Estimating Direct Medical Cost Using Health Plan Administrative Data

2.1.1 Commercially insured research database

Lewin has access to a proprietary OptumInsight health research database that contains longitudinal medical and pharmacy claims, and enrollment information for a cumulative of more than seventy million privately insured members between year 1993 and 2010. In 2009, there were approximately fourteen million covered individuals with both medical and pharmacy coverage and an additional nine million enrollees with medical benefits only. Underlying information is geographically diverse across the U.S. and generally representative of the U.S. population.

Medical Claims

Medical claims, or encounter data, are collected from all available health care sites including, but not limited to: inpatient hospitals, outpatient hospitals, emergency rooms, outpatient offices, and surgery centers. These claims are available for the entire spectrum of provided services, including specialty, preventive, and office-based treatments. The medical claims and coding conform to insurance industry standards. Claims for ambulatory services submitted by individual providers, such as physicians, use the HCFA-1500 format. Claims for facility services submitted by institutions, such as hospitals, use the UB-82 or UB-92 format. Medical claims include: multiple diagnosis codes recorded with the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes; procedures recorded with ICD-9-CM procedure codes, Current Procedural Terminology (CPT), or Healthcare Common Procedure Coding System (HCPCS) codes; site of service codes; provider specialty codes; revenue codes (for facilities); paid amounts by health plan, patient, and other payers, etc.. Typically, facility claims do not include any drugs administered in the hospital. A lag of approximately 6 months following the delivery of services usually occurs in processing the claims. We therefore use 2009 data (instead of 2010) to ensure that the claims data for a calendar year are complete.

Pharmacy Claims

Claims for pharmacy services are typically submitted electronically by the pharmacy at the time prescriptions are filled. The claims history is a profile of all outpatient prescription pharmacy services provided and covered by the health plan. Pharmacy claims data include drug name, dosage form, drug strength, fill date, days of supply, financial information, and de-identified patient and prescriber codes, allowing for longitudinal tracking of medication refill patterns and changes in medications. Pharmacy claims are typically added to the research database within 6 weeks of dispensing.

2.1.1.1 Study Sample

The inclusion criteria for this analysis using commercial claims data are the following:

First, patients must have received at least one diagnosis at any time during the year 2009 with any of the ICD-9 diagnoses listed in Exhibit 2-1 at primary or secondary diagnosis positions.

Exhibit 2-1: ICD-9 Diagnosis Codes of the Diseases

Diagnosis	ICD-9 diagnosis Codes
Amyotrophic Lateral Sclerosis (ALS)	335.20, 335.21, 335.22
Congenital muscular dystrophy (CMD)	359.0
Hereditary progressive muscular dystrophy (HPMD)	359.1[b]
Myotonic muscular dystrophy (MMD)	359.21
Spinal muscular atrophy [a]	335.0,335.10,335.11, 335.19

[a] Patients with a diagnosis of SMA were further classified as SMA Early Onset (SMA1, SMA2, and SMA3 patients age three or younger) and SMA Other (later onset SMA2 and SMA3, as well as SMA4).

[b] ICD-9 code 359.1 for HPMD that covers DMD, BMD, and LGMD will be used as a proxy for DMD in the direct medical cost analysis using claims data.

Second, we only included people younger than 65 years of age. Although the commercial claims database includes beneficiaries older than 65 who have Medicare supplemental insurance or are covered by employers, the claims filed through the commercial plan may not reflect the complete medical history of beneficiaries older than 65.

Third, we only included people who had complete medical and pharmacy coverage for 12 months in 2009 to ensure complete coverage of medical costs. Inclusion of people with partial year coverage (therefore annualized costs) could bias the estimate of annual cost if the partial-year medical care use was not representative of medical care use over the course of a full year.

However, it should be noted that requiring 12 months of continuous coverage may result in some of the most severely affected patients being excluded from the study as they did not survive the full year. This is assumed to be especially the case for SMA Early Onset patients (i.e., patients aged three or younger with any of the ICD-9 diagnosis codes 335.0, 335.10, 335.11, or 335.19) as many of them do not survive beyond age two. Hence, for SMA Early Onset, in addition to estimating medical cost using patients who were covered for the full year, we also conducted a sensitivity analysis by calculating medical cost of patients who had a diagnosis of SMA in 2009 but were not necessarily covered for the full 12 months.

2.1.1.2 Data Analysis

All medical encounters and pharmacy records in 2009 were extracted for the study sample. We calculated health care cost by types of service including outpatient and physician office visit, inpatient admission, durable medical equipment, and prescription drug use. Health expenditures were not only assessed from the health care payer's perspective (amount paid to providers by health insurance) but also from patient's perspective (out-of-pocket expenses including copayments, coinsurance, and deductibles), and other payer's perspective. The other payer portion includes the amount of any payments made to the provider by a source other than the patient or the primary health plan (such as the amount paid by a spouse's insurance). We then calculated per capita annual health care cost. In order to calculate medical cost associated with the diseases of interest in 2010, we inflated 2009 claims paid amount to the 2010 dollar value using the medical and pharmacy components of the Consumer Price Index. All analyses were conducted using SAS software version 9.1 (SAS Institute, Cary, NC).

Health care costs were calculated for the study sample identified from commercial claims data, for each disease and by type of service (e.g., inpatient or outpatient). Descriptive statistics on study sample baseline characteristics and per-capita cost were calculated.

2.1.2 Medicare Five Percent Sample Claims Data

Medicare Standard Analytical Files (SAFs) contain information collected by Medicare to pay for health care services provided to a Medicare beneficiary. SAFs are available for each institutional (inpatient, outpatient, skilled nursing facility, hospice, or home health agency) and non-institutional (physician and durable medical equipment providers) claim type. The record unit of SAFs is the claim (some episodes of care may have more than one claim). SAFs do not contain specific service dates. All dates are presented as a quarter and year; age is presented as a 5-year age range; unique physician identification number (UPIN) is encrypted; and the lowest level of geographic identification in the Limited Data Set (LDS) SAF is the county. LDS SAFs are calendar year files and are available for 2000 through 2008. For this study, we have obtained access to the 5% sample SAFs for 2008 through the Centers for Medicare & Medicaid Services (CMS).

SAFs include diagnosis and procedure codes such as ICD-9 diagnosis, ICD-9 procedure code, Healthcare Common Procedure Coding System (HCPCS codes for outpatient and carrier files), Diagnosis Related Group (DRG for inpatient claims), dates of service, reimbursement amount, outpatient provider number, revenue center codes and beneficiary demographic information. Specifically, the following types of claims files are available:

- **Denominator File:** containing demographic and enrollment information about each beneficiary enrolled in Medicare during a calendar year.
- **Inpatient Claim file:** containing final action claims data submitted by inpatient hospital providers for reimbursement of facility costs.
- **Skilled Nursing Facility (SNF) Claim File:** containing final action claims data submitted by SNF providers.
- **Outpatient Claim File:** containing final action claims data submitted by institutional outpatient providers. Examples of institutional outpatient providers include hospital outpatient departments, rural health clinics, renal dialysis facilities, outpatient rehabilitation facilities, comprehensive outpatient rehabilitation facilities, and community mental health centers.
- **Home Health Agency (HHA) Claim File:** containing final action claims data submitted by HHA providers. Some of the information contained in this file includes the number of visits, type of visit (skilled nursing care, home health aides, physical therapy, speech therapy, occupational therapy, and medical social services).
- **Carrier Claim File:** containing final action claims data submitted by non-institutional providers. Examples of non-institutional providers include physicians, physician assistants, clinical social workers, nurse practitioners, independent clinical laboratories, ambulance providers, and free-standing ambulatory surgical centers.
- **Hospice Claim File:** containing final action claims data submitted by hospice providers. Some of the information contained in this file includes the level of hospice care received (e.g., routine home care, inpatient respite care) and the terminal diagnosis (ICD-9 diagnosis).

- **Durable Medical Equipment (DME) Claim File:** containing final action claims data submitted by DME suppliers.

2.1.2.1 Study Sample

The Medicare study sample included beneficiaries with at least one diagnosis of ALS, CMD, DMD, MMD, SMA Early Onset, or SMA Other at the primary or secondary diagnosis positions from medical claims filed to Medicare in 2008. ICD-9 diagnosis codes for these diseases are shown in Exhibit 2-1 above. Beneficiaries who died during 2008 were excluded from the study sample to be consistent with the commercial claims analysis.

2.1.2.2 Data Analysis

All medical encounters and pharmacy records in 2008 were extracted for the study sample. We calculated health care cost by large categories of types of service including outpatient and physician office visit (including home health), inpatient admission (acute vs. non-acute or long-term care), and durable medical equipment use. Medical care expenditures were assessed from both the Medicare perspective and from the patient and other payer perspectives. The patient paid portion includes out-of-pocket expenses such as Part A and Part B coinsurances and deductibles, and the other payer portion includes the amount of any payments made to the provider from a source other than Medicare or the patient, such as supplemental coverage under private insurance. We then calculated per- capita annual health care cost by inflating 2008 cost to the 2010 dollar values, using the medical CPI. All analyses were conducted using SAS software version 9.1 (SAS Institute, Cary, NC).

Since the Medicare 5% sample claims data do not include pharmacy claims, we calculated the Medicare prescription drug cost using the percentages observed from the OptumInsight commercial claims data assuming that the proportion of pharmacy cost over total cost under Medicare would be similar to that of the commercial insurance. Per-capita total health care cost under Medicare was then calculated by adding the estimated prescription drug cost to the medical cost proportion calculated from Medicare 5% sample data.

Health care costs were calculated for the Medicare study sample for each disease and by type of service (e.g., inpatient or outpatient). Descriptive statistics on the study sample baseline characteristics and per-capita cost were conducted.

2.2 Estimating Direct Non-Medical Cost and Indirect Cost Using the MDA Cost-of-Illness Survey

In addition to estimating direct medical costs using commercial and Medicare claims data, we also estimated the direct non-medical cost (e.g., home and motor vehicle modification, etc.) and indirect productivity cost as reflected in the loss of total family income. Below we describe the design and implementation process of the MDA Cost-of-Illness survey study.

2.2.1 Survey Development

A mail-based household survey questionnaire, with a web-based option, that included fifty-five questions was designed to collect data on both the direct and indirect costs associated with the diseases. Survey components included patients' (also referred to as the affected person) and family members' demographic and socio-economic characteristics (e.g., age, gender, education

attainment, health insurance coverage); health care characteristics of the patient population (e.g., disease duration and severity); employment status; individual and family income; and other economic outcomes associated with these diseases, such as family expenses spent caring for the patient or facilitating the patient's daily living, and estimates of out-of-pocket expenses for medical care.[i] Exhibit 2-2 shows the survey domains and key data elements.

Exhibit 2-2: MDA Cost-of-Illness Survey Domain and Key Data Elements

Survey Domain	Key Data Elements
Health status and disease history of the affected persons	Number of persons affected by the disease Disease diagnosis Disease duration Ventilator use Cognitive impairment Functional status (mobility and daily living activities) Comorbidities Level of daily care needed Quality of life
Demographic, socio-economic characteristics, and insurance coverage of affected persons and family members	Household size Age, gender, race/ethnicity, education attainment, marital status, insurance coverage for patients and adult family members who are either working or contributing to the care of the patient
Work situation, employment, and income of the affected persons and family members	Current employment status Weekly hours worked Occupation Annual individual and family income Time missed from work due to disease (or caring for patients) Impact of the disease on employment situation Employment situation and income before changes Employment prospect in five years Level of care by each family member to the affected person Other impact of disease on education and employment
Direct non-medical and medical costs to patient and family	Costs related to home and car/motor vehicle modification in the past 12 months and since disease diagnosis Costs of hiring paid professional caregivers Costs of institutional long-term care Direct medical costs (family out-of-pocket) by type of service (e.g., inpatient, outpatient, emergency room, pharmacy, medical equipment and supplies, etc.)

Many of the key questions were designed to be as similar as possible to some of the nationally representative health surveys. To measure disease-caused functional impairment, we created a mobility rating scale and a daily living rating scale based on disability rating scales described in the literature [32, 33] for patients older than age five. For patients younger than age five, we designed

[i] We did not attempt to capture direct medical cost as paid by insurance and other parties due to input from family focus groups stating that questions on non-family paid amount/proportion to health care providers by insurance companies tend to result in item non-response or recall errors.

a single question to capture the functional status of the children affected as compared to children without the disease at the same age.

In the process of designing the survey, a technical advisory group comprised of academic physicians, nurses/nurse practitioners, social workers, patient advocates, and others, was convened to advise the development of the survey. We also conducted three expert interviews on ALS, MD, and SMA, as well as four family member focus groups (i.e., ALS, DMD, MMD, and SMA) to inform the survey development and to collect feedback on the draft survey instrument. The final survey instrument incorporated comments from various stakeholders and clinical experts.

2.2.2 Sampling

The sampling frame for the survey study consists of households who are registered with MDA and who have one or more household members diagnosed with ALS, DMD, MMD, or SMA, representing a broad profile of families with demographic and socio-economic variations.

A power analysis found that when assuming a one-sample mean income loss of $10,000 and a standard deviation of $20,000, a sample size of approximately 128 would be needed at the 0.05 significance level and 80% power in order to detect a difference from a "population" mean income loss of ±$5,000. In order to obtain a representative study sample with sufficient sample size for potential subgroup analysis, we developed a balanced stratified random sampling approach where 600 sample households were targeted for each of the five diseases (i.e., ALS, DMD, MMD, SMA1, and combined SMA2, 3, and 4) regardless of the size of the total population registered with MDA. Based on disease, patient age group, and gender, we then created seven strata for ALS and SMA groups, six strata for DMD, and nine strata for MMD. We allocated the total sample of 600 in proportion to the total registrants in each strata for each disease category and selected a stratified random sample based on a fractional sampling interval. Strata with small cell sizes were oversampled to ensure that final sample size meets minimum requirement for strata level analysis. For those strata that had a very small number of subjects to begin with, we set a floor for sampling to ensure that a sufficient sample size would be obtained.

2.2.3 Survey Administration

In addition to a paper-based survey, a web-version of the survey was also created to provide flexibility and choice to respondents who prefer online access. A hyperlink to the web survey was provided on each paper-based survey. A phone number of MDA was also provided to answer any questions that the respondents may have regarding the survey. To ensure confidentiality and privacy, the surveys were tracked with de-identified family ID and an associated survey ID, and were mailed to the target sample by the MDA National Office located in Tucson, Arizona. During the entire process, neither The Lewin Group nor the contractor producing the paper and web survey had the capability of linking or identifying individual patients or their families. The MDA served as the central organization to ensure privacy and confidentiality. On the survey instruction page, respondents were informed that by filling out the survey they were considered as providing consent to participate in the study.

One week prior to sending out the survey, an introductory letter was sent to the target sample to motivate participation. MDA also posted online advertisement of the survey to raise awareness and participation. In the two week period after the cut-off date required for response, follow-up letters were sent to non-respondents to encourage participation.

Upon receiving the survey responses, MDA excluded any personally identifiable information (e.g., the address on envelopes) and forwarded de-identified survey responses to the contractor for data scan. Responses to all close-ended questions were electronically scanned and stored in an Excel database and responses to the open-ended questions or respondents' comments were entered into the database manually. A final database was then sent to The Lewin Group for data analysis.

2.2.3 Data Analysis

We conducted descriptive statistical analysis on the characteristics (e.g., age, gender, race/ethnicity, education attainment, etc.) of the most affected person in each household surveyed. Most affected person is defined as the person who was most severely affected by a disease. [ii] Descriptive statistics on the disease status of the most affected person, including disease duration, ventilator use, whether the person is cognitively impaired, major comorbid diseases, and level of daily care needed were also performed. A non-response adjusted weight was derived for each survey respondent by taking the reciprocal of the multiplication of a base weight (i.e., the probability of each subject in a particular strata being selected from the sampling frame) and the probability of responding to the survey. For the baseline characteristics as well as per-capita direct non-medical and indirect cost, we calculated weighted proportions and sample means, while presenting the raw sample size (of respondents) for easy reference. Per-capita direct non-medical costs were calculated as the weighted mean cost for each disease and by type of expenses (e.g., home and motor vehicle modification, paid care, etc.). We also provide 95% confidence intervals for the average per-capita non-medical costs.

Indirect cost was calculated using a human capital approach where it is hypothesized that a chronic disease is likely to result in lower labor market earnings and income for those suffering from the disease and for family members who provide informal care. These effects are not only reflected in lower employment rates and underemployment given the individual's demographic characteristics and education level, but also poorer labor market performance when the individual is employed.

The human capital literature has established that more highly educated individuals are more likely to be employed and earn more while employed, assuming other characteristics are the same. A severe disease such as ALS, MD, and SMA are likely to affect both the labor market participation of the persons affected by the disease as well as family caregivers who forgo some labor market earnings and income in order to provide daily care to the affected persons. Specifically, a chronic and highly disabling disease may affect patients and their families in multiple aspects including education attainment, whether and to what extent they participate in the labor force, and finally, their ability to devote time to their job while employed. Family members may even choose jobs that provide the opportunity for caregiving. Those individuals who are diagnosed with the disease and are employed may earn less in the labor market because of the effects that the diseases may have on their working hours and other labor market behavior. This phenomenon not only affects patients and their primary caregivers, but also other family members who provide financial and other types of support such as occasional care.

[ii] Several subtypes of these generic diseases tend to affect multiple family members.

As a result, the indirect impact of these diseases goes beyond just absenteeism and presenteeism by affecting the earning ability of family members and therefore the total household income. We formulated two regression equations to test the effect of the diseases (and the severity of the diseases as indicated by intensity of care) on earnings (approximated by household income) using two different dependent variables including: 1) the total family income in the past 12 months, and 2) the total self-estimated income loss in the past 12 months.

The effects of disease on earnings were estimated using ordinary least squares (OLS) regression analysis with a human capital specification. In Equation 1 below, total family income (a sum of individual income of adult family members in the past 12 months) was estimated as a function of primary earner's demographic factors, including age (as a proxy for work experience), gender, race/ethnicity, and education; disease characteristics of the most affected person, and other family characteristics. In this model, we examined the effects of disease and intensity of care while controlling for other known determinants of family income. The estimation equation is shown below:

Equation 1:

$$Income = \beta_0 + \beta_1 \times Demo_i + \beta_2 \times Family_i + \beta_3 \times Dis_i + \beta_4 \times Care\_Level + \varepsilon_i$$

where

Income is the dependent variable representing total family income in the past 12 months;

"Demo" is a vector of demographic variables representing age, gender, race/ethnicity of the primary earner (defined as the person with the highest individual income within the family in the past 12 months);

"Family" is a vector of variables representing family characteristics including whether there is only one person affected by the disease within the family, whether the primary earner has a college degree, number of adults in the family, whether the primary earner is the most affected person, whether the most affected person is receiving Social Security Disability Income, and whether the most affected person is receiving paid daily care at home;

"Dis" is a vector of variables including disease duration of the most affected person, and dummy variables indicating what disease the family is affected with;

"Care_Level" are dummy variables indicating the intensity of care required by the most affected person in the family as represented by the number of hours of daily care needed due to disease.

This model compares the household income of individuals diagnosed with a disease who require intensive daily care to a comparison group of individuals who also have the disease but do not require daily care. This method implicitly assumes that families with a patient who can function almost independently are earning similar levels of income as those families who are not affected by any disease, conditional on other things being equal. Specifically, the primary earner's demographic characteristics and other family characteristics are known predictors of family income. In terms of family characteristics, the number of family members with a college degree or who are employed, have a direct impact on the total family income. However, in this study, education attainment and employment status are endogenous to the disease, meaning that one of

the outcomes of the disease could be lower education achievement or lower chance of being employed. Thus including such variables in the predicting equation may lead to over control of the disease effect. We, therefore, used the primary earner's education and number of adults in the family instead to measure the family's earnings potential.

Due to a lack of an external control group, the use of the group requiring least amount of care as the comparison group is necessary because we cannot directly observe the earnings a household affected with such a disease would have had if a family member not had this disease. Based on the earnings equation (Equation 1) and by using the least severe group as an "internal" control group, we first estimated the expected family income given all the predicting factors under the circumstances where no care (due to disease) is needed. We then calculated the predicted family income loss due to intensive care by calculating the difference between actual self-reported family income and expected family income when patients do not require any care.

To validate family income loss as derived from Equation 1, and also to further investigate the effects of disease (and intensity of care) on family income loss, we constructed a second equation using the self-reported income loss from a separate survey question that asked families to provide a best estimate of income loss due to the disease for each of the adult members of the family, including the disease affected persons, in the past 12 months. Total family income loss was a sum of all individual income loss. In this model, we examined the effects of disease and intensity of care while controlling for other variables that may contribute to family income loss. The estimation equation is shown below:

Equation 2:

$$Income\_Loss = \beta_0 + \beta_1 \times Demo_i + \beta_2 \times Family_i + \beta_3 \times Dis_i + \beta_4 \times Care\_Level + \varepsilon_i$$

where

Income_Loss is the dependent variable representing total family income loss in the past 12 months;

"Demo" is a vector of demographic variables representing age, gender, race/ethnicity of the primary caregiver (defined as the person who reported as providing most care to the affected persons in the past 12 months);

"Family" is a vector of variables representing family characteristics including whether there is only one person affected by the disease within the family, whether the primary caregiver has a college degree, number of adults in the family, whether the primary earner is the most affected person, whether the most affected person is receiving Social Security Disability Income, and whether the most affected person is receiving paid daily care at home;

"Dis" is a vector of variables including disease duration of the most affected person, whether the most affected person is on ventilator, and dummy variables indicating what disease the family is affected with;

"Care_Level" are dummy variables indicating the intensity of care required by the most affected person in the family as represented by the number of hours of daily care needed due to disease.

Based on the income loss equation (Equation 2) and by using the group requiring least amount of care as an "internal" control group, we calculated the regression-predicted mean income loss by intensity of care adjusting for other covariates in the model. We hypothesized that everything else being equal, families with patients who require more intensive care tend to have a greater income loss. We produced this regression-adjusted income loss by level of care intensity and compared the results with the results from Equation 1.

3. Results

3.1 Direct Medical Cost for Commercially Insured

We identified a total of 4,866 patients with any of the diseases of interest from the OptumInsight commercial insurance claims database. Among them, 1,966 (40%) patients with a diagnosis of HPMD (i.e., DMD, BMD, LGMD) were used as a proxy-sample for DMD. 945 (19%) had a diagnosis of ALS. SMA Early Onset had the smallest sample size of 14, representing only 0.3% of the total patients identified. As expected, the majority (77.3%) of ALS patients was between 45 and 64 years of age and over 40% of CMD patients were 17 or younger. For all diseases, except for CMD and SMA Other, most patients were in the age group of 45-64, indicating the improved life expectancy for these diseases due to advancing disease management techniques. Gender distribution was relatively balanced between males and females; males represented over half of the sample for ALS, CMD, and HPMD and SMA Early Onset; females represented more than half of the sample for MMD and SMA Other.

Exhibit 3-1: Study Sample Demographic Characteristics (Commercial Insurance)

			ALS	CMD	HPMD [a]	MMD	SMA Early Onset	SMA Other	All
All			945	832	1,966	378	14	731	4,866
Age	**<18**	**N**	26	355	432	55	14	71	953
		%	2.75	42.67	21.97	14.55	100.00	9.71	19.58
	18-21	**N**	13	37	152	11	0	20	233
		%	1.38	4.45	7.73	2.91	0	2.74	4.79
	22-44	**N**	176	195	546	118	0	421	1,456
		%	18.62	23.44	27.77	31.22	0	57.59	29.92
	45-64	**N**	730	245	836	194	0	219	2,224
		%	77.25	29.45	42.52	51.32	0	29.96	45.70
	Mean		51.05	28.38	36.9	41.24	2.57	38.67	38.70
	Std		11.86	21.16	18.70	17.06	0.51	14.23	18.74
	Min		1	1	2	2	2	4	1
	Max		64	64	64	64	3	64	64
Gender	**Female**	**N**	399	408	873	204	6	470	2,360
		%	42.22	49.04	44.40	53.97	42.86	64.30	48.50
	Male	**N**	546	424	1,093	174	8	261	2,506
		%	57.78	50.96	55.60	46.03	57.14	35.70	51.50

* Ns are based on un-weighted raw counts. Percentages are weighted.

[a] Patients with ICD-9 diagnosis code of 359.1(HPMD) is used as a proxy sample for DMD.

Exhibit 3-2 shows the per-capita health care cost (in 2010 dollar values) by type of service for each disease. The bolded row is the total cost from all types of services for each disease where SMA Early Onset ($121,682) represents the highest per-capita total cost, followed by CMD, ALS, HPMD, SMA Other, and MMD. In the sensitivity analysis for SMA Early Onset where we did not require full-year insurance coverage, per-capita total medical cost for SMA Early Onset increased

from $121,682 to $136,675. Among costs associated with different types of service, outpatient care is the largest cost category, indicating a higher need among patients for physician consultation, disease evaluation, and disease management (such as physical and occupational therapies). Acute inpatient care is the next highest cost driver followed by prescription drug use. Overall, approximately 89% of the medical costs were paid by insurance, and the remaining costs were paid by the patients or other payers on behalf of the patients.

Exhibit 3-2: Per-capita Health care Cost by Disease and Type of Care (Commercial Insurance)

		ALS	CMD	HPMD [a]	MMD	SMA Early Onset [b]	SMA Other
N		945	832	1,966	378	14	731
Inpatient (Acute)	Mean	$10,290	$12,537	$9,393	$6,870	$90,175	$8,163
	StdErr	$1,374	$3,140	$1,179	$1,885	$89,345	$1,089
Inpatient (Non-Acute or Long-term)	Mean	$617	$346	$615	$328	$0	$132
	StdErr	$132	$122	$247	$167	$0	$61
Outpatient	Mean	$17,555	$16,969	$11,960	$9,450	$30,794	$10,826
	StdErr	$1,710	$1,452	$881	$759	$13,936	$1,175
Durable Medical Equipment	Mean	$1,810	$1,563	$1,108	$588	$6,445	$622
	StdErr	$217	$214	$91	$162	$4,215	$114
Prescription Medication	Mean	$2,473	$2,488	$2,154	$1,589	$713	$964
	StdErr	$176	$316	$158	$324	$446	$131
Total Cost	**Mean**	**$30,934**	**$32,341**	**$24,122**	**$18,236**	**$121,682**	**$20,085**
	StdErr	$2,336	$3,688	$1,667	$2,224	$98,898	$1,811
Insurance Paid Amount	Mean	$27,281	$29,655	$21,196	$15,803	$119,388	$17,678
	StdErr	$2,254	$3,653	$1,633	$2,165	$98,602	$1,720

* Ns are based on un-weighted raw counts. Means are weighted.

[a] Cost of patients with ICD-9 diagnosis code of 359.1(HPMD) is used as a proxy for DMD cost.

[b] Total medical cost was estimated at $136,675 when SMA Early Onset patients (N=47) were not required to be covered with medical and pharmacy benefits for the full year.

3.2 Direct Medical Cost for Medicare Insured

We identified a total of 1,440 patients with any of the diseases of interest from the 2008 Medicare 5% SAF claims data. Among them, 583 (40%) had a diagnosis of ALS and 533 (37%) were diagnosed with HPMD (e.g., DMD, BMD, LGMD). None of the SMA patients covered by Medicare were age three or younger. Hence, the medical cost for Medicare beneficiaries cannot be estimated for SMA Early Onset. SMA Other had the smallest sample size of 68 patients. Using an approximate weighting method of 20:1 based on the 5% sample, these 1,440 patients represent a total of 28,800 patients with these diseases who are covered by Medicare in 2008 (ALS: 11,660; CMD: 2,380; HPMD: 10,660; MMD: 2,740; and SMA Other: 1,360).

As expected, the majority (54%) of ALS patients covered by Medicare were 65 years or older, whereas the majority of patients with other diseases who were covered by Medicare were younger than 65 years of age, indicating severe disabilities that qualified them for Medicare prior

to age 65. With the exception of SMA Other, males represented the majority of the patients for all diseases.

Exhibit 3-3: Study Sample Demographic Characteristics (Medicare)

			ALS	CMD	HPMD [a]	MMD	SMA Other	All
All			583	119	533	137	68	1,440
Age	<65	N	268	72	376	112	35	863
		%	45.97	60.5	70.54	81.75	51.47	59.93
	65-74	N	187	32	111	14	21	365
		%	32.08	26.89	20.83	10.22	30.88	25.35
	>=75	N	128	15	46	11	12	212
		%	21.96	12.61	8.63	8.03	17.65	14.72
	Mean		63.21	63.20	54.60	52.10	51.70	57.00
	Std		13.60	13.60	18.70	17.10	14.00	19.10
	Min		25	25	21	19	22	22
	Max		98	98	94	92	89	88
Gender	Female	N	257	57	242	66	37	659
		%	44.08	47.9	45.4	48.18	54.41	45.76
	Male	N	326	62	291	71	31	781
		%	55.92	52.1	54.6	51.82	45.59	54.24

* Ns are based on un-weighted raw counts. Percentages are weighted.

[a] Patients with ICD-9 diagnosis code of 359.1(HPMD) is used as a proxy sample for DMD.

Exhibit 3-4 shows the per-capita health care cost (in 2010 dollar values) by type of service for each disease. As mentioned in the method section, since the Medicare 5% sample claims data do not include pharmacy claims, we calculated Medicare prescription drug cost based on the percentages (4.8% to 8.9%) of pharmacy cost (over total cost) observed from the OptumInsight commercial claims data. Total per-capita health care cost (the bolded row) for the Medicare study sample was therefore the total of per-capita medical cost (from Medicare) and estimated prescription drug cost.

Total cost from all types of services for each disease shows that CMD has the highest per-capita total cost, followed by ALS, HPMD, MMD, and SMA Other. Among costs associated with different types of service, overall outpatient care (i.e., physician office, occupational/physical therapy, and other) is the largest cost category, indicating a higher need among patients for physician consultation, disease evaluation, and disease management. Acute inpatient care is the next largest cost driver. Overall, about 83% of the medical costs were paid by Medicare, and the remaining costs were paid by the patients or other payers on behalf of the patients.

Exhibit 3-4: Per-capita Health care Cost by Disease and Types of Care (Medicare)

		ALS	CMD	HPMD [c]	MMD	SMA Other
N		583	119	533	137	68
Inpatient (Acute)	Mean	$9,411	$14,746	$7,653	$4,939	$4,687
	StdErr	$1,041	$3,078	$881	$1,013	$1,033
Inpatient (Non-Acute or Long-term)	Mean	$3,913	$3,018	$1,995	$1,685	$1,415
	StdErr	$460	$865	$340	$606	$750
Outpatient	Mean	$10,745	$16,129	$8,455	$9,512	$7,376
	StdErr	$527	$2,114	$586	$1,801	$1,065
Durable Medical Equipment	Mean	$5,158	$2,444	$2,709	$1,079	$2,298
	StdErr	$413	$576	$282	$177	$730
Total Medical Cost	Mean	$29,227	$36,337	$20,811	$17,215	$15,776
	StdErr	$1,570	$4,782	$1,499	$2,604	$2,300
Medicare Paid Amount	Mean	$24,744	$29,517	$17,627	$14,749	$12,676
	StdErr	$1,425	$4,167	$1,330	$2,242	$2,002
Prescription Medication [a]	Mean	$2,336	$2,796	$1,859	$1,500	$757
Total Cost [b]	Mean	**$31,563**	**$39,132**	**$22,670**	**$18,715**	**$16,533**

* Ns are based on un-weighted raw counts. Means are weighted.

[a] Percentage of pharmacy cost (over total cost) used for Medicare pharmacy cost calculation: ALS: 7.99%, CMD: 7.69%, DMD: 8.93%, MMD: 8.71%, and SMA Other: 4.80%.

[b] Total cost is the sum of total medical cost (based on Medicare data) and the estimated cost of prescription medication as described in the footnote above.

[c] Cost of patients with ICD-9 diagnosis code of 359.1(HPMD) is used as a proxy for DMD cost.

3.3 Cost of ALS, DMD, MMD, and SMA based on the Survey Study

3.3.1 Survey Response Rate and Sample Characteristics

Exhibit 3-5 shows the survey response rate by disease. The response rates of the survey for the five diseases were consistently between 21% (MMD) and 26% (SMA1) with an overall response rate of 24%. While the vast majority of the ALS, DMD, and MMD respondents reported having the specific type of disease as indicated in the membership record, only 39% of the SMA1 target sample self-reported as having the specific type of SMA; 61% of the targeted SMA1 patients self-identified as having other types of SMA, indicating the diagnostic uncertainties surrounding some of the neuromuscular diseases. When weighted using the non-response adjusted weights, the 657 survey respondents self-reported as actually having the target disease represent a total of 35,120 families, with the largest group having at least one family member diagnosed with ALS (12,324), followed by MMD (9,975), and DMD (7,217).

Exhibit 3-5: Response Rate by Disease

	Target Sample	Number of Respondents	Response Rate	Self-reported as having the disease	Weighted number of subjects
ALS	600	146	24.3%	124	12,324
DMD	600	139	23.2%	131	7,217
MMD	601	123	20.5%	123	9,975
SMA1	601	153	25.5%	59	864
Combined SMA 2,3,4	600	150	25.0%	220	4,740
Total	3,002	711	23.7%	657	35,120

There are significant difficulties and uncertainties in diagnosing SMA patients due to variation in disease severity and symptoms of individual patients. Although in designing the stratified sampling, we sampled persons affected with SMA1 vs. combined SMA2, 3, & 4 separately, in the data analysis stage, we combined all four types of SMA and then grouped the affected persons into those that can be called SMA Early Onset (age 3 and younger) vs. SMA Other, given that age of onset is often the most important indicator of disease subtype and severity for SMA patients. Exhibit 3-6 shows the number of individuals in a family affected by the diseases. More than 90% of the families affected with ALS, SMA Early Onset, and SMA Other have only one person in the family with the disease. However, for MMD, 27% of the families have two persons affected with the disease, and 13% of the families have three persons affected with the disease. For DMD, almost 90% of the families have only one patient with the disease, while approximately 10% of the families have two persons diagnosed with the disease.

Exhibit 3-6: Number of Persons Affected by Disease per Family

	ALS	DMD	MMD	SMA Early Onset	SMA Other	Total
One	117	116	75	15	238	561
	95.34	89.12	60.20	81.45	92.33	
Two	6	14	32	2	20	74
	4.21	9.87	26.85	18.55	6.15	
Three	1	1	16	0	4	22
	0.45	1.01	12.96	0	1.52	
Total	124	131	123	17	262	657

* Ns are based on un-weighted raw counts. Percentages are weighted.

Exhibit 3-7 shows the demographic characteristics of the most affected persons from the survey sample. For ALS (91%) and MMD (55%), the majority of the most affected persons are aged 45 and above. For DMD (97%), SMA Early Onset (100%) and SMA Other (76%), the majority of the most affected persons are younger than 45 years. While 97% of DMD patients, 54% of ALS patients, and 62% of SMA Early Onset patients are males, more than 50% of the persons affected with MMD and SMA Other are females. For all five diseases, over 75% of the most affected persons self-reported as being non-Hispanic White. A number of respondents reported that the most affected member of their household had died. By disease type, there were 28 (24%)

individuals who were deceased among the ALS group, 6 (7.8%) among DMD group, 6 (4.5%) among MMD, 2 (18.6%) among SMA Early Onset, and 13 (4.5%) among SMA Other.[iii]

Exhibit 3-7: Baseline Characteristics of the Most Affected Person

			ALS	DMD	MMD	SMA Early Onset	SMA Other	All
All			124	131	123	17	262	657
Age	<18	N	2	79	13	17	74	185
		%	0.73	56.55	8.08	100.00	27.91	
	18-21	N	1	14	2	0	30	47
		%	0.19	11.55	1.69	0.00	9.89	
	22-44	N	25	32	40	0	93	190
		%	7.84	29.12	35.14	0.00	38.48	
	45-64	N	49	4	53	0	55	161
		%	48.07	1.92	44.68	0.00	19.17	
	>=65	N	47	2	15	0	10	74
		%	43.17	0.86	10.41	0.00	4.55	
Gender	Female	N	53	7	67	8	141	290
		%	45.54	2.90	53.92	37.80	50.71	
	Male	N	71	124	56	9	121	367
		%	54.46	97.10	46.08	62.20	49.29	
Race/ethnicity	Not Available/ applicable	N	4	10	8	2	20	44
		%	3.20	8.07	6.87	5.93	7.13	
	Black	N	4	4	0	0	8	16
		%	3.04	3.51	0.00	0.00	4.36	
	Hispanic	N	8	7	6	1	27	49
		%	4.92	5.92	5.00	3.21	8.56	
	White	N	103	102	107	13	192	517
		%	84.10	75.84	86.07	88.15	74.94	
	Other	N	5	8	2	1	15	31
		%	4.74	6.66	2.07	2.72	5.01	
Death	No	N	96	121	117	15	249	598
		%	76.19	92.20	95.53	81.45	95.54	
	Yes	N	28	10	6	2	13	59
		%	23.81	7.80	4.47	18.55	4.46	

* Ns are based on un-weighted raw counts. Percentages are weighted.

[iii] Due to sample size concerns, these members were not excluded from the cost analysis. In the survey, families were asked to report their experience during the one year prior to death of an affected family member when answering questions about costs incurred during the "past 12 months".

Exhibit 3-8 shows the distribution of education attainment and marital status for affected persons who are age 18 or above (all SMA Early Onset patients are younger than 18 and therefore not included in this table). In terms of education attainment, 33% of ALS patients and 48% of SMA Other patients have college or post-graduate degrees, while only 20% and 16% of DMD and MMD patients, respectively, are college or post-college graduates. 70% and 51% of ALS and MMD patients, respectively, reported as being married or living with someone, while only 4% and 26% of DMD and SMA Other patients, respectively, reported as being married or living with someone.

Exhibit 3-8: Education Attainment and Marital Status of the Most Affected Person

			ALS	DMD	MMD	SMA Other	All
All			122	52	110	188	472
Education Attainment	Not Available/applicable	**N**	3	3	6	8	20
		%	3.19	6.55	5.68	4.30	
	Less than high school	**N**	5	7	7	8	27
		%	1.75	11.52	5.79	6.11	
	High school graduate	**N**	39	15	42	28	124
		%	35.01	27.50	40.28	13.49	
	Some college/Associate Degree/Post high school education	**N**	38	16	36	56	146
		%	27.30	34.03	31.39	27.72	
	College graduate	**N**	21	11	13	51	96
		%	18.14	20.40	11.89	29.60	
	Post-graduate degree	**N**	16	0	5	37	58
		%	14.61	0.00	4.10	18.77	
	Not sure	**N**	0	0	1	0	1
		%	0.00	0.00	0.86	0.00	
Marital Status	Not Available/applicable	**N**	7	4	7	7	25
		%	5.75	8.87	6.78	4.08	
	Married or living with someone	**N**	81	3	60	48	192
		%	70.20	4.30	51.11	25.98	
	Widowed	**N**	6	0	3	3	12
		%	5.70	0.00	2.50	1.92	
	Divorced	**N**	10	0	8	12	30
		%	9.59	0.00	8.02	6.17	
	Separated	**N**	2	0	1	1	4
		%	1.15	0.00	0.93	0.66	
	Never married	**N**	16	45	30	117	208
		%	7.61	86.83	29.55	61.20	
	Not Applicable	**N**	0	0	1	0	1
		%	0.00	0.00	1.10	0.00	

Exhibit 3-9 shows the disease status and history of the most affected person. About 72% of ALS patients, 43% of DMD patients, and all the SMA Early Onset patients have a disease duration (duration between when first symptoms began or when first diagnosis was made, whichever the earliest, to the year 2010) of less than 10 years while more than 86% of MMD and SMA Other affected persons have had the diseases for more than 10 years. About 30% of persons most affected with ALS and SMA Early Onset, 34% with DMD, 30% with SMA Other, and 11% with MMD are on ventilators. Among those who are using ventilators, the majority are on a non-invasive ventilator (i.e., Bipap or Cpap). In terms of cognitive impairment, while 16%, 28%, and 35% of ALS, DMD, and MMD patients are, to some extent, cognitively impaired by the disease, only 3-4% of SMA patients are cognitively impaired.

When asked about comorbidities, 14% (92 of the 657) of the patients reported as having heart, kidney or circulation problems. And about 10% of the patients reported as having asthma, anxiety, or depression. When asked about the level of daily care needed by the most affected person due to his or her disease, 51% of ALS, 59% of DMD, 81% of SMA Early Onset, and 50% of SMA Other responded that the most affected person needed "16 to 24 hour a day attendance" (including just being present at home if the affected person cannot be left alone) while only 23% of the persons most affected by MMD reported as needing this level of daily care.

Exhibit 3-9: Disease Status of the Most Affected Person

			ALS	DMD	MMD	SMA Early Onset	SMA Other	All
All			124	131	123	17	262	657
Disease duration	Not Available/ applicable	N	8	6	16	0	9	39
		%	0.07	0.05	0.14	0.00	0.05	
	less than 6 years	N	53	31	8	17	16	125
		%	48.00	21.45	7.62	100.00	4.63	
	between 6 and 10 years	N	31	29	7	0	23	90
		%	24.36	21.54	6.42	0.00	9.45	
	between 11 and 20 years	N	20	36	35	0	75	166
		%	18.87	31.84	31.88	0.00	31.65	
	between 21 and 30 years	N	5	19	26	0	43	93
		%	2.14	18.41	25.22	0.00	17.35	
	between 31 and 40 years	N	5	6	22	0	47	80
		%	4.41	4.74	20.97	0.00	19.36	
	between 41 and 50 years	N	1	3	7	0	21	32
		%	1.03	1.45	6.41	0.00	6.99	
	over 50 years ago	N	1	1	2	0	28	32
		%	1.19	0.56	1.49	0.00	10.57	
Using Ventilator/ respirator	No	N	77	92	109	8	174	460
		%	60.93	66.33	89.47	60.96	70.12	
	On invasive ventilator/ respirator	N	14	15	1	3	27	60
		%	10.00	13.04	0.79	8.15	9.80	

			ALS	DMD	MMD	SMA Early Onset	SMA Other	All
	On non-invasive ventilator (i.e., Bipap or Cpap)	N	33	24	13	6	61	137
		%	29.08	20.63	9.74	30.89	20.08	
Cognitive impairment	No	N	103	92	79	16	252	542
		%	84.31	71.71	64.99	97.28	96.32	
	Yes	N	21	39	44	1	10	115
		%	15.69	28.29	35.01	2.72	3.68	
Comorbid Diseases	Cancer	N	6	0	4	0	8	18
		%	4.96	0.00	3.39	0.00	2.45	
	Heart, kidney or circulation problems	N	17	24	26	0	25	92
		%	13.57	19.50	21.26	0.00	10.22	
	Diabetes or obesity	N	8	5	21	0	29	63
		%	6.99	4.08	17.76	0.00	12.94	
	Asthma	N	10	10	14	1	31	66
		%	6.62	6.83	10.64	2.72	9.34	
	Chronic infections	N	4	4	9	1	15	33
		%	2.92	2.44	7.15	3.21	7.72	
	Anxiety or depression	N	21	16	24	0	31	92
		%	17.31	13.29	20.78	0.00	12.25	
	Other chronic disease	N	11	13	15	1	31	71
		%	8.30	9.58	12.67	15.83	10.58	
Hours of daily care needed	Not Available/applicable	N	15	19	31	2	26	93
		%	9.77	14.12	24.09	18.55	12.75	
	16 to 24 hour a day attendance	N	62	71	29	15	145	322
		%	50.63	59.24	23.08	81.45	49.68	
	8 to less than 16 hours	N	18	17	3	0	42	80
		%	14.84	10.96	2.96	0.00	15.98	
	1 to less than 8 hours	N	16	17	18	0	36	87
		%	14.29	11.30	15.27	0.00	15.66	
	Care not needed	N	13	7	42	0	13	75
		%	10.47	4.39	34.60	0.00	5.92	

* Ns are based on un-weighted raw counts. Percentages are weighted.

3.3.2 Non-Medical Costs

Exhibit 3-10 shows the weighted average (and 95% confidence intervals) per-household non-medical costs. Such costs include home or motor vehicle purchase/modification; professional home care (e.g., by personal or home care aides, home health aides, skilled nurses or nurse assistants, or relatives/friends who are paid by families or state programs to care for the affected persons); and other costs (e.g., food and food supplements, travel, training, etc.) incurred by the family or others (e.g., case allowance, donations, government programs, insurance, etc.) due to

caring for the affected persons. For the large item cost categories (i.e., home, motor vehicle, and professional caregiving), the survey asked the families to provide cost by expense category both in the past 12 months and for the entire time since the first affected person was diagnosed. Our exploratory analysis found that annualized expenses (cumulative expenses since diagnosis divided by disease duration) were more stable than the expenses incurred during the past 12 months as the latter is significantly affected by disease duration of the patient. We therefore used the annualized expenses to calculate non-medical costs.

Per-household cost was calculated by expense category and disease. Total non-medical costs from all expense categories were also presented. For each type of expense, we excluded the item non-responses and calculated the average cost using families with a valid response as the denominator, including families who responded as having the type of expense (with a valid cost) and those who responded as not having the type of expense. For instance, where home modification is concerned, we excluded families who reported as having home modifications but had a missing value on the cost of home modification (for either self-paid or amount paid by others). Since the entire study sample reported at least one type of non-medical expense, total non-medical cost is calculated as the per-household cost of the total expenses from all types of expense categories using the entire sample for each disease as the denominator.

Overall, households with SMA Early Onset patients incurred the highest amount of non-medical cost ($51,665) followed by ALS ($17,889), SMA Other ($14,295), DMD ($12,939), and MMD ($5,157). For ALS, the largest cost category was incurred for moving to a new home or modifying an existing home, followed by "other non-medical cost category" (e.g., food and food supplements, travel, training, etc.). For DMD, MMD, and SMA Other, the largest cost category was "other non-medical costs". Families with SMA Early Onset patients had a high cost of $50,542 associated with hiring professional caregivers mostly due to a need to provide 24 hour a day intensive care to the affected persons. However, likely due to the small sample size for this group, the high non-medical cost is not statistically significant.

Exhibit 3-10: Direct Non-Medical Cost (Self and Other Paid) by Type of Expenses and Disease

Disease	Type of Expenses	N	Mean	Std Error	95% CL for Mean	
ALS	Moving or modifying home	109	$7,106	$2,096	$2,950	$11,261
	Purchase or modifying motor vehicle	107	$2,064	$385	$1,300	$2,827
	Professional caregiving	111	$4,570	$1,446	$1,704	$7,435
	Other non-medical cost (e.g., food, travel, dietary supplements, etc.)	118	$5,908	$975	$3,977	$7,840
	Total non-medical cost	**124**	**$17,889**	**$3,265**	**$11,426**	**$24,351**
DMD	Moving or modifying home	113	$3,050	$615	$1,832	$4,268
	Purchase or modifying motor vehicle	119	$1,680	$216	$1,252	$2,107
	Professional caregiving	113	$3,189	$1,315	$583	$5,794
	Other non-medical cost (e.g., food, travel, dietary supplements, etc.)	123	$6,605	$1,837	$2,969	$10,240
	Total non-medical cost	**131**	**$12,939**	**$2,465**	**$8,063**	**$17,816**

Disease	Type of Expenses	N	Mean	Std Error	95% CL for Mean	
MMD	Moving or modifying home	113	$990	$687	-$371	$2,350
	Purchase or modifying motor vehicle	116	$435	$356	-$269	$1,139
	Professional caregiving	109	$925	$712	-$487	$2,338
	Other non-medical cost (e.g., food, travel, dietary supplements, etc.)	121	$3,067	$900	$1,285	$4,850
	Total non-medical cost	**123**	**$5,157**	**$1,820**	**$1,554**	**$8,761**
Early Childhood Onset SMA	Moving or modifying home	12	$3,685	$2,231	-$1,225	$8,594
	Purchase or modifying motor vehicle	15	$1,814	$1,041	-$419	$4,046
	Professional caregiving	13	$50,542	$42,439	-$41,924	$143,008
	Other non-medical cost (e.g., food, travel, dietary supplements, etc.)	16	$2,106	$706	$601	$3,610
	Total non-medical cost	**17**	**$51,665**	**$39,501**	**-$32,074**	**$135,404**
SMA Other	Moving or modifying home	231	$3,389	$810	$1,793	$4,984
	Purchase or modifying motor vehicle	239	$2,292	$345	$1,612	$2,972
	Professional caregiving	224	$5,247	$1,266	$2,752	$7,742
	Other non-medical cost (e.g., food, travel, dietary supplements, etc.)	252	$4,861	$803	$3,279	$6,442
	Total non-medical cost	**262**	**$14,295**	**$1,651**	**$11,044**	**$17,546**

* Ns are based on un-weighted raw counts. Means are weighted.

3.3.3 Indirect Cost-Disease Impact on Household Income

Exhibit 3-11 shows the results of the multivariate regression analysis based on the first model (Equation 1) described in the method section. This regression analysis on family income used 470 observations (out of a total of 657 observations) with non-missing values on any of the explanatory variables. The model achieved a goodness-of-fit with an R-Square of 0.27 and an adjusted R-Square of 0.24, indicating that about 24% of the income variation could be explained by the explanatory variables included in the model. Although not all of the coefficients are statistically significant, they are generally in agreement with expectations.

When looking at the effect of the primary earner's age on family income, families with a primary earner between the age of 45 and 64 earn, on average, $14,813 more annually than families whose primary earner is aged 65 and above. Black and Hispanic race/ethnicity are associated with lower family income (both significant at a 10% significance level) while the Other category (including American Indian or Alaska Native, Asian, Native Hawaiians or other Pacific Islanders, etc.) is not statistically different from White category. Among other covariates, when the primary earner is a male as opposed to a female, the total family earns $13,245 more in a year. Also as expected, when the primary earner has a college degree, the family earns $28,590 more per year. One additional adult living in the family leads to a significant increase of $10,228 in total family income. The most affected person receiving paid daily care is associated with higher family income, possibly due to family members being able to devote more time to workforce activities. Covariates that have a negative coefficient include: a dummy variable indicating whether there is only one person affected by the disease as opposed to more than one; disease duration of the most affected person; whether the primary earner is the most affected person in the family; and whether the most affected person is receiving Social Security Disability Income.

When looking at the effect of intensity of care on family income, the coefficients on the level of care dummy variables show that as compared to the group of patients who are functioning almost independently (and therefore do not require daily care), the increase in level/intensity of care is negatively associated with the total family income. The group where the affected individuals require 16-24 hours of daily care earns a significant $21,600 less than the group of families with the most affected person requiring no daily care. Finally, when controlling for other factors, the SMA Early Onset sample has a total family income that is higher than families with other diseases, although the difference is not statistically significant (except when compared with the MMD group). Note that factors that are associated with **reduced family income** enter with a negative sign in the regression equation.

Exhibit 3-11: OLS Regression on Total Family Income (Equation 1)

Regression on impact of disease and level of care on family income		Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept		$70,177.0	$21,972.0	3.19	0.0015
Primary earner's age	21 or younger	-$473.8	$15,776.0	-0.07	0.9464
	22 to 44	-$1,488.8	$7,248.4	-0.16	0.8726
	45 to 64	$14,813.0	$6,207.0	2.39	0.0172
	>=65 (Omitted)	$0.0	$0.0	0	0
Primary earner's race/ethnicity	Black	-$30,998.0	$17,070.0	-1.83	0.0685
	Hispanic	-$32,475.0	$11,957.0	-2.72	0.0068
	Other	-$12,708.0	$9,289.5	-1.34	0.1795
	White (Omitted)	$0.0	$0.0	0	0
Disease	ALS	-$14,485.0	$14,148.0	-1	0.3195
	DMD	-$17,519.0	$13,564.0	-1.44	0.1499
	MMD	-$28,307.0	$15,048.0	-2.26	0.0242
	SMA Other	-$9,820.9	$13,504.0	-0.63	0.5315
	SMA Early Onset (Omitted)	$0.0	$0.0	0	0
Level of care needed	16 to 24 hours	-$21,600.0	$7,710.2	-2.79	0.0054
	8 to 15 hours	-$7,325.0	$8,914.5	-0.83	0.4068
	1 to 7 hours	-$4,172.2	$8,570.3	-0.5	0.6182
	Care not needed (Omitted)	$0.0	$0.0	0	0
Primary earner is male		$13,245.0	$4,576.1	2.89	0.0040
Primary earner has a college degree		$28,590.0	$4,773.4	5.99	<.0001
Primary earner is the most affected person		-$11,676.0	$6,011.1	-1.94	0.0527
Only one affected person		-$3,941.7	$7,027.9	-0.56	0.5752
Number of adults in the family		$10,228.0	$2,718.0	3.76	0.0002
Disease duration of the most affected		-$343.8	$182.3	-1.89	0.0600
Most affected person is receiving Social Security Disability Income		-$6,095.9	$4,744.9	-1.28	0.1996
Most affected person is receiving care from paid caregivers		$9,280.3	$5,086.9	1.82	0.0688
R-Square		0.2738			
Adj R-Sq		0.2398			

Exhibit 3-12 shows the un-weighted and weighted per-household annual income (actual and expected) and predicted family income loss by level of care and disease. The income loss can only be calculated for the 470 families that were included in the regression analysis. Examining the un-weighted per-household income loss by level of care, the data demonstrates that the level of care is positively associated with family income loss. Families with the most affected person not requiring daily care incurred no income loss compared to the more care-intensive groups, while the groups requiring 1-8 hours of care and 8-16 hours of care incurred an income loss of $4,170 and $7,323, respectively. For the group with an individual requiring 16-24 hours of care per day, a significantly higher amount of $21,598 of income loss was incurred by the family as a whole. When weighted using the non-response adjusted weights, the estimated family income loss follows a similar pattern with the exception of the group that requires 1-8 hours of care. For this group, the actual family income is, on average, $3,112 more than the expected family income. When looking at income loss by disease, the weighted income loss is consistent with the un-weighted estimates where families affected by SMA Early Onset incurred the highest weighted income loss of $17,759, followed by DMD ($15,481), ALS ($14,682), SMA Other ($13,252), and MMD ($9,628). These weighted family income loss estimates (bolded column) are considered the indirect costs associated with these diseases.

Exhibit 3-12: Predicted Income Loss (Equation 1) by Disease and Level of Care Needed

			Un-weighted				Weighted			
	Disease	N	Mean	StdErr	95_LCLM	95_UCLM	Mean	StdErr	95_LCLM	95_UCLM
Self-reported family income	16 to 24 hour a day attendance	322	$60,225	$2,649	$55,014	$65,437	$57,233	$2,625	$52,069	$62,397
	8 to less than 16 hours	80	$73,469	$6,720	$60,093	$86,844	$67,582	$6,410	$54,823	$80,341
	1 to less than 8 hours	87	$69,799	$5,896	$58,079	$81,519	$71,379	$6,383	$58,691	$84,067
	Care not needed	75	$60,267	$6,620	$47,075	$73,458	$56,054	$5,681	$44,734	$67,375
	ALS	124	$62,339	$4,968	$52,504	$72,173	$62,996	$4,917	$53,262	$72,729
	DMD	131	$59,313	$4,470	$50,470	$68,156	$58,259	$4,420	$49,514	$67,004
	MMD	123	$49,675	$3,927	$41,901	$57,449	$47,623	$3,685	$40,329	$54,918
	SMA Early Onset	17	$76,765	$13,768	$47,578	$105,952	$82,775	$12,319	$56,659	$108,891
	SMA Other	262	$67,815	$3,300	$61,316	$74,314	$66,565	$3,427	$59,817	$73,313
Expected family income	16 to 24 hour a day attendance	267	$85,025	$1,703	$81,673	$88,378	$82,467	$1,725	$79,072	$85,863
	8 to less than 16 hours	72	$82,045	$2,988	$76,087	$88,004	$84,325	$2,874	$78,595	$90,056
	1 to less than 8 hours	74	$77,920	$3,133	$71,677	$84,164	$76,277	$3,387	$69,526	$83,028

	Disease	N	Un-weighted				Weighted			
			Mean	StdErr	95_LCLM	95_UCLM	Mean	StdErr	95_LCLM	95_UCLM
	Care not needed	57	$66,928	$3,200	$60,517	$73,339	$64,573	$2,982	$58,600	$70,546
	ALS	86	$82,021	$2,954	$76,148	$87,894	$83,040	$3,000	$77,074	$89,005
	DMD	95	$84,415	$2,562	$79,329	$89,502	$84,706	$2,606	$79,532	$89,881
	MMD	68	$60,656	$2,675	$55,317	$65,996	$60,479	$2,509	$55,472	$65,487
	SMA Early Onset	14	$104,813	$4,837	$94,364	$115,262	$108,900	$4,205	$99,816	$117,985
	SMA Other	207	$84,661	$1,903	$80,909	$88,412	$84,941	$1,974	$81,048	$88,833
Loss of income	16 to 24 hour a day attendance	267	$21,598	$2,485	$16,705	$26,491	$21,225	$2,380	$16,540	$25,911
	8 to less than 16 hours	72	$7,323	$5,763	-$4,168	$18,814	$13,599	$5,787	$2,059	$25,139
	1 to less than 8 hours	74	$4,170	$5,357	-$6,507	$14,848	-$3,112	$5,701	-$14,475	$8,250
	Care not needed	57	-$2	$7,088	-$14,201	$14,197	$4,489	$6,164	-$7,859	$16,836
	ALS	86	$14,201	$5,267	$3,729	$24,674	**$14,682**	$5,186	$4,370	$24,994
	DMD	95	$14,968	$4,623	$5,790	$24,146	**$15,481**	$4,469	$6,608	$24,353
	MMD	68	$8,046	$4,835	-$1,605	$17,698	**$9,628**	$4,589	$469	$18,787
	SMA Early Onset	14	$21,598	$13,163	-$6,838	$50,035	**$17,759**	$12,207	-$8,612	$44,130
	SMA Other	207	$15,023	$3,159	$8,795	$21,251	**$13,252**	$3,185	$6,973	$19,531

Exhibit 3-13 shows the result of the multivariate regression analysis based on the OLS regression Equation 2 as described in the method section. The final model on self-reported family income loss used 466 observations (out of a total of 657 observations) with non-missing values on any of the explanatory variables. The final model achieved an R-Square of 0.12 and an Adjusted R-Square of 0.08, indicating that about 8% of the variation on self-reported income loss could be explained by the explanatory variables included in the model. While many of the coefficients are not statistically significant, they are mostly in agreement with expectations. When looking at the effect of the primary caregiver's age on family income loss, as compared to families whose primary caregiver is aged 65 and above, families whose primary caregiver is aged between 18 and 44 years lost $408 more income; and families whose primary caregiver is aged between 45 and 64 years lost, on average, $5,202 more income annually. Age groups "17 and younger" had less income loss than the omitted group. The differences are not statistically significant.

Although not statistically significant, Black, Hispanic, and Other race/ethnicity seem to incur less income loss than Whites. This disparity is expected as it is known that White families tend to have higher annual income, and therefore the income forfeited by the family due to caring for the affected persons could also be higher. Among other covariates, when the primary caregiver is a male as opposed to a female, the families lose $3,872 less income in a year. The primary caregiver having a

college degree leads to an increase of $4,361 in total family income loss. The primary earner of the family being the most affected person, the number of adults in the family, the most affected person receiving Social Security Disability Income, and the most affected person receiving paid daily care are positively associated with income loss. Covariates that have a negative coefficient include a dummy variable indicating whether there is only one person affected by the disease as opposed to more than 1, and disease duration of the most affected person.

When considering the effect of intensity of care on family income loss, the coefficients on the level of care dummy variables show that as compared to the group of patients who are functioning almost independently (and therefore do not require daily care), the increase in level/intensity of care is positively associated with the total family income loss, although none of these coefficients are statistically significant. Note that factors that **increase the loss** enter with a positive sign in the regression equation.

Exhibit 3-13: OLS Regression on Family Income Loss (Equation 2)

Regression on impact of disease and level of care on family income loss		Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept		$33,806.0	$14,814.0	2.28	0.0230
Primary caregiver's age	17 or younger	-$3,896.2	$13,269.0	-0.29	0.7692
	18 to 44	$408.3	$4,095.0	0.1	0.9206
	45 to 64	$5,201.6	$3,952.2	1.32	0.1888
	>=65 (Omitted)	$0.0	$0.0	0	0
Primary caregiver's race/ ethnicity	Black	-$2,115.7	$11,255.0	-0.19	0.8510
	Hispanic	-$5,215.0	$7,866.9	-0.66	0.5077
	Other	-$3,621.1	$6,140.3	-0.59	0.5557
	White (Omitted)	$0.0	$0.0	0	0
Ventilator use	On invasive ventilator	$12,198.0	$5,208.7	2.34	0.0196
	On non-invasive ventilator	$5,613.1	$3,688.3	1.52	0.1288
	Not on ventilators	$0.0	$0.0	0	0
Disease	ALS	-$18,464.0	$9,383.8	-1.97	0.0497
	DMD	-$19,628.0	$9,018.5	-2.18	0.0301
	MMD	-$27,671.0	$9,928.0	-2.79	0.0055
	SMA Other	-$23,761.0	$9,113.8	-2.61	0.0094
	SMA Early Onset (Omitted)	$0.0	$0.0	0	0
Level of care needed	16 to 24 hours	$4,428.9	$5,336.1	0.83	0.4070
	8 to 15 hours	$2,966.0	$6,210.5	0.48	0.6332
	1 to 7 hours	$2,247.4	$5,886.3	0.38	0.7028
	Care not needed (Omitted)	$0.0	$0.0	0	0
Primary caregiver is male		-$3,871.9	$3,451.8	-1.12	0.2626
Primary caregiver has a college degree		$4,361.2	$3,287.3	1.33	0.1853
Primary earner is the most affected person		$5,224.6	$4,144.9	1.26	0.2082
Only one affected person		-$11,492.0	$4,795.0	-2.4	0.0170
Number of adults in the family		$899.7	$1,852.7	0.49	0.6275

Regression on impact of disease and level of care on family income loss	Parameter Estimate	Standard Error	t Value	Pr > |t|
Disease duration of the most affected	-$39.4	$136.6	-0.29	0.7732
Most affected person is receiving Social Security Disability Income	$2,035.8	$3,208.0	0.63	0.5260
Most affected person is receiving care from paid caregivers	$11,427.0	$3,444.5	3.32	0.0010
R-Square	0.1208			
Adj R-Sq	0.0751			

Exhibit 3-14 shows the actual observed family income loss and the regression adjusted family income loss based on the Equation 2. Both un-weighted and weighted per-household annual income loss (actual and adjusted) by level of care and disease are presented. The adjusted income loss can only be calculated for the 466 families that were included in the regression model. When looking at per-household income loss by level of care, the data show that the level of care is positively associated with family income loss, from both the actual and adjusted income loss, weighted and un-weighted. When looking at the adjusted income loss by disease, both the weighted and un-weighted income loss show the same pattern where SMA Early Onset has the highest income loss, followed by ALS, DMD, SMA Other, and MMD.

Exhibit 3-14: Predicted Income Loss (Equation 2) by Disease and Level of Care Needed

			Un-weighted				Weighted			
	Disease	N	Mean	StdErr	95_LCLM	95_UCLM	Mean	StdErr	95_LCLM	95_UCLM
Self-reported family income loss	16 to 24 hr a day attendance	322	$15,643	$2,009	$11,691	$19,596	$19,116	$2,485	$14,227	$24,006
	8 to less than 16 hrs	80	$10,639	$2,475	$5,712	$15,566	$10,933	$2,370	$6,217	$15,650
	1 to less than 8 hrs	87	$6,438	$1,743	$2,974	$9,902	$5,619	$1,514	$2,609	$8,630
	Care not needed	75	$3,960	$1,387	$1,197	$6,724	$5,242	$1,682	$1,891	$8,593
	ALS	124	$15,565	$2,898	$9,829	$21,302	$15,946	$3,022	$9,964	$21,927
	DMD	131	$11,408	$2,831	$5,808	$17,008	$12,509	$3,105	$6,366	$18,653
	MMD	123	$6,225	$1,779	$2,703	$9,747	$6,296	$1,778	$2,777	$9,815
	SMA Early Onset	17	$30,298	$11,741	$5,409	$55,187	$32,041	$12,818	$4,867	$59,214
	SMA Other	262	$10,785	$1,680	$7,477	$14,092	$16,539	$2,891	$10,847	$22,231
Estimated family income loss	16 to 24 hr a day attendance	279	$16,708	$675	$15,380	$18,037	$17,582	$661	$16,281	$18,884
	8 to less than 16 hrs	64	$13,285	$1,218	$10,851	$15,718	$15,844	$1,261	$13,324	$18,363
	1 to less than 8 hrs	68	$7,446	$778	$5,893	$8,998	$8,032	$843	$6,350	$9,714

Disease	N	Un-weighted				Weighted			
		Mean	StdErr	95_LCLM	95_UCLM	Mean	StdErr	95_LCLM	95_UCLM
Care not needed	55	$4,310	$1,001	$2,303	$6,316	$5,114	$1,040	$3,028	$7,200
ALS	92	$19,001	$1,031	$16,953	$21,049	$19,217	$1,039	$17,153	$21,280
DMD	97	$13,785	$1,024	$11,751	$15,818	$14,735	$1,041	$12,668	$16,802
MMD	68	$4,683	$999	$2,688	$6,677	$5,200	$1,022	$3,159	$7,240
SMA Early Onset	14	$35,934	$2,304	$30,955	$40,912	$35,623	$2,462	$30,304	$40,942
SMA Other	195	$12,043	$677	$10,709	$13,378	$11,110	$627	$9,874	$12,347

3.4 Population Inferences

In this section, we estimate the total costs of the five diseases, ALS, DMD, MMD, SMA Early Onset, and SMA Other, in the U.S. in year 2010. Total per-capita cost associated with each of these diseases is calculated as the sum of medical cost (from the claims data analysis), non-medical cost (from the survey study), and indirect cost defined as family income loss (from the survey study).

3.4.1 Medical Cost Estimates by Insurance Coverage

In order to calculate the per-capita direct medical cost for a population with a particular disease, it is important to take into account the types of insurance coverage the population has, as insurance type is considered an important determinant of healthcare expenditure.[34] A challenge in calculating cost-of-illness for rare diseases such as ALS, muscular dystrophy, and SMA is a lack of well-documented epidemiologic data and other literature such as those describing the proportion of patients covered by different types of insurance and the cost differentials across insurances in treating these diseases. We therefore relied on our survey sample to estimate the distribution of patient population by types of insurance for each disease.

Weighted percentages from Exhibit 3-15 show that among ALS patients, about 66% are covered by Medicare, 17% are covered by private insurance, 9% by Military or VA insurance coverage, and a little over 2% are covered by Medicaid. About 43% of DMD patients are covered by Medicaid or SCHIP, 30% by private insurance, and 20% by Medicare. About 40% of MMD patients are covered by Medicare, 30% by private insurance, and 14% by Medicaid/SCHIP. For SMA Early Onset, 53% of the patients are covered by Medicaid/SCHIP, 33% by private insurance, and 11% by Military or VA insurance. 34% of SMA Other patients are covered by Medicaid/SCHIP, 28% by private insurance, and 26% by Medicare. Uninsured individuals represent a small proportion of the patients from the survey sample.

Exhibit 3-15: Distribution of Insurance Coverage by Disease

Disease		Commercial	Medicare	Medicaid or SCHIP	Military or VA	Other	Uninsured	Total
ALS	N	22	80	4	10	8	0	124
	%	17.49	65.82	2.32	9.15	5.22	0	
DMD	N	42	28	52	0	9	0	131
	%	30.28	20.4	42.51	0	6.8	0	
MMD	N	37	49	18	4	12	3	123
	%	29.71	39.88	14.07	3.15	10.02	3.16	
SMA Early Onset	N	4	0	11	1	1	0	17
	%	33.18	0	53.18	10.93	2.72	0	
SMA Other	N	68	84	83	5	19	3	262
	%	28.18	26.16	33.95	2.5	7.86	1.35	
Total	N	173	241	168	20	49	6	657

*Ns are based on un-weighted raw counts. Percentages are weighted.

Based on the distribution of the insurance coverage from the survey sample, we estimated the per-capita medical cost by disease based on the weighted average cost from the claims-based per-capita cost presented in Exhibit 3-2 (for commercially covered patients) and Exhibit 3-4 (for Medicare covered patients). As previously mentioned, during the family focus group discussion to inform/test the survey development, one concern emerged that questions asking families to report the amount of medical payments made by insurance and other parties (e.g., additional insurer) directly to the healthcare providers tend to result in item non-response and/or recall errors. Therefore for the direct medical cost component of the final total cost-of-illness calculations, we used the medical costs calculated from commercial and Medicare claims data. These medical cost estimates include not only cost to the insurer, but also amounts paid by patients and other parties to healthcare providers.[iv]

Due to a lack of data on Medicaid beneficiaries, uninsured individuals, and patients with other coverage (e.g., Military and VA, etc.), we impute the medical cost for these insurance types using the following assumptions:

1. Per-capita cost under Medicaid is 90% of the commercial cost for each disease.
2. Per-capita cost under other insurance is the same as commercial insurance.
3. Per-capita cost for the uninsured is the average of Medicare and Medicaid cost.

It is known that the cost of healthcare differs between private and public health insurance due to factors such as differing administrative costs, provider payment rates, and insurance premium charges.[35] One study found that, after adjusting for health differences, public insurance was approximately ten percent less expensive than private insurance for children and about 30 percent less expensive for adults.[36] However, it is also understandable that without risk adjustment, per-capita cost under Medicare and Medicaid could be higher than that of the privately insured

[iv] The family out-of-pocket cost estimates from the survey are presented in the Appendix B.

simply because Medicare and Medicaid patients are either older or poorer and in general less healthy than those with private insurance. For example, one recent study found that average medical expenditures in 2005 for non-elderly, low-income adults in Medicaid were $4,684 per individual, compared to $3,669 for privately insured individuals.[37] It is unclear to what extent the cost of treating ALS, MD, and SMA under Medicaid would be different than under private insurance or Medicare. Therefore, we made a conservative assumption that the cost incurred by Medicaid patients with these diseases would be ten percent less than the cost incurred by the privately insured (as shown in Exhibit 3-16).

For various reasons, such as comprehensiveness of healthcare coverage and potential group discounts, we assume that patients who are covered by other insurance (e.g., TRICARE, VA, or other government programs) incur the same costs as do the privately insured. Regarding the uninsured patients, there is evidence that they are sometimes charged significantly more than privately or publicly insured patients.[38] However, it has also been reported that hospitals sometimes give more discounts to the uninsured by writing off as much as 40% to 50% of what they charge.[39] Regardless of how much uninsured patients ultimately pay, the cost of their care (that may be paid or partially paid by sources such as charitable organizations or left as uncompensated care) is assumed to be similar to the cost of care (for these diseases) under private or public insurance. One study using data from California found that uninsured patients pay prices similar to those of Medicare patients.[38] For the purpose of this study, we assume that the per-capita medical costs of uninsured patients with ALS, MD, and SMA, are somewhere between those of Medicare and Medicaid beneficiaries.

In addition, since DMD is not associated with a specific ICD-9 diagnosis code, we use the medical cost associated with HPMD (ICD-9 code 359.1 including diagnosis for DMD, BMD, and LGMD) to approximate medical cost associated with DMD in the total cost calculation. As mentioned in the method section, requiring full-year insurance coverage may lead to certain most severely affected patients (individuals who died during the year) being excluded from the study, especially SMA Early Onset patients who usually do not survive beyond the second year of life. Our sensitivity analysis for SMA Early Onset shows that per-capita annual total medical cost would be $136,675 when patients were not required to have full-year insurance coverage (N=47) as compared to $121,682 when patients were required to have full-year coverage (N=14), representing a 12% increase. However, to be consistent in our methodology, we use the per-capita cost of $121,682 in the calculations of direct medical cost for SMA Early Onset.

Finally, the Medicare 5% sample claims data did not include pharmacy cost. We assumed that the percentage of pharmacy cost of total healthcare cost within Medicare would be the same as that observed in commercial data. We therefore calculated the Medicare pharmacy cost using the percentages observed from the commercial claims data and added these estimated pharmacy cost to the medical cost estimated from Medicare data.

Based on the distribution of insurance coverage and the above described assumptions, we estimate that final, weighted average per-capita total medical cost is the highest for SMA Early Onset ($115,223), followed by ALS ($31,277), DMD ($22,798), SMA Other ($18,203), and MMD ($17,592).

Exhibit 3-16: Estimated Per-Capita Medical Cost by Disease

Disease	Commercial		Medicare [c]		Medicaid [d]		Other [e]		Uninsured [f]		Total	
	Cost	%	Cost	%	Cost	%	Cost	%	Cost	%	Cost	%
ALS	$30,934	17.5	$31,563	65.8	$27,841	2.3	$30,934	14.4	$29,702	0.0	$31,277	100
DMD [a]	$24,122	30.3	$22,670	20.4	$21,710	42.5	$24,122	6.8	$22,190	0.0	$22,798	100
MMD	$18,236	29.7	$18,715	39.9	$16,413	14.1	$18,236	13.2	$17,564	3.2	$17,592	100
SMA Early Onset [b]	$121,682	33.2	NA	NA	$109,514	53.2	$121,682	13.7	$0	0.0	$115,223	100
SMA Other	$20,085	28.2	$16,533	26.2	$18,076	34.0	$20,085	10.4	$17,305	1.4	$18,203	100

[a] Medical cost estimated using the cost of HPMD (ICD-9 code 359.1) that includes DMD, BMD, and LGMD. Likely to be an underestimate of true medical cost for DMD because BMD and LGMD that are covered by the same ICD-9 code 359.1 tend to be less severe than DMD.

[b] Based on estimates from small sample size.

[c] We calculated the pharmacy cost using the percentages (4.8-8.9%) observed from OptumInsight data and added these estimated pharmacy cost to medical cost calculated from Medicare data.

[d] Medicaid data is not available so the per-capita total healthcare cost is assumed to be 90% of commercial cost for each disease.

[e] Other includes both Military/VA insurance coverage, unknown insurance coverage, and 14 missing responses; it is assumed that per-capita cost is the same as commercial insurance.

[f] It is assumed that per-capita cost for the uninsured is the average of Medicare and Medicaid cost.

3.4.2 Population Prevalence Rates

There is very limited U.S.-specific epidemiologic data on ALS, DMD, MMD, and SMA. In order to estimate the prevalence of these diseases in the U.S., we conducted a literature review that captured prevalence estimates from U.S. and international literature. We identified the lowest prevalence rate per 100,000 individuals as cited in the literature, the highest prevalence rate cited, and a moderate prevalence rate for each disease. Since there is no literature found discussing the prevalence of SMA Early Onset, we use the prevalence rate of either SMA1 or "childhood" SMA as a proxy for SMA Early Onset. When the prevalence rate for each disease was multiplied with the total U.S. population in 2010, we were able to calculate a low, high, and moderate disease prevalence in the U.S. in 2010. Exhibit 3-17 shows the estimated prevalence of each disease in the U.S. Appendix A contains a comprehensive list of literature identified on disease-specific prevalence rate.

Exhibit 3-17: Estimated Disease Prevalence in the U.S.

	Prevalence Per 100K Population			Total US Population (Census data 2010)	US Prevalence		
	Low	High	Moderate		Low	High	Moderate
ALS	1.1 (Alcaz 1996) [8]	7.4 (Worms 2001) [9]	5.2 (Orphanet 2011) [27]	308,745,538	3,396	22,847	16,055
DMD	2.9 (Peterlin 1997) [40]	8.3 (Norwood 2009) [41]	5.0 (Orphanet 2011) [27]	308,745,538	8,954	25,626	15,437
MMD	2.1 (Pinessi 1982) [42]	10.6 (Norwood 2009) [41]	4.5 (Orphanet 2011) [27]	308,745,538	6,484	32,727	13,894

	Prevalence Per 100K Population			Total US Population (Census data 2010)	US Prevalence		
	Low	High	Moderate		Low	High	Moderate
SMA Early Onset [a]	0.1 (Norwood 2009) [41]	1.3 (Orphanet 2011) [27]	1.2 (Pearn 1978) [43]	308,745,538	309	3,859	3,705
SMA Other	1.86 [b] (Derived from Norwood 2009) [41]	2.0 [c] (Derived from Orphanet 2011) [27]	1.93 [d] (Average of Low and High)	308,745,538	5,743	6,175	5,959

[a] Prevalence of SMA type 1 (Norwood 2009) or childhood SMA (Pearn 1978) were used as a proxy for SMA Early Onset.

[b] Norwood et al 2009 reported a prevalence rate of 0.1/100k population for SMA 1 and an overall prevalence rate of 1.87/100k for all types of SMA. Since we used Norwood SMA 1 prevalence rate as a proxy for SMA Early Onset, prevalence rate of SMA Other was therefore calculated by subtracting SMA 1 prevalence rate from that of the SMA overall: 1.87-0.1=1.86.

[c] Orphanet 2011 reported a prevalence rate of 1.3 (SMA1), 1.42 (SMA2), 0.26 (SMA3), and 0.32 (SMA4) per 100k population, with a prevalence rate of 3.3/100k for SMA overall. Since we used Orphanet SMA 1 prevalence rate as a proxy for SMA Early Onset, prevalence rate of SMA Other was therefore calculated by subtracting SMA 1 prevalence rate from that of the SMA overall: 3.3-1.3=2.

[d] Moderate prevalence rate per 100k populated for SMA Other was calculated as the average of low and high estimates for SMA Other.

3.4.3 Estimated National Costs

Using the low, high, and moderate disease prevalence as shown in Exhibit 3-17, we calculated the total national cost associated with each disease by multiplying the total per-capita cost (direct and indirect) with the three prevalence estimates. The per-capita medical costs shown in Exhibit 3-18 were based on the medical cost analysis using commercial and Medicare insurance claims. The non-medical and indirect cost estimates were based on the survey study. We calculate the total per-capita cost as the sum of medical, non-medical, and indirect costs.

Individually, based on the moderate estimates, ALS is associated with a total of $1,025 million dollars, followed by DMD ($791 million), SMA Early Onset ($684 million), MMD ($450 million), and SMA Other ($273 million). In total, these five diseases caused a total national economic burden ranging from $1.2 billion to $4.8 billion with a moderate estimate of $3.2 billion.

Exhibit 3-18: Estimated Total National Cost of Disease in the U.S.

Disease	Direct Cost		Indirect Cost [c]	Total Per-capita Cost	Prevalence Estimates			Total National Cost (in millions)		
	Medical Cost [a]	Non-Medical Cost [b]			Low	High	Moderate	Low	High	Moderate
ALS	$31,277	$17,889	$14,682	$63,848	3,396	22,847	16,055	$217	$1,459	$1,025
DMD	$22,798	$12,939	$15,481	$51,217	8,954	25,626	15,437	$459	$1,312	$791
MMD	$17,592	$5,157	$9,628	$32,378	6,484	32,727	13,894	$210	$1,060	$450
SMA Early Onset	$115,223	$51,665	$17,759	$184,647	309	3,859	3,705	$57	$713	$684
SMA Other	$18,203	$14,295	$13,252	$45,750	5,743	6,175	5,959	$263	$282	$273
Total								$1,205	$4,826	$3,222

[a] See Exhibit 3-16

[b] See Exhibit 3-10

[c] See Exhibit 3-12.

4. Discussion

4.1 Direct Medical and Non-Medical Cost

Our estimates show that SMA Early Onset is associated with a per-capita total medical cost of $115,223, followed by ALS ($31,277), DMD ($22,798), SMA Other ($18,203), and MMD ($17,592). These cost estimates are comparable with what is noted in the literature. In a 1996 study by Klein and Forshew, the medical cost of diagnosed ALS was found to be $12,000 to $24,000 depending on the equipment being used to identify and treat ALS.[5] A recent U.S. based study also found that individuals with MD had average medical expenditures 10 to 20 times greater than individuals without MD. The incremental annual expenditures of medical care for privately insured individuals with MD averaged $18,930 and ranged from $13,464 at ages 5 to 9 to $32,541 at ages 15 to 19.[44] Overall, our estimates show that the total medical cost from all five diseases could be as low as $1.2 billion and as high as $4.8 billion, with a moderate estimate of $3.2 billion in year 2010.

It should be noted that total medical cost for DMD from our estimate ($22,798) could be an underestimate of the true medical cost of DMD. This is because there is no specific ICD-9 diagnosis code to identify DMD and the code 359.01 that we use in the commercial and Medicare claims data analysis includes not only DMD, but also BMD and LGMD, two more variable and often less severe types of MD. The true medical cost of DMD, based on the nature and severity of the disease, is likely to be higher - possibly more similar to the values calculated for CMD, which we estimated as being associated with a per-capita medical cost between $32,341 (based on commercial claims data) and $39,132 (based on Medicare claims data).

The estimated medical cost of $115,223 for SMA Early Onset is significantly higher than that of ALS, DMD, MMD, and SMA Other, primarily due to the extremely intensive and costly care needed by infants with this most severe form of SMA. However, this cost estimate is not statistically significant due to a small sample size of only 14 patients from the commercial claims data.

We were unable to identify any literature estimating the direct annual medical cost associated with SMA (type 1 or other types). However, a study by Little et al [6] evaluated the cost-effectiveness of prenatal screening for SMA and estimated that the total lifetime cost of care was $322,126 for a child with severe SMA and $819,762 for a child with mild SMA. Children with a milder form of SMA have a greater lifetime cost because children who live longer will receive additional years of care. The cost estimates for children with severe SMA were based upon published data on the cost of respiratory support, which accounts for the majority of healthcare expenditures for SMA. These cost estimates are similar to our findings. For instance, when assuming a three-year life expectancy from the time of diagnosis for the most severe cases (often diagnosed in the first year of life), the annualized cost of $107,735 is close to our estimate of $115,223.

We defined the non-medical cost associated with these diseases as costs incurred by families for moving to a new home or modifying homes, purchasing or modifying family motor vehicles, cost of hiring professional caregivers to provide daily care to the affected individuals, and cost of other miscellaneous items (e.g., travel, food and food supplements, home maintenance, housekeeping, and caregiver training, etc.). Together, the non-medical costs cause an additional burden of as low as $308 million and as high as $1.2 billion with a moderate estimate of about $835 million.

There is limited literature quantifying the non-medical costs associated with these diseases. However, there is evidence that non-medical cost such as home/motor vehicle modification, professional caregiving, etc. represent a significant financial burden to families who need to care for their loved ones with functional limitations or disabilities. Home modifications (e.g., ramps, handrails, bathroom and kitchen modifications, and modifications to vehicles such as car conversion for wheelchair accessibility) often place a significant financial burden on the individual and his/her family. One Australian study found that mobility aids and home/car modifications cost about $2,600 per person with MD per annum.[2] It was also reported that terminally ill patients with substantial care needs were more likely to report that they or their families had to take out a loan or mortgage, spend their savings, or obtain an additional job in order to meet needs for transportation, nursing care, homemaking, and personal care.[3] Another study reported that home nursing services account for 40% of the total expenditures for children with MD compared to only 15% for children living with other chronic illnesses.[45] The direct and indirect costs of supporting a ventilator-assisted individual at home can range from $7,642 per month if employing a licensed practical nurse to $8,596 per month if employing a registered nurse for private duty care.[46] In our study, we found that patients who were on invasive ventilators, on average, require $18,965 a year in hiring professional caregivers while patients on non-invasive ventilators require $5,650 and patients not on any type of ventilators only require $1,653 a year in receiving professional caregiving at home.

4.2 Indirect Household Income Loss

In terms of the disease impact on household income, the estimated family income losses from regression Equation 1 (on family income) are $14,682, $15,481, $9,628, $17,759, and $13,252 respectively for ALS, DMD, MMD, SMA Early Onset, and SMA Other. The regression adjusted family income losses from Equation 2 (on self-reported family income loss) are $19,217, $14,735, $5,200, $35,623, and $11,110 respectively for these diseases. The estimated income losses from Equation 1 tend to be higher than the estimated income losses from Equation 2 for DMD, MMD, and SMA Other and lower than estimates from Equation 2 for ALS and SMA Early Onset but in general comparable. It is plausible that Equation 1 tends to underestimate family income loss because the expected family income was estimated relative to when the patients did not require daily care rather than to a general control group of families who have similar characteristics but are not at all affected by the diseases. However, the income loss estimates from regression Equation 2 may overestimate true indirect cost of the diseases, especially for those more severe disease types. Due to the consideration that self-reported "income loss" could be more subjective than more objective measures of income loss such as that derived from Equation 1, we use the more conservative estimates of family income loss from Equation 1, the difference between actual and expected family income, to calculate the indirect costs associated with these diseases. Based on our estimates, the indirect cost associated with the five diseases combined could be as low as $332 million and as high as $1.2 billion, with a moderate estimate of $753 million.

A 2009 study in Spain estimated a mean annual cost per patient with ALS of EUR 36,194 where the indirect cost due to reduction of working time, sick leave, and early retirement was estimated to be at EUR 8,575 per-patient per-year, excluding the cost of informal care (EUR 19,125).[47] A more recent study in Germany estimated that total annual costs from the societal perspective were EUR 36,380 (95% CI 27,090–47,970) per patient with ALS with the indirect cost mounting to an estimated EUR 21,400 from temporary disability, premature retirement, and informal care.[48]

4.3 Total Per-Capita Cost

Overall, our study found that the total per-capita cost (including direct medical, non-medical, and indirect costs) is about $63,848 for ALS, $51,217 for DMD, $32,378 for MMD, $184,647 for SMA Early Onset, and $45,750 for SMA Other. Based on these estimates, the total national cost associated with the five diseases combined could be as low as $1.2 billion and as high as $4.8 billion, with a moderate estimate of $3.2 billion in 2010.

The per-capita total cost of $63,848 for ALS is higher than the EUR 36,194 from the Spain study and the EUR 36,380 from the German study as mentioned above. In terms of the per-capita cost of DMD and MMD, from a 2005 Australian study of cost of MD in general, it was estimated that the total financial cost of MD amounts to $125,975 (U.S. dollars) per person with MD per annum.[2] Differences between our estimates and that of these international studies could be a result of multiple reasons, including differences in study design and analytical approach, cost categories investigated, definitions of cost measures, as well as some systematic differences such as those of the payment structure, quality and efficiencies of healthcare delivery, and characteristics of the patient population studied. For instance, the Australian study estimated a much higher per-capita indirect cost than ours likely due to the inclusion in their study of deadweight loss from monetary transfers such as welfare payments (mainly Disability Support Pension and Carer Payment), taxation forgone, and other items such as funeral costs. Overall our study represents a more conservative estimate of total national burden in the U.S. due to five specific diseases (i.e., ALS, DMD, MMD, SMA Early Onset, and SMA Other) in 2010.

The total (direct and indirect) cost estimates from our study are similar to other chronic, disabling diseases in the U.S. A study in 2006 on multiple sclerosis estimated that the average costs are about $47,215 per-patient per-year. Of these, 53% were for direct medical and non-medical costs, 37% for productivity losses, and 10% for informal care.[49] Annual direct medical costs per patient with Parkinson's disease were estimated to be between $10,043 and $12,491, more than double that of patients without the disease. Annual indirect cost of Parkinson's disease, including lost workdays for patients and caregivers, is estimated at $9,135.[50, 51] It was also found that the additional cost of annual informal caregiving per person with severe dementia (e.g., due to Alzheimer's) was $17,700.[52]

4.4 Study Limitations

This study has several limitations. The first limitation concerns how we calculate the prevalence of the five diseases of interest. Our prevalence figures were based on a literature review where we captured both the "lowest" and "highest" cited prevalence estimates, and calculated a moderate prevalence based on the available literature identified. These prevalence estimates do not account for the likely heterogeneity from different studies. The studies may vary significantly in terms of study design, sample selection, study quality, prevalence definition, etc. A systematic review of the literature coupled with a meta-analysis synthesizing prevalence rates (ideally by patient age and gender strata) accounting for random effects of study variation could further improve the accuracy of prevalence estimates. However, a lack of sufficient literature (especially in the case of SMA) may limit the benefits from such an approach.

A second limitation of the study is due to a limitation in obtaining additional data sources to calculate Medicaid and Military/VA-specific specific medical cost and to estimate medical cost for

the uninsured. In this study, we used healthcare claims data from a large, nationally diverse commercial insurance and Medicare claims data to estimate the direct medical cost for the five diseases of interest and used crude cost ratios (of commercial insurance or Medicare relative to other types of insurance) to approximate medical cost that could be incurred by Medicaid and other payers such as Military and/or VA insurance. Due to the constraints in obtaining other payer-specific data, certain nationally representative survey data such as the National Health Interview Survey, National Survey of Children's Health, The National Ambulatory Medical Care Survey (NAMCS), and The National Hospital Ambulatory Medical Care Survey (NHAMCS), could provide additional information on disease and insurance-specific medical cost. However, potential limitations of using such national survey data include either the small sample sizes or insufficient level of diagnosis information to identify the rare diseases being studied.

The third limitation is the lack of an explicit comparison group for income loss estimates. We estimated the indirect cost of disease as the family income loss from a regression prediction equation. The expected family income (without disease-induced intensive care) was estimated using the families with the healthiest patients as the comparison group, assuming that their family income approximates the income of families that have similar characteristics but without a person affected by the disease in the household. Income loss was defined as the difference between the expected income and the actual reported income. This income loss, however, may underestimate the actual productivity loss to the families affected by the disease. This is because the comparison group with patients least affected by these five diseases, in reality, may still earn less than a control group that is free of any chronic disease. A randomly selected, external control group (free of chronic disease) from sources such as the American Community Survey or Current Population Survey might help mitigate this problem. However, the measurement inconsistency and other challenges associated with this alternative analytical strategy precluded this approach in this study.[v]

A final limitation of the study is that families that responded to the survey may not be a completely randomized group. The survey took some time to complete, so it might be expected that the families most affected by the disease (e.g. families with multiple family members affected) were less likely to return the survey.

Despite these limitations, this report is the first comprehensive cost-of-illness study conducted in the United States concerning the economic impact of five specific types of neuromuscular diseases, including ALS, DMD, MMD, SMA Early Onset, and SMA Other. Moreover, it is one of only a few studies that have attempted to estimate the total cost of a debilitating disease to the families affected by such disease. The findings of this study—the total cost of these diseases—help underscore the importance of research on the cause and treatment of these diseases. In addition, the results suggest a possible role for additional policy initiatives to better support individuals and families affected, in terms of treatment and long-term care, disease management, employment and occupational training to improve quality of life and alleviate human and economic burden.

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[v] Additionally, a Heckman 2-step adjustment econometric model first estimating the probability of employment and then the income loss conditional on employment, adjusting for "selection bias" caused by the propensity of being employed could provide further insight on the scope and magnitude of indirect economic burden associated with these diseases.

APPENDIX A: REFERENCES FOR PREVALENCE CALCULATION

Exhibit A-1: References for Prevalence Calculation

Disease	Prevalence per 100,000	Reference
ALS	5.4	Guidetti et al, 1996, Italy [53]
ALS	1.07	Alcaz et al, 1996, Yugoslavia [8]
ALS	4.7	Traynor et al, 1999, Ireland [54]
ALS	2.7-7.4	Worms, 2001, European and North American studies [9]
ALS	4.02	Mandrioli et al, 2003, Italy [55]
ALS	4.02-4.91	Hoppitt et al, 2011, UK [56]
ALS	5.2	Orphanet Report Series, 2011 [27]
DMD	6.0	Radhakrishnan et al,1987, Libya [57]
DMD	3.16	Mostacciuolo et al., 1987, Italy [58]
DMD	7.13	Nakagawa et al, 1991, Japan [59]
DMD	6.3	Emery 1991, survey of word literature [60]
DMD	4.7	MacMillan & Harper, 1991, South Wales [61]
DMD	5.4	Essen et al 1992, Netherlands [62]
DMD	2.9	Peterlin et al, 1997, Slovenia [40]
DMD	5.5	Jeppesen et al, 2003, Denmark [63]
DMD	8.29	Norwood et al. 2009, Northern England [41]
DMD	5.0	Orphanet Report Series, 2011 [27]
MMD	2.1	Pinessi et al , 1982, Italy [42]
MMD	5.0	Harper 1989, UK [24]
MMD	7.1	MacMillan & Harper, 1991, South Wales [61]
MMD	5.0	Emery 1991, survey of word literature [60]
MMD	8.4	Hughes et al, 1996, Ireland [64]
MMD	10.6	Norwood et al. 2009, Northern England [41]
MMD	4.5	Orphanet Report Series, 2011 [27]
Childhood SMA (arrested type 1, type 2, and type 3)	1.2	Pearn, 1978, Northern England [43]
SMA type 1	0.1	Norwood et al. 2009, Northern England [41]
SMA type 1	1.25	Orphanet Report Series, 2011 [27]
SMA type 2	0.57	Norwood et al. 2009, Northern England [41]
SMA type 2	1.42	Orphanet Report Series, 2011 [27]
SMA type 3	0.64	Norwood et al. 2009, Northern England [41]
SMA type 3	0.26	Orphanet Report Series, 2011 [27]
SMA type 4	0.32	Orphanet Report Series, 2011 [27]
SMA	1.4	Hughes et al, 1996, Ireland [64]
SMA	2.8	Darin and Tulinius, 2000, Sweden [65]
SMA	1.87	Norwood et al. 2009, Northern England [41]
SMA	3.0	Orphanet Report Series, 2011 [27]

APPENDIX B: FAMILY OUT-OF-POCKET MEDICAL COST FROM THE SURVEY ANALYSIS

Although not included in the per-capita or total medical cost calculation, we also calculated the family out-of-pocket medical cost for a comparison with the claims-based analysis. Exhibit B-1 shows the weighted average (and 95% confidence intervals) family out-of-pocket medical cost including copay, coinsurance, deductible, etc. paid by the family in the past 12 months for both the most affected and second most affected persons. Per-household cost was calculated by type of healthcare services and disease.[vi] For each type of expenses, we excluded the item nonresponses and calculated the average cost using families with a valid response as the denominator. This method is consistent with how we calculated per-household non-medical cost as described earlier in section 3.3.2.

Across the board, medical equipment and supply represents the largest cost category. Families with SMA Early Onset patients had the largest amount of total out-of-pocket cost ($9,078) (though the sample was small) and families with MMD had the lowest amount of out-of-pocket cost ($1,003) for medical services, even though families with MMD are more likely to have more than one person affected with the disease (See Exhibit 3-6). The total annual medical cost paid by families out-of-pocket (for both the most and second most affected persons) is slightly higher but very similar to the patient-paid amount from an analysis using the commercial insurance data where the per-capita patient-paid amount was $2,123 for ALS, $1,811 for DMD, $1,771 for MMD, $2,286 for SMA Early Onset, and $1,471 for SMA Other.

Exhibit B-1: Direct Medical Cost (Family Out-of-Pocket Payment) by Type of Service and Disease

Disease	Type of Service	N	Weighted Mean	Std Error	95% CL for Mean	
ALS	Emergency Room	95	$132	$47	$38	$226
	Hospital Admission	96	$182	$80	$24	$340
	Ambulance Service	107	$74	$26	$22	$126
	Medical equipment and supply	91	$1,727	$652	$432	$3,022
	Outpatient Surgical Procedures	110	$79	$54	-$27	$186
	Physician office, Outpatient clinic, or Urgent care	74	$291	$69	$154	$428
	Prescription Drugs	83	$881	$245	$394	$1,368
	Total Medical	124	$2,353	$567	$1,231	$3,476
DMD	Emergency Room	98	$19	$7	$5	$32
	Hospital Admission	102	$56	$41	-$25	$136
	Ambulance Service	110	$2	$2	-$2	$7
	Medical equipment and supply	90	$2,252	$1,463	-$656	$5,159
	Outpatient Surgical Procedures	114	$52	$47	-$40	$145

[vi] Due to concerns for measurement accuracy as indicated by family focus group discussions, medical payments made by insurance and other non-family cost were not captured in the survey. The family out-of-pocket cost estimates are presented in this report; however, for final total cost-of-illness calculation we use the medical costs calculated from commercial and Medicare claims data that includes plan paid, patient paid, and other party paid amount.

Disease	Type of Service	N	Weighted Mean	Std Error	95% CL for Mean	
	Physician office, Outpatient clinic, or Urgent care	87	$339	$105	$131	$547
	Prescription Drugs	69	$315	$59	$197	$433
	Total Medical	131	$1,965	$1,013	-$40	$3,969
MMD	Emergency Room	95	$305	$178	-$49	$658
	Hospital Admission	95	$151	$100	-$48	$349
	Ambulance Service	109	$29	$12	$5	$52
	Medical equipment and supply	93	$441	$323	-$200	$1,081
	Outpatient Surgical Procedures	106	$89	$63	-$36	$213
	Physician office, Outpatient clinic, or Urgent care	77	$405	$150	$107	$704
	Prescription Drugs	74	$274	$67	$141	$406
	Total Medical	123	$1,003	$339	$332	$1,674
SMA Early Onset	Emergency Room	11	$112	$56	-$14	$237
	Hospital Admission	10	$2,521	$1,909	-$1,798	$6,839
	Ambulance Service	14	$1,775	$1,529	-$1,528	$5,078
	Medical equipment and supply	12	$3,023	$2,232	-$1,890	$7,936
	Outpatient Surgical Procedures	14	$33	$35	-$43	$108
	Physician office, Outpatient clinic, or Urgent care	12	$321	$222	-$167	$810
	Prescription Drugs	10	$206	$91	$0	$411
	Total Medical	17	$9,078	$5,584	-$2,759	$20,914
SMA Other	Emergency Room	202	$198	$157	-$112	$509
	Hospital Admission	211	$67	$26	$16	$118
	Ambulance Service	226	$19	$8	$2	$35
	Medical equipment and supply	186	$1,554	$464	$639	$2,470
	Outpatient Surgical Procedures	227	$26	$11	$5	$47
	Physician office, Outpatient clinic, or Urgent care	166	$356	$87	$184	$528
	Prescription Drugs	121	$294	$75	$146	$442
	Total Medical	262	$1,723	$385	$965	$2,482

*Ns are based on un-weighted raw counts and means are weighted.

Appendix C: Reference List

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