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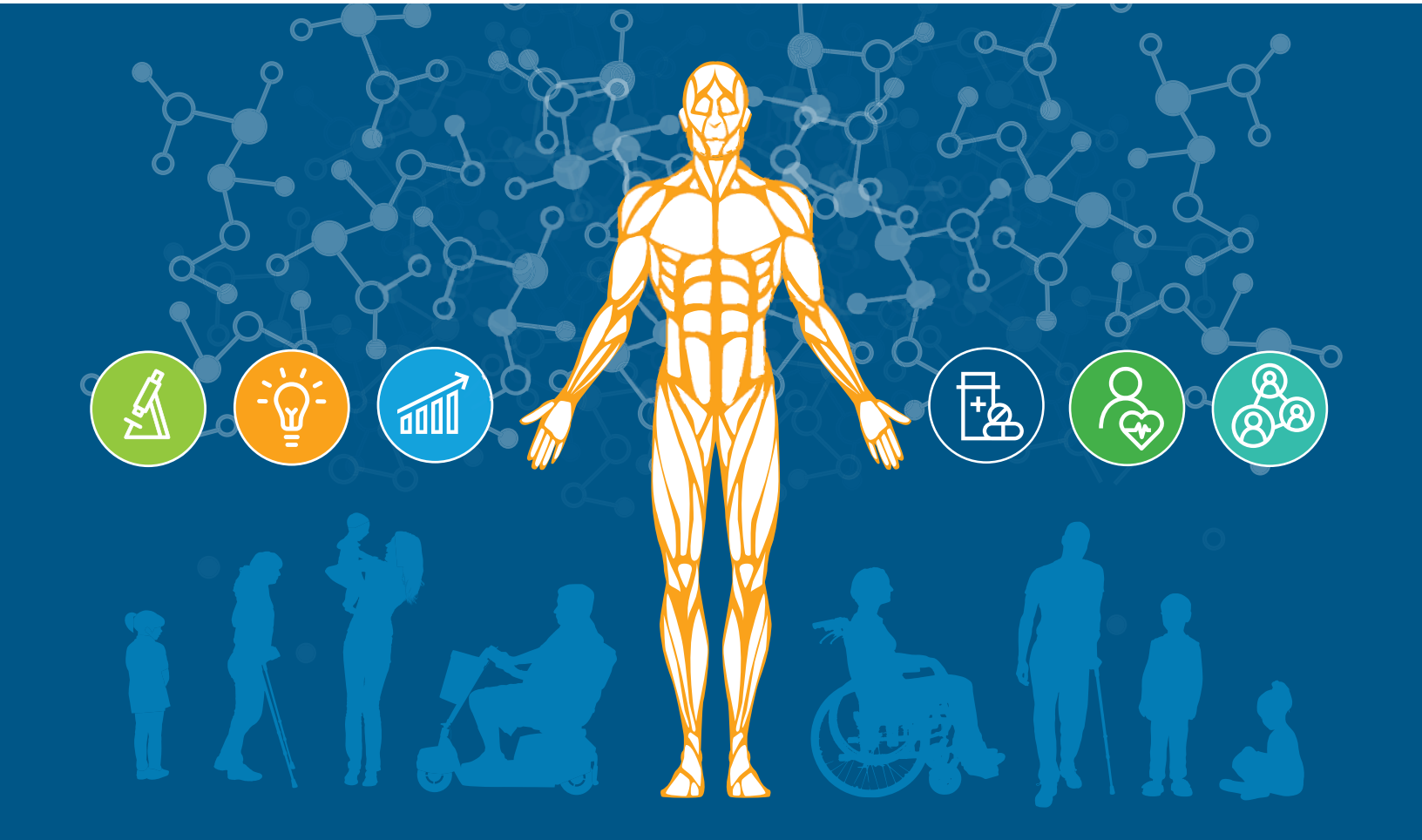
OCTOBER 2018

Understanding Neuromuscular Disease Care

Current State and Future Prospects



Introduction

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Individuals living with neuromuscular disease (NMD) have seen improvements in symptom management in recent years and are now living longer lives. However, the burden of these diseases remains considerable from personal, societal and economic perspectives. Many NMDs are still potentially lethal with lifelong debilitating symptoms that are often difficult to treat and take a high toll on patients and caregivers alike. As with many degenerative diseases, the treatment landscape is rapidly evolving due to advances in disease knowledge and technology. For the first time, the intersection between data (e.g., big data, patient registries) and the therapeutic pipeline offers broad new opportunities to improve patient care. Support networks for affected patient groups are also significant. In addition, improving genetic diagnosis and disease subtype distinction offers opportunities to customize care. As investments in NMD and innovative therapies grow, it is increasingly important to consider how to capitalize on opportunities to accelerate improvements in the care of neuromuscular diseases.

This report seeks to highlight both the gaps in care and opportunities to address them for patients with neuromuscular diseases. By examining current approaches to care and leveraging input from thought leaders in the clinical and genetic testing space, it seeks to identify where advancements within the current treatment paradigm are likely to occur and where hurdles remain. It further examines progress that could offset these challenges, including the investments being made to develop innovative and disease-modifying therapies to treat NMD, and examines the outlook for current and future patients. Finally, it explores ways for multiple stakeholders to capitalize on a range of opportunities to achieve optimal patient care and outcomes.

The research in this report was undertaken independently by the IQVIA Institute for Human Data Science with external funding. The contributions to this report of Michael Kleinrock, Deanna Nass, Katherine Roberts and dozens of others at IQVIA are gratefully acknowledged.

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MDA Muscular Dystrophy Association

This report was produced with funding from the Muscular Dystrophy Association (MDA)

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Executive summary

Neuromuscular diseases are a broad group of disorders that are individually rare but collectively impact an estimated 250,000 patients and their caregivers in the United States. These diseases are among the most devastating in terms of years of life lost, and many disproportionately affect children. Until very recently, treatment options were limited, but new technologies are now bringing life to the pipeline and hope to the community. Opportunities are forming to leverage data, build infrastructure and share insights that can optimize patient care and accelerate the emergence of new therapies.

There is vast diversity among the neuromuscular diseases, which have divergent causes, severity and trajectories even within a class or diagnosis. Their symptoms are similarly varied, although progressive muscle weakness is a central feature, andfatigue and immobility are also common. This heterogeneity, combined with the low prevalence of most neuromuscular diseases, has made it challenging to determine the mechanisms of pathology and develop targeted treatments.

Despite limited treatment options, the cost of neuromuscular disease is considerable. Available estimates of total economic burden indicate an annual national cost of $3.2 billion for four of the more prevalent neuromuscular diseases. The majority is attributed to healthcare expenses, with the remainder reflecting non-medical costs such as home modifications and the lost earning potential of patients and family members who commit their time to care. Since many neuromuscular diseases are not included in this cost analysis but have similar per-patient annual medical expense estimates and symptom impact, the full cost for all neuromuscular diseases is certain to be much higher. Analysis of healthcare charges using IQVIA Real-World Data indicates that total annual charges across all neuromuscular patients exceed $46 billion. Annual medical expenses across neuromuscular disease groups vary significantly but are upwards of $40,000 annually for the upper quartile in many disease groups, with median estimates between $10,000 and $20,000. Recent approval of disease-modifying treatments, which can cost upwards of $750,000 per patient per year, are also likely to have a significant impact on the total.

Insights gained from a survey of 90 healthcare professionals focused on the care of patients with neuromuscular disease – The Neuromuscular Disease Healthcare Provider Survey – sheds light on current care challenges. Patients with neuromuscular disease and their caregivers face many obstacles. Diagnosis of neuromuscular disease can often take upwards of a year, although improvements in the speed, price and comprehensiveness of available genetic testing is accelerating the process. Treatment for neuromuscular disease is generally provided through a multi-disciplinary care model, allowing patients to visit a range of specialists synchronously in a dedicated center. However, care paradigms and provider treatment decisions may be inconsistent, reflecting the challenges of small patient populations, varied symptoms and a lack of official guidelines, particularly for many of the less prevalent diseases.

Psychological symptoms stand out as an ongoing challenge, affecting 75% of patients and recognized by 90% of neuromuscular disease healthcare professionals as a high unmet need. Further, as new therapies are approved, care paradigms are having to evolve to incorporate more frequent visits, additional specialists and new administrative challenges, and 70% of providers indicate that obtaining insurance coverage for new treatments is a frequent barrier.

Recently approved treatments are at the forefront of a burgeoning pipeline, with 195 unique molecules currently in development by 165 companies in 20 countries. Research and development (R&D) efforts are focused in diseases where there have been recent successes, such as Duchenne muscular dystrophy (DMD), likely due to a growing understanding of underlying disease mechanisms in these areas or applicability of emerging technologies. However, the opportunities to address the root causes of disease with gene therapies, replacement proteins or antisense oligonucleotides are now allowing companies to target an increasingly broad range of neuromuscular diseases. Only 43% of pipeline products for neuromuscular disease are small molecules, reflecting the promise of and focus on investment in these 'Next-Generation' therapies.

As these therapies move through the pipeline, they may face challenges at every level: patient identification and recruitment, selection of appropriate endpoints, integration into the care paradigm and reimbursement from payers. Accelerating optimal patient outcomes will rely on a concerted effort to capitalize on a range of opportunities that could offset these challenges, including:

- Widening the use of genetic testing through effective newborn screening programs and other genetic testing access programs in order to speed diagnosis and improve overall disease understanding
- Increasing the use of patient registries, data hubs and other ways to centralize data (especially for diseases with a small patient population) to improve understanding of disease natural history, facilitate patient identification, identify biomarkers and benchmark health outcomes for appropriate endpoint selection
- Adopting technologies for remote appointments and real-time monitoring to improve care management by minimizing patient travel and increasing communication with healthcare providers
- Preparing existing clinics and specialist offices to participate in clinical trials thereby helping to streamline trial execution and expand the pool of eligible patients
- Collating and synthesizing the latest information improving our understanding of disease development and progression to support emerging therapeutic advances and to help improve and standardize care
- Developing innovative approaches to pricing and reimbursement to tackle rising costs for patients

Neuromuscular diseases and their characteristics

- Neuromuscular diseases represent a broad group of disorders characterized by muscle and/or nerve dysfunction which leads to progressive muscle weakness.
- These disorders are rare, with a limited understanding of their prevalence, but as a group these are estimated to affect upwards of 250,000 individuals in the United States.
- Disease severity varies depending on the underlying disorder but usually leads to significant, lifelong morbidity.
- Symptoms of neuromuscular diseases are diverse and affect many organ systems in addition to the muscles.
- Immobility, fatigue, respiratory and psychological symptoms all affect more than 70% of patients according to Neuromuscular Disease Healthcare Provider Survey respondents.

DIVERSITY IN NEUROMUSCULAR DISEASE

Neuromuscular disease is a broad term that encompasses a variety of disorders characterized by progressive muscle weakness due to abnormal muscle or nerve function. This muscle weakness may be caused by direct muscle pathology (e.g., from underlying defects in genes that encode muscle proteins) or be the result of defects in the nerves or neuromuscular junctions that provide stimulation to the muscles. Many neuromuscular disorders that fall within the overarching category of disease can be grouped as detailed in Exhibit 1, however, over 850 specific disease variants associated with almost 500 genes are catalogued[1],and not all are captured in the seven classes shown. Regardless of cause, dysfunction from neuromuscular diseases can lead to lifelong morbidities that vary in severity and may cause premature mortality for certain conditions.

All of these disorders are rare, affecting less than 40 individuals per 100,000, or fewer than 200,000 within the United States, thereby meeting the rarity criteria as specified by the Orphan Drug Act.[2] Many neuromuscular diseases affect fewer than five in 100,000 individuals and prevalence estimates are often wide ranging (see Exhibit 2 and Appendix Exhibit A). Many of these diseases are further thought to be underdiagnosed as well. Taken together as a group, neuromuscular diseases are estimated to affect upwards of 80 per 100,000 individuals, or more than 250,000 patients in the United States. Despite the commonality of muscle weakness, there are notable differences across disease types, including the presence of an underlying genetic component, time of disease manifestation, natural history of disease progression and severity of impact. Onset of symptoms may vary; one disease may manifest at birth or childhood, while another may emerge later in adulthood. There are several neuromuscular diseases where patients have a wide range in age of onset and may be separately classified as early- and adult-onset forms. Following onset, neuromuscular diseases also vary in severity, with life expectancies ranging from severely shortened to unaffected or normal. Importantly, the diversity described is seen within classes of neuromuscular disease, and even between patients with the same diagnosis.

Exhibit 1: Classes of Neuromuscular Diseases

Muscular Dystrophies	Motor Neuron Diseases	Ion Channel Diseases	Mitochondrial Diseases	Myopathies	Neuromuscular Junction Diseases	Peripheral Nerve Diseases
Becker muscular dystrophy (BMD)	Amyotrophic lateral sclerosis (ALS)	Andersen-Tawil syndrome	Friedreich's ataxia (FA)	Congenital myopathies	Congenital myasthenic syndromes (CMS)	Charcot-Marie-Tooth disease (CMT)
Congenital muscular dystrophies (CMD)	Spinal-bulbar muscular atrophy (SBMA)	Hyperkalemic periodic paralysis	Mitochondrial myopathies	Distal myopathies	Lambert-Eaton myasthenic syndrome (LEMS)	Giant axonal neuropathy (GAN)
Duchenne muscular dystrophy (DMD)	Spinal muscular atrophy (SMA)	Hypokalemic periodic paralysis		Endocrine myopathies	Myasthenia gravis (MG)	
Emery-Dreifuss muscular dystrophy (EDMD)		Myotonia congenita		Inflammatory myopathies		
Facioscapulo-humeral muscular dystrophy (FSHD)		Paramyotonia congenita		Metabolic myopathies		
Limb-girdle muscular dystrophy (LGMD)		Potassium-aggravated myotonia		Myofibrillar myopathies (MFM)		
Myotonic dystrophy (DM)				Scapuloperoneal myopathy		
Oculopharyngeal muscular dystrophy (OPMD)						

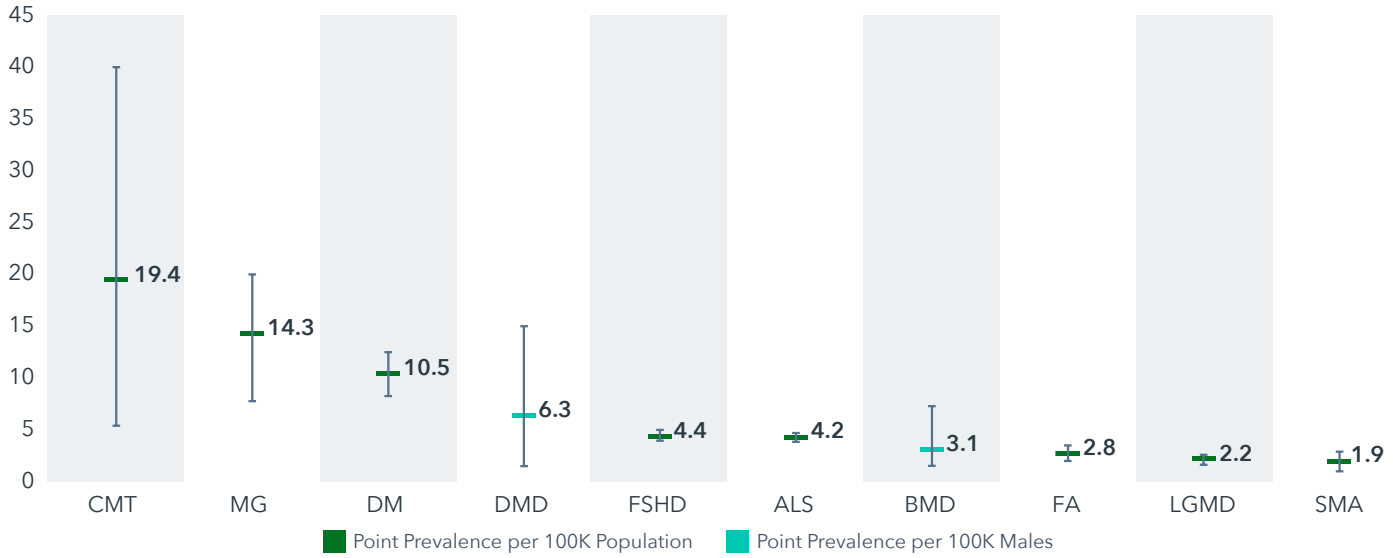
Source: MDA Classification of Diseases, Jul 2018

Note: Diseases listed are exemplary diseases or groups of diseases from each category. This classification of diseases by MDA does not include malignant hyperthermias, hereditary cardiomyopathies or hereditary paraplegias, which are also considered to be neuromuscular diseases. A full list of neuromuscular diseases with causes known to be found in the nuclear genome can be found at www.musclegenetable.fr and a list of known mitochondrial polymorphisms and mutations of human mitochondrial DNA, and associated known pathologies, can be found at www.mitomap.org.

The majority of neuromuscular diseases are hereditary. While our understanding of the genetic component of neuromuscular diseases has greatly advanced in the last few decades, the landscape continues to evolve as new genetic markers are identified. Genetic studies in the 1970s identified the linkage of Duchenne muscular dystrophy (DMD) to the X chromosome and, a decade later, specifically to mutations in the dystrophin gene.[3] With continued advancements in genetic studies – most recently next generation sequencing (NGS) – numerous genes have been linked to neuromuscular disorders. Notably, seven novel genes have been associated with amyotrophic lateral sclerosis (ALS) since 2014,[4] via studies examining patient genomes. In addition to pinpointing specific causes of disease within subpopulations of ALS patients, these findings also suggest a common molecular mechanism underpinning many types of ALS.

While initial studies across neuromuscular diseases have focused on identifying genes whose mutation directly caused neuromuscular disease for larger populations, recent work has expanded to map unique mutations in individual cases or to better understand prognosis for individuals with de novo mutations (i.e., sporadic, newly occurring, non-inherited mutations).[5] Improving technologies will additionally fuel the search for genetic, epigenetic or environmental modifiers (factors that modulate the impact of a particular genetic mutation) that might help explain the phenotypic heterogeneity that characterizes these disorders.[6] Increasing knowledge about these modifiers will lead to more precise disease definitions – better segmenting populations within a given disorder – and will help to achieve faster, more accurate, diagnoses. Over time, a clear understanding of the underlying genetic landscape of an individual's disease could inform disease prognosis and help to dictate treatment regimen.

Exhibit 2: Prevalence Estimates Across Neuromuscular Diseases per 100,000 Individuals



Source: Published Literature, see Appendix Table 1
Notes: Data includes prevalence estimates for both United States and ex-United States. Detail on origins of estimates are included in Appendix Table 1. Neuromuscular diseases not plotted have no identified reliable point prevalence estimates available. Mitochondrial myopathies are thought to affect approximately 6 per 100,000, all other disease are thought to affect <1 in 100,000 individuals. Estimates for DMD and BMD, which are tied to X-linked mutations are reported per 100 thousand males. Dotted lines denote range of included estimates. CMT = Charcot-Marie-Tooth syndrome, DM = myotonic dystrophy, MG = myasthenia gravis, DMD = Duchenne muscular dystrophy, FSHD = facioscapulohumeral muscular dystrophy, ALS = amyotrophic lateral sclerosis, BMD = Becker muscular dystrophy, LGMD = limb-girdle muscular dystrophy, FA = Friedreich's ataxia, SMA = spinal muscular atrophy.

CLASSES OF NEUROMUSCULAR DISEASES

Muscular dystrophies include a variety of disorders that show degeneration on muscle biopsy and lead to progressive muscle weakness and muscle deterioration.[7] Respiratory, cardiac and swallowing muscles can also be affected. The discovery of genetic variants within muscular dystrophies has led to increased specificity in their classification beyond clinical features and age of onset. For example, there are over 30 subtypes of limb-girdle muscular dystrophy (LGMD) that vary in their onset from childhood to adulthood.[1] Among muscular dystrophies, DMD is often suggested to be the most common, with an estimated 4–15 cases per 100,000 males aged 5–24 (see Exhibit 2). Both DMD and the related Becker's muscular dystrophy (BMD) have an X-linked recessive inheritance and are caused by mutations in the dystrophin gene, however DMD is more severe and manifests earlier than BMD, at two to three years of age.[8] Of the muscular dystrophies that typically manifest in adulthood, myotonic dystrophy type 1 (DM1) may be the most common, followed by facioscapulohumeral muscular dystrophy (FSHD) and milder forms of LGMD. Importantly, published prevalence estimates are few in number and generally relate to a single geographical location, with only a limited number of epidemiological studies

> *"We are just starting to understand genetic modifiers in neuromuscular diseases. There will be more [discoveries] to come for FSHD, LGMD and DM1 as genome sequencing is rolled out on a large scale"*
>
> Louis Kunkel, Ph.D., Director of the Program in Genomics at Boston Children's Hospital, Professor of Pediatrics and Genetics, Harvard Medical School

focused on the United States. The prevalence of DM1 is estimated at around 11 per 100,000 individuals and that of FSHD at approximately 4 per 100,000.[9,10] However, some FSHD prevalence estimates are as high as 13 per 100,000,[11] highlighting the lack of certainty regarding the size of these patient populations.

Motor neuron diseases affect the function of nerve cells that control skeletal muscles and result in muscle weakness and eventual loss of function of the motor neurons.[12] The specific motor neurons affected vary by disease. The most common progressive motor neuron disease is ALS, which affects an estimated 12,700 individuals in the United States based on a prevalence rate of around 4 per 100,000,[13] and eventually leads to progressive loss of both upper and lower motor neurons. Although familial genetic mutations cause ALS in some cases, the underlying cause is unknown in around 90% of cases.[4,12] Due to ALS's speed of progression, median survival is 3–5 years with eventual death due to respiratory paralysis.[12] Spinal muscular atrophy (SMA), another motor neuron disease that often presents at birth, specifically affects the lower motor neurons and is characterized by deterioration of the spinal cord and lower brainstem.[14] SMA is classified based on time-to-onset and clinical course, from type 0 occurring prenatally through type 4 (adult-onset); all forms typically involve symmetric proximal muscle weakness that is greater in the lower limbs.[14] The prevalence of SMA Types 1–3* in the United States is estimated between 8,526 and 10,333 based on birth prevalence.[15] Other motor neuron disorders include X-linked forms of SMA, which may cause weakness in the bulbar or distal muscles depending on subtype, as well as bulbar and pseudobulbar palsies, which affect the lower or upper motor neurons, respectively.

Ion channel diseases are characterized by muscle weakness and/or episodic paralysis due to altered function in cell ion channels or membrane proteins.[16] Prevalence is uncertain for many of these diseases. For the myotonia congenita group, an inherited myopathy that causes delayed muscle relaxation and occasionally leads to muscle enlargement and increased muscle strength, prevalence is 1–5 per 100,000.[10,17] Myotonia congenita is a childhood-onset disease, but symptoms are typically episodic and intermittent. By contrast, other ion channel diseases, with the exception of paramyotonia congenita, are progressive, with patients typically experiencing worsening muscle weakness in addition to periodic paralysis. These more severe ion channel diseases (including hyperkalemic, hypokalemic and Andersen-Tawil periodic paralyses) are very rare, with estimated collective prevalence of 1.5 in 100,000 and tend towards onset in childhood or adolescence.[10] As a group, the ion channel diseases do not typically decrease life expectancy and, with the exception of Andersen-Tawil syndrome, are not associated with cardiovascular or respiratory difficulties.

Mitochondrial diseases are a group of disorders where the mitochondria (cellular organelles responsible for energy production) malfunction and fail to produce enough energy. Mitochondrial dysfunction typically leads to pathologies in multiple organ systems, including the muscles, which have inherently high demand. Weakness, spontaneous muscle contractions and associated myopathies are often the result.[18,19] Estimates for the prevalence of mitochondrial myopathies have been increasing over time, reflecting new abilities to diagnose them correctly due to advances in genetic technologies. Recent studies suggest that the prevalence of mitochondrial disease is around 12.5 in 100,000,[20] however, it is important to note that not all individuals with mitochondrial disease experience myopathy. As a result of large genetic variability, the age of onset and natural history of mitochondrial disease is exceptionally varied. In addition to muscle weakness, patients often also experience cardiomyopathy, neurological problems (e.g., hearing loss, vision impairment, seizures, learning difficulties) and metabolic complications such as diabetes and liver disease. Mitochondrial myopathies are classified into types of similar syndromes according to age of onset and associated symptoms, but association with a particular syndrome is insufficient to predict disease progression and life expectancy.

* SMA Type 0 and Type 4 are extremely rare relative to Types 1-3

NEUROMUSCULAR DISEASES AND THEIR CHARACTERISTICS

Myopathies encompass a range of disorders caused by malfunction of muscle fibers that results in muscular weakness. This is a broad group in which diseases are generally categorized according to their underlying cause, when possible. Examples include the following:

- **Inflammatory myopathies are characterized by chronic inflammation of the muscle**, although other organ systems may also be affected, contributing to overall morbidity and mortality.[21] This class includes polymyositis, dermatomyositis, and inclusion-body myositis. Distinctions between the inflammatory myopathies were historically based on histopathology, however recent work has been done to classify patients based on the presence of specific auto-immune antibodies.[21] Although the original cause of inflammation is often not known, inflammatory myopathies are generally considered to be a form of autoimmune disorder, whereby dysregulation or dysfunction of the immune system results in direct damage to muscle tissue (polymyositis) or disruption of the blood supply to the muscle (dermatomyositis). Interestingly, some patients recover completely from these diseases, especially when initial onset occurred during childhood. However, some patients do not recover and may develop difficulties with respiration or swallowing. Inclusion-body myositis is often late-onset and is typically gradually degenerative with many patients ultimately requiring a wheelchair.

- **Metabolic myopathies are usually the result of inborn errors of metabolism that affect the ability of the muscle to generate and maintain energy.** This may be due to specific mutations in enzymes that facilitate metabolism of glycogen, such as for Pompe disease (as well as McArdle disease and Cori disease), or genes involved in the processing or storage of lipids, sugars or nucleotides.[22] Metabolic myopathies have a wide range in age of onset, symptoms and clinical prognosis that mirrors the variety in underlying cause. Some, such as Pompe disease, may present within the first few months of life (although both early- and late-onset forms exist) and can drastically shorten life expectancy, while others present as mild muscle weakness in adults that is slowly progressive.

- **Distal myopathies are forms of muscular dystrophy that are typically less severe.** They are defined by their specific targeting of distal muscles, which may include the hands, feet and/or vocal cords. Age of onset and progression is varied, but distal muscles usually weaken gradually.

- **Endocrine myopathies are not inherited but arise as a consequence of abnormal hormone levels.** Endocrine myopathies are often late-onset, appearing in adulthood, and are rare among myopathies in that potentially curative treatment options exist through the correction of the underlying endocrine disturbance. Limited information is available on prevalence of distal and endocrine myopathies.

- **Congenital myopathies have an onset at birth, and the most severe are first detected as muscle weakness in newborns (neonatal hypotonia).** The birth prevalence of congenital myopathies is estimated at around 4 per 100,000,[23] and reflects a wide range of genetic causes, including hereditary mitochondrial and metabolic myopathies detailed above that present in newborns. Severity and progression are varied, with some patients requiring respiratory support, tube feeding or becoming wheelchair-dependent. Decreased life expectancy is also common.

Neuromuscular junction diseases are caused by the destruction, malfunction or absence of one or more proteins involved in the transmission of signals between muscles and nerves, which leads to impaired muscle stimulation and causes muscle weakness and fatigue. The majority of neuromuscular junction diseases result from autoimmune targeting of junction components, although similar symptoms can be caused by toxins that disable neuromuscular junction enzymes. The

most common of these is myasthenia gravis (MG), which affects an estimated 7–20 in 100,000 individuals followed by Lambert-Eaton Myasthenic Syndrome (LEMS), which has a prevalence closer to 1 in 100,000 (see Appendix Exhibit A). The causes of MG and LEMS are not well understood, although genetic susceptibility to autoimmune disease is believed to contribute to both. Roughly half of LEMS cases are associated with cancer and are thought to be due to cross-recognition of junctional ion channels by tumor-targeted antibodies. Both disorders are typically adult-onset and lead to progressive weakness of slightly different muscle groups, with MG primarily affecting the eye, jaw and neck muscles whereas LEMS symptoms center on weakness in the legs and arms. Congenital myasthenic syndromes are rare, typically present during early childhood and are heterogeneous in severity and progression.

Peripheral nerve diseases include the hereditary neuropathies Charcot-Marie-Tooth disease (CMT) and giant axonal neuropathy (GAN), which are caused by abnormalities in the peripheral nerve structure that lead to impaired sensation, movement and other functions. Other hereditary motor sensory neuropathies also fall into this class. CMT is the most common of the inherited neuropathies, and global prevalence estimates typically land around 25 in 100,000,10,[10,24] with U.S. estimates closer to 40 in 100,000. There are several sub-types of CMT, each of which is associated with different gene mutations, contributing to variation in disease severity and trajectory. Prevalence of GAN is estimated to be much lower. Both CMT and GAN typically present during childhood or early adulthood but have differing natural histories. CMT progression is typically slow, confined to the peripheral nervous system and is not life threating, whereas GAN is associated with more rapid loss of muscle control, decline in cognitive function and shortened life expectancy.

THE NEUROMUSCULAR DISEASE HEALTHCARE PROVIDER SURVEY

Integrated throughout this report are insights gained from a survey of healthcare professionals focused on the care of patients with neuromuscular disease. The Neuromuscular Disease Healthcare Provider Survey, as it will be referred to in this report, was performed by the IQVIA Institute on behalf of the Muscular Dystrophy Association (MDA) from March through June of 2018. Ninety responses from 51 neurologists and 39 non-neurologists, including physical medicine and rehabilitation clinicians, neuromuscular nurses, nurse practitioners, physical therapists and social workers, were collected. Data represented within this publication reports the results across all respondents and care provider types rather than narrowing to a set of neurologists only, that typically serve as the key treating specialists. This decision was made based on an internal analysis that showed very similar averages and trends and opinions expressed, for care providers as whole in comparison to neurologists only.

Survey questions were designed to understand how patients are currently diagnosed and treated, and what the drivers are for healthcare providers when making decisions about patient care. In addition, respondents were asked to identify issues with current treatment options, including gaps in available treatments and barriers to helping patients access the best available care options. The Neuromuscular Disease Healthcare Provider Survey is intended to establish a benchmark across neuromuscular diseases, mapping current expert opinions on care standards, unmet needs and imminent advances. Future follow-up surveys will identify improvements made and outstanding needs in these areas, helping to map the impact of improvements in therapy options, data sources and scientific understanding.

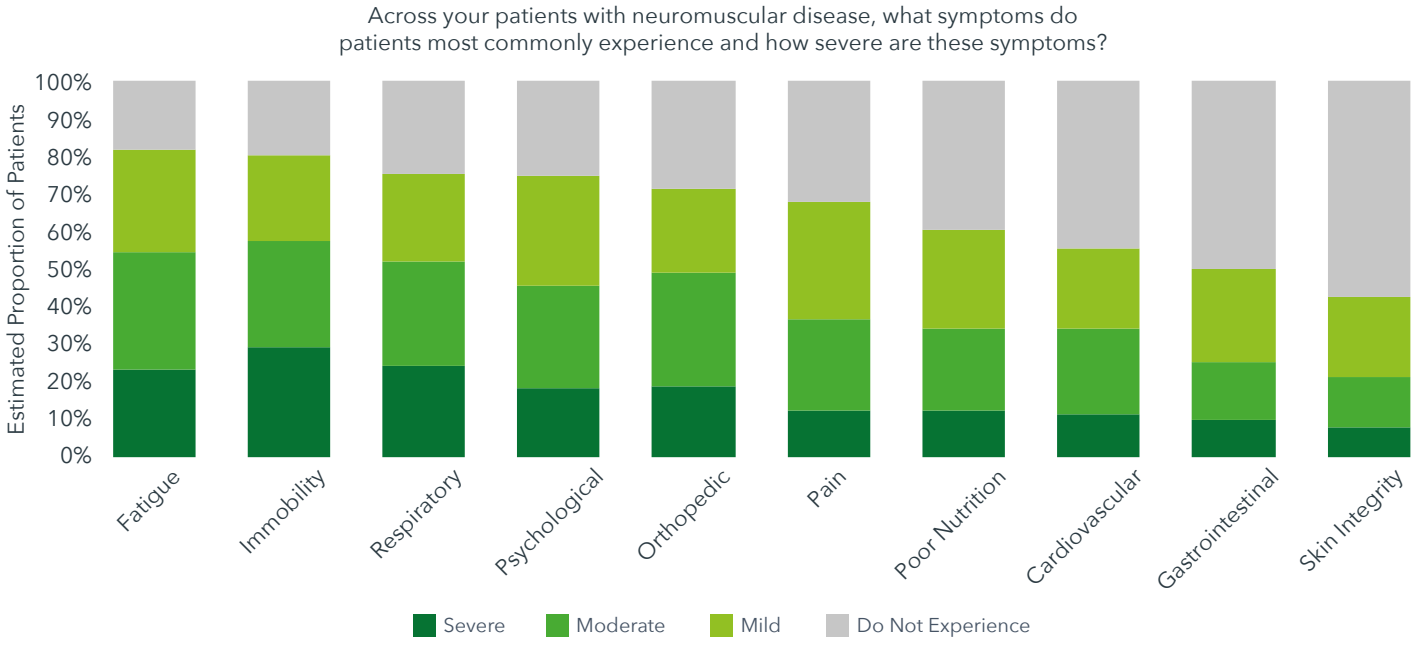
SYMPTOM LOAD ACROSS DISEASES

Neuromuscular diseases can manifest in a variety of common symptoms that require specialized care and close management: worsening ambulation, respiratory insufficiency, cardiac involvement, dysphagia, poor nutrition, fatigue and depression. Respondents to the Neuromuscular Disease Healthcare Provider Survey were asked to estimate the prevalence of specific symptoms among the patients they treat with neuromuscular disease (see Exhibit 3).

- The most prevalent symptom is fatigue, experienced by 82% of patients, and likely reflects limited treatment options for this issue, which is thought to have multiple drivers in neuromuscular disease.
- Immobility and respiratory symptoms are commonly associated with neuromuscular disease and are estimated to affect 80% and 75% of patients, respectively.
- Psychological symptoms are estimated to affect 75% of patients. As mental health issues comorbid with neuromuscular disease are being increasingly recognized, 60% of respondents notably rated the unmet need in managing psychological symptoms as high or medium-high (shown in Exhibit 10).

The signature symptom associated with neuromuscular disease is immobility that compromises dexterity and the ability to walk (ambulation), caused by progressive worsening of muscle function and weakness. In addition, some neuromuscular diseases can lead to the progressive shortening and hardening of muscles (contracture) and deformities. Patients with muscular dystrophies (e.g., DMD, BMD), or peripheral nerve disease (e.g., CMT) often develop contractures of the hands and feet, especially following loss of ambulation, and may also experience scoliosis. To prolong patient ability to walk and limit the number and severity of contractures, physiotherapy interventions are recommended as a standard treatment. Regular stretching of structures at risk of deformity, and in some cases, low-impact exercise (e.g., swimming, cycling) is recommended in DMD to delay progression.

Exhibit 3: Frequency in Symptom Severity Associated with Neuromuscular Diseases



Source: Neuromuscular Disease Healthcare Provider Survey, Jun 2018
Notes: Based on 88 respondents.

However, physiotherapy recommendations vary according to neuromuscular disease, especially regarding exercise, which is often controversial as it can exacerbate symptoms of some disorders. Therapies aimed at the maintenance of mobility also include assistive devices such as orthoses, serial casts and – as ability to walk decreases – wheelchairs. In DMD, patient ability to walk is also prolonged through use of steroids, which improve muscle cell repair and may decrease fibrosis-promoting inflammation. However, steroid treatments (particularly glucocorticoids) may result in bone weakening (osteotoxicity) and therefore contribute to an increased risk of orthopedic symptoms in DMD patients, such as patient propensity to fractures. These may also be compounded by nutritional deficiencies (see Exhibit 3).

Cardiovascular complications may arise when neuromuscular diseases affect the cardiac nerves or muscles in addition to skeletal muscles – their primary target. Lower overall prevalence of cardiac symptoms was noted by respondents to the Neuromuscular Disease Healthcare Provider Survey, as compared with other issues (see Exhibit 3), reflecting variation in the risk, severity and onset of cardiac complications across the different neuromuscular diseases. Cardiomyopathy and conduction defects with arrhythmias are most common, and genetic diagnosis is critical to predict the likelihood of cardiovascular symptoms for a given patient. For example, DMD, BMD and Friedrich's ataxia are associated with cardiomyopathy and heart failure, while Emery-Dreifuss muscular dystrophy (EDMD), some forms of LGMD and DM1 increase the risk of arrhythmia and sudden death.[25] Clinical guidelines recommend initial cardiac evaluation at time of diagnosis for patients with any neuromuscular disease, with ongoing cardiac monitoring varying in frequency and intensity depending on the disorder.[25] While therapeutic interventions are recommend in certain cases – such as with angiotensin-converting enzyme inhibitors, angiotensin receptor blocker therapies and β-adrenergic blockade – therapeutic use depends on the underlying disease.[25]

Respiratory difficulties typically appear later in disease progression as the oropharyngeal, diaphragm and intercostal muscles are affected. Weakness in the respiratory muscles is seen in advanced-stage neuromuscular diseases including muscular dystrophies (e.g., DMD, BMD, CMD), motor neuron diseases (e.g., ALS, SMA), mitochondrial myopathies and neuromuscular junction diseases (e.g., MG, LEMS).[26] This weakness, along with chest wall stiffness, leads to difficulty expanding the lung, increasing the potential for respiratory difficulties, and patients may experience difficulty swallowing (dysphagia) and chronic aspiration, where food or saliva is inhaled. Weakness in respiratory and abdominal muscles may also contribute to difficulty coughing.

Ongoing monitoring of respiratory function and timely intervention when difficulties begin is important for individuals with neuromuscular diseases. Clinical guidelines for DMD and ALS recommend close monitoring of respiratory function during disease development, through techniques such as measuring forced vital capacity (forcible exhalation as a measure of functional lung volume) and performing analysis of breathing patterns during sleep. Guidelines also advise the use of therapeutic techniques such as assisted coughing, lung volume recruitment and nocturnal assisted ventilation as certain thresholds are reached. Recent guideline updates have advocated for respiratory therapy use to commence earlier in disease progression, especially during sleep, to commence earlier in disease[27,28] as evidence that it improves quality of life, decreases long-term respiratory complications and prolongs survival has grown.

Gastrointestinal symptoms and associated nutritional issues are seen in some patients with neuromuscular disease, although they are typically less severe than other symptoms.[29] The importance of nutrition for maintaining muscle function and the need for standard nutritional guidelines to be adapted for neuromuscular disease patients are both well recognized, however robust research is required to enable an optimal diet tailored for each disease.[27,30] Patients may have difficulty with nutrition as a consequence of limited

mobility, weight gain or of treatment regimens; for example, glucocorticoids prescribed for DMD increase obesity risk. Alternatively, symptoms may be a direct result of disease. Patients with DM1 often experience gastrointestinal difficulties including difficulty swallowing as a result of weakness in oropharyngeal muscles and constipation due to ineffective peristalsis.[31] As stomach muscle tone is lost, delayed gastric emptying can lead to a loss of appetite and sensations of satiety, which can lead to individuals with neuromuscular disease being underweight. Dehydration, as a result of swallowing difficulties, in combination with loss of abdominal muscle tone, contributes to frequent constipation in individuals with neuromuscular disease.[27, 31] Treatment options for nutritional issues include dietary supplementation, pharmacological therapy to directly address gastrointestinal symptoms (e.g., constipation, nausea, satiety) and gastronomy tubes.

General fatigue is also common across neuromuscular diseases, and many of the symptoms already discussed are likely contributors, including disordered nocturnal breathing (e.g., sleep apnea), nutritional deficiencies and the elevated effort to perform daily tasks due to decreased mobility. Respiratory difficulties and heart failure may also contribute to fatigue. The multifaceted etiology of fatigue in neuromuscular disease precludes its easy resolution, but optimal management of the underlying causes, including proper ambulation assistive devices, may reduce its severity.

In addition to physical symptoms, some neuromuscular diseases including DMD, mitochondrial myopathies, DM1 and most syndromes that affect multiple organs, may also directly affect the central nervous system and lead to cognitive deficiencies. These symptoms are more often seen in childhood-onset forms of these disorders than adult-onset counterparts (where relevant), and treatment options are limited to supportive measures. As treatment paradigms improve, a larger number of young neuromuscular disease patients may find themselves attending mainstream educational facilities, and it will be increasingly important to understand how such central nervous system symptoms affect learning style and ability. For example, studies in DMD suggest that language processing ability may often be compromised, suggesting that a smaller classroom size and visual presentation of information is likely to be key for these patients.[32]

Cognitive impairments may result in multiple symptoms including personality change, irritability and executive dysfunction, with most ALS patients experiencing more than one of these effects and up to 20% experience a form of associated dementia.[33] Patients with adult-onset DM1 also frequently experience cognitive difficulties, including daytime sleepiness, and executive and visuospatial dysfunction. For both ALS, and DM1, cognitive difficulties are linked to damage to the central nervous system.[34,35] In general, treatment options for cognitive impairment are limited, and these symptoms typically progress with the overall disease.

In addition to direct cognitive effects, the challenges of living with neuromuscular disease also has psychological ramifications for many patients, along with their family members and caretakers. Decreasing ability to keep up physically with daily life, coupled with isolation, uncertainty about the future and pervasive fatigue, contribute to heightened risk of depression in neuromuscular diseases including DMD and ALS, mirroring the risks seen in individuals diagnosed with other chronic illnesses.

Disease burden and costs associated with neuromuscular diseases

- Neuromuscular disease patient burden is considerable, with up to 420,000 healthy years of life estimated to be lost annually in the United States.
- Total estimated economic burden is significant, ranging from $450 million per year for myotonic dystrophy to $1.03 billion per year for amyotrophic lateral sclerosis.
- Direct medical costs are estimated to account for over half of all costs related to neuromuscular diseases, driven by outpatient care.
- Analysis of healthcare charges across all neuromuscular diseases indicates annual medical expenditure in excess of $46 billion.
- Healthcare charges per patient range considerably within disease groups, and annual expense exceeds $40,000 for the upper quartile of patients with diagnoses across most diagnosis groups, with median estimates between $10,000 and $20,000.
- In general, costs associated with neuromuscular diseases are not well understood, highlighting a need for additional research particularly in measuring indirect costs, such as loss of income for patients or caregivers.

DISEASE BURDEN

The overall burden of disease is significant for neuromuscular diseases, whether it is measured by associated morbidity, mortality or economic costs. The number of healthy years of life lost to neuromuscular disease (measured in disability-adjusted life years, DALYs) across the U.S. population in 2016 was 200,000–420,000,[36†] indicating the significant detrimental impact of these disorders, despite their low prevalence. These findings align with the identification of muscular dystrophies as among the top three most burdensome childhood health conditions,[37] as a result of the considerable functional difficulties faced by children with muscular dystrophy.

Quality of life for individuals with neuromuscular disease is varied. The direct impact of disease symptoms has already been discussed, but there is also significant indirect impact on life trajectory. For example, individuals with neuromuscular disease often find it challenging to continue their education. Although an estimated 48% of SMA patients are able to obtain college or post-graduate education, which exceeds that of the general population (approximately 31%), this compares to only 11–20% and 16–18% of DMD and DM patients, respectively.

Estimates of symptom burden and disease impact on quality of life are challenging to quantify but are increasingly referenced during drug development and review. Indeed, the FDA's Patient-Focused Drug Development (PFDD) initiative actively seeks input from patients on symptom burden and impact of quality of life[40] and publishes findings in 'Voice of the Patient' reports. To date, PFDD meetings have gathered accounts from patients with SMA, Friedreich's ataxia (FA), CMT, and Myotonic Dystrophy, reflecting a desire to systematically collect patient perspectives and integrate them into the drug review process, at

† Upper bound represents combined DALYs for motor neuron disease and 'other neurological disorders', a broad category which includes all other neuromuscular disorders as well as Huntington's disease

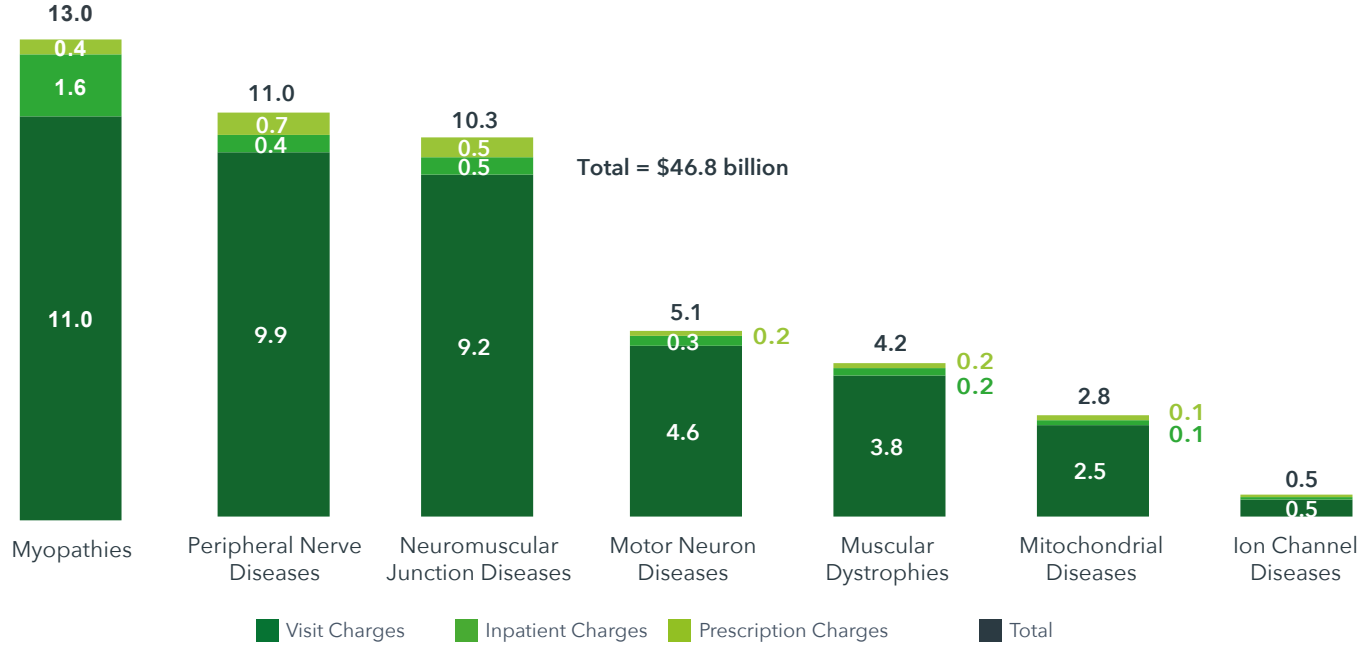
some level. As new disease-modifying therapies are developed, the development of standard frameworks to analyze cost effectiveness in rare disease – an ongoing topic of research and debate – will become increasingly important, as regulatory bodies and healthcare systems attempt to understand the relative merits of new therapy options in addressing disease burden, versus their potential economic impact. The applicability of standard value assessment criteria, such as QALYs (quality-adjusted life years), which considers both the quality and the quantity of life lived for patients, is a current topic of conversation among drug developers, payers and patient organizations.

TOTAL ECONOMIC BURDEN

Given the progressive nature of neuromuscular diseases and symptoms that require intensive monitoring and management, the associated costs can be a significant burden to patients and their families, as well as the healthcare system more broadly. There is limited research on total costs – which include the direct medical costs, nonmedical costs (e.g., transportation, home modifications) and indirect costs (e.g., loss of income) – associated with neuromuscular diseases in the United States, despite an increasing interest in understanding overall burden to better assess the impact of new therapies.

Although few estimates of the total national economic burden have been made for individual neuromuscular diseases, those that exist range between $448 million per year for DM to $1.03 billion per year for ALS, with over half of these driven by the direct medical costs associated with these diseases.[41] One moderate estimate of annual costs in the United States for four neuromuscular diseases – DMD, ALS, DM1 and SMA – totaled $3.2 billion, including medical, non-medical and

Exhibit 4: Average Total Annual Medical Charges per Disease Group, Un-projected Data US$Bn



Source: IQVIA Real World Data (RWD) including Medical Claims and Prescription Datasets, July 2018; IQVIA Institute, July 2018
Notes: Shows the average of annual un-projected medical charges for two years Jul 2015-Jul 2017. Total charges depicted per disease group are driven by both the number of patients as well as cost per patient. Excludes some costs such as those for over-the-counter medicines that would not go through claims processing. Total annual charges for the entire U.S. population are expected to be higher, while adjudicated costs may be higher or lower than depicted. Un-projected Medical Claims Data is estimated to represent 60% of patients in the United States. Unadjudicated charges exceed amount reimbursed by payers, and are estimated to range from 40-60% depending on payer type. Prescription charged are estimated to represent 90.2% of the U.S. market across retail, mail, and long term care channels of distribution. Methodologically, if any patients had multiple diagnoses within two or more disease groups, their charges would be counted once in each group.

indirect costs.[38] These figures represent a significant cost for a small proportion of the overall population.

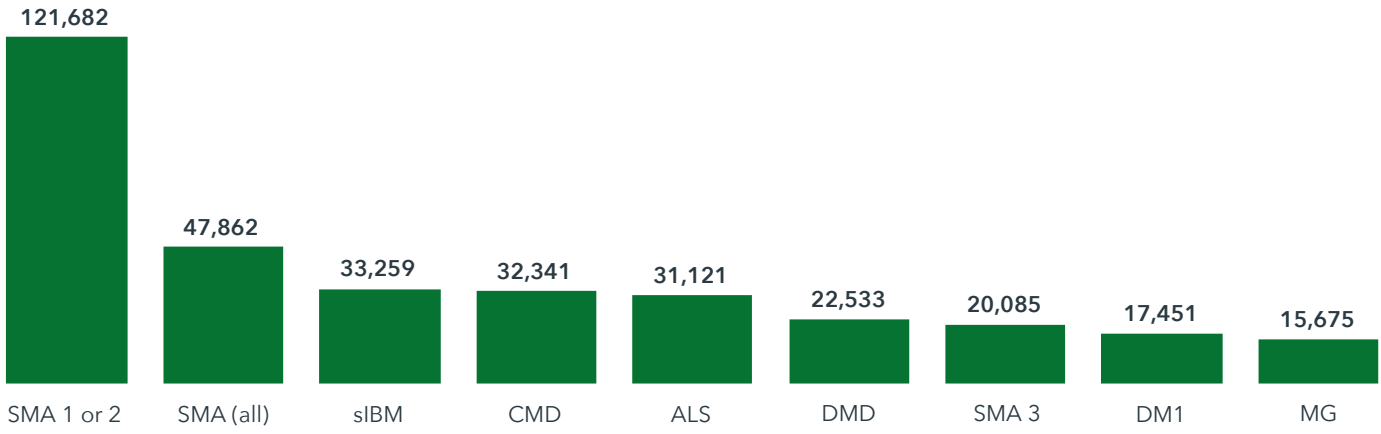
Since published findings cover only a small number of the total neuromuscular diseases, they are thus certainly an underestimate of the total national burden of these diseases. To explore further, an analysis of the charges in IQVIA Real-World Data associated with medical care for neuromuscular diseases was performed (see Methodology) and showed total medical charges in the United States that greatly exceeded estimates published to date (see Exhibit 4). Across all considered disease groups, annual charges totaled more than $46 billion, with neuromuscular junction disorders, peripheral nerve diseases and myopathies each accounting for more than $10 billion in charges. Even accounting for likely downwards negotiation of these charges during adjudication, the amounts are considerable. Further research is needed to better understand the non-medical costs associated with neuromuscular diseases, which are not quantifiable through claims analysis.

Direct medical costs

Among the direct medical costs of managing neuromuscular disease, published research identifies outpatient care as the largest cost driver. This includes outpatient visits, physician visits, and physical and occupational therapy.[38,41] Interestingly, estimates that break down direct medical costs into their components find that prescription medications are responsible for only a small fraction of these (5% or less).[42,43] This is likely due to the historical lack of approved therapies to treat these diseases, and generics accounting for the majority (>95%[44]) of medications used. In line with published research, this analysis of IQVIA Real-World Data found outpatient visits to be the greatest contributor to direct medical charges, accounting for 89% of total charges across all diagnosis groups (see Exhibit 4).

High annual per-patient medical costs are seen across individual neuromuscular diseases in reported estimates (see Exhibit 5). Unsurprisingly, diseases with a greater symptom burden are typically associated with higher overall costs. In the United States, estimated

Exhibit 5: Published Estimates of Annual Per Patient Healthcare Costs Across Neuromuscular Diseases US$



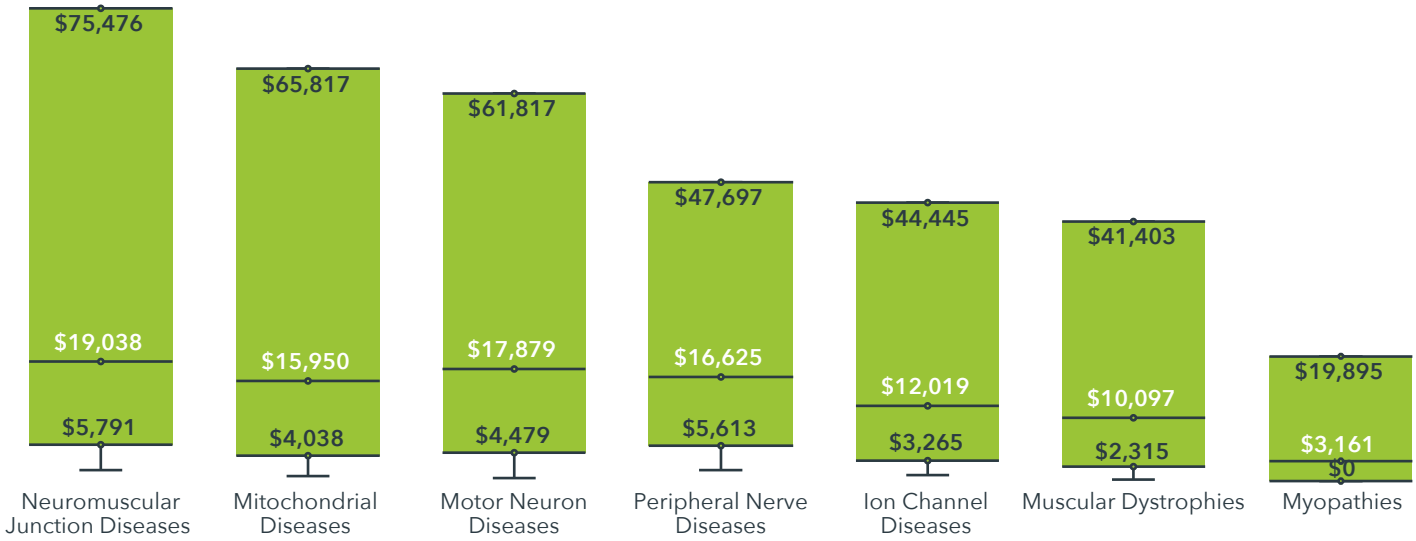
Source: Larkindale J, Yang W, Hogan PF, Simon CJ, Zhang Y, Jain A, et al. Cost of illness for neuromuscular diseases in the United States. Muscle Nerve. 2014 Mar;49(3):431-8. Armstrong EP, Malone DC, Yeh WS, Dahl GJ, Lee RL, Sicignano N. The economic burden of spinal muscular atrophy. J Med Econ. 2016 Aug;19(8):822-6. Guptill JT, Sharma BK, Marano A, Soucy A, Krueger A, Sanders DB. Estimated cost of treating myasthenia gravis in an insured U.S. population. Muscle Nerve. 2012 Mar;45(3):363-6. Capkun G, Callan A, Tian H, Wei Z, Zhao C, Agashivala N, Barghout V. Burden of illness and healthcare resource use in United States patients with sporadic inclusion body myositis. Muscle Nerve. 2017 Nov;56(5):861-867. The Lewin Group. Cost of Amyotrophic Lateral Sclerosis, Muscular Dystrophy, and Spinal Muscular Atrophy in the United States. 2012 Mar 1. Available from: https://www.mda.org/sites/default/files/Cost_Illness_Report_0.pdf.
Notes: Estimates are based on annual costs in time frames are all between 2008 and 2012. Estimates from SMA1 or 2, and SMA3 come from the Lewin group. Estimate for SMA overall comes from Armstrong et al. SMA = spinal muscular atrophy; sIBM = sporadic inclusion body myositis; CMD = congenital muscular dystrophies; ALS = amyotrophic lateral sclerosis; MG = Myasthenia gravis; DMD = Duchenne muscular dystrophy; DM1 = myotonic dystrophy type 1.

total annual per-patient medical costs for ALS range from $27,841 to $31,766 based on insurance coverage, with Medicare costs estimated to be highest.[38,41] Costs associated with DM have been reported to be around $17,451 to $17,592 annually per patient.[38] Studies estimate annual per-patient medical costs for DMD as $22,533–$24,122,[38,45] roughly 10 times the costs of unaffected individuals. Costs increase an estimated 16-fold between early ambulatory and late non-ambulatory stages, reaching $40,132 for non-ambulatory patients 14–29 years of age.[43] Medical costs for DMD are likely underestimated because DMD and other muscular dystrophies share a diagnosis code (in both ICD-9 and ICD-10), and DMD is among the most severe. Costs for BMD, another muscular dystrophy, are approximately a quarter of those for DMD.[43] The annual per-patient healthcare expenditure of an individual with SMA has been reported at $47,862 in the United States, although the range is considerable ($24,845–$201,420, 25th–75th percentile).[42] Release of novel disease-modifying treatments have already begun to increase overall costs considerably for subsets of patients in both SMA and DMD.

Importantly, data analyzed to date (previously published or herein), mostly pre-dates the approval of novel high cost therapies, indicating that prescription costs are likely to rise considerably as these therapies are approved (see sidebar, Rising Prescription Costs for Neuromuscular Diseases). It remains to be seen what effect these therapies will have on overall healthcare expenditure.

These findings are supported by the analysis of IQVIA Real-World Data for each of the different diagnosis groups of neuromuscular diseases (see Exhibit 6), which show high median annual per-patient costs across all diagnoses. Notably, annual per-patient costs range considerably within a disease group, as well as for each individual disease (see Appendix Exhibit B), reflecting the heterogeneity in treatment. Annual medical expenses across neuromuscular disease groups range significantly but are likely to be upwards of $40,000

Exhibit 6: Median and Quartile Annual Medical Charges Per Patient for Neuromuscular Diseases



Source: IQVIA Real World Data (RWD) including Medical Claims and Prescription Datasets, July 2018; IQVIA Institute, July 2018

Notes: Shows the average of annual un-projected medical charges for two years Jul 2015-Jul 2017. Total annual charges for the entire U.S. population are expected to be higher, while adjudicated costs may be higher or lower than depicted. Un-projected Medical Claims Data is estimated to represent 60% of patients in the United States. Unadjudicated charges exceed amount reimbursed by payers, and are estimated to range from 40-60% depending on payer type. Prescription charged are estimated to represent 90.2% of the U.S. market across retail, mail, and long term care channels of distribution. Green bar denotes 25th-75th percentile for annual total charges for one patient. Horizonal line shows median annual per patient charges. Lower whisker shows 10th percentile. 90th percentile not shown due to large range, available in Appendix Table 2; Analysis was performed at the diagnosis code level and rolled up to their disease grouping. Methodologically, if any patients had multiple diagnosis codes, then the patient charges would be included within the analysis for both codes and would be therefore represented more than once. This resulted in only a minimal impact on data presented. Excludes some costs such as those for over-the-counter medicines that would not go through claims processing.

RISING SPEND ON PRESCRIPTIONS FOR NEUROMUSCULAR DISEASE

Of current direct medical costs for neuromuscular diseases, approximately 5% is currently attributed to prescription costs. However, the approval of new therapies in recent years is having a noteworthy effect on the pharmaceutical costs associated with neuromuscular disease treatment. The prospect of additional breakthrough therapies where none exist today, in combination with relatively small patient populations for these diseases, suggests that prices for emerging neuromuscular disease therapies may be high. This trend is not unique to neuromuscular disease; the average cost per patient for medications for orphan indications was recently estimated to be five times higher than for non-orphan indications.[46]

Nusinersen (Spinraza) was the first approved therapy for SMA to show an effect on disease progression. Following the launch of the therapy, the cost associated with use of medications for SMA increased dramatically, with Biogen reporting 2017 annual revenues of more than $650 million from nusinersen sales in the United States.[47] Before the release of nusinersen, annual prescription expenditure for SMA was less than 4% of this figure,[48,49] demonstrating the dramatic impact of a disease-modifying therapy for an orphan condition. Almost 2,000 U.S. patients are now receiving the medicine. The first year of treatment with nusinersen includes loading doses that double the annual cost when compared with subsequent years, which may account for some of this dramatic increase, however, with new patients continuing to start therapy, any drop in cost from existing patients is likely to be offset.

Within DMD treatments, approval of eteplirsen (Exondys 51) has had a more modest effect on overall expenditure, in part due to the smaller number of patients for whom the therapy is applicable. Company-reported U.S. revenues for eteplirsen in 2017 were $155 million, however 2018 revenues look set to triple this figure.[48] Approval of the glucocorticoid deflazacort (Emflaza) for DMD has also had an impact on the price of treatment for most DMD patients. With five or more other antisense or gene therapies in clinical trials – several of which would expand the pool of patients for whom disease modifying medications are available – the overall cost of prescriptions for DMD is set to increase dramatically over the next few years.

The impact of approval of eculizumab (Soliris) on the cost of treatment for MG is less clear, but an uptick in sales of the medication of around 12% following approval for MG suggests that around $50 million of sales were for neuromuscular patients in 2017.[44]

As more disease modifying therapies come onto the market, questions are increasingly asked about whether the healthcare budget can accommodate such dramatic changes. In an ideal world, curative therapies would justify their high list prices by almost completely offsetting other costs, including nonmedical and societal burden. However, for intermediary options that modify disease trajectory, the assessments may be more complex. Within the United States, there has historically been a high tolerance for the price tags of medications for rare diseases, or those that dramatically alter disease trajectory, but reception outside the United States has been subject to stricter criteria or additional budget concerns, exemplified by U.K. restrictions on curative hepatitis C medications as a result of budget concerns and a 30–60% reimbursement rate in Europe for orphan medications that obtain regulatory approval.[50]

annually for the upper quartile in many disease groups, with median estimates between $10,000 and $20,000.

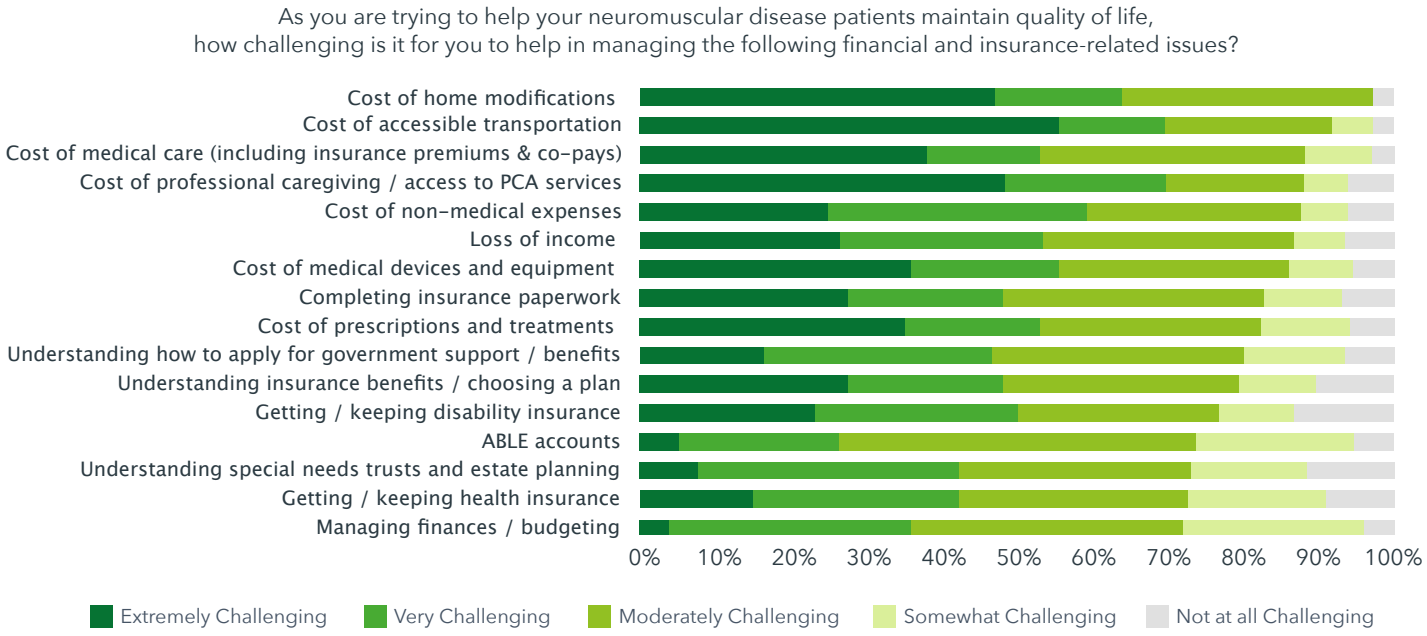
Nonmedical and indirect costs

Research focused on nonmedical costs, such as home modifications, transportation and paid caregiver support, and indirect costs, such as loss of income, is very sparse. However, it is well known that nonmedical costs and indirect costs for families and caregivers represent an enormous financial burden. Patients require increasing support from caregivers as a neuromuscular disease progresses in severity, sometimes requiring full-time care to move, eat and perform other basic functions. One study found that anxiety and depression among caregivers of DMD patients was significantly associated with annual household cost burden and time spent on providing informal caregiving to their family member,[49] which can be considerable. An estimated 50% of individuals with ALS, DMD, SMA or DM required 16 or more hours of care per day. In the United States, difficulty with access to government support programs is often associated with administrative hurdles and delays that may compound these problems.

Survey respondents confirmed that finance and insurance-related issues are particularly challenging to manage (see Exhibit 7):

- Every insurance or financial issue listed was considered as at least somewhat challenging to help manage by more than 65% of healthcare providers.
- 'Non-medical' expenses, such as accessible transportation and home modifications, were considered as the most challenging to help manage. This likely reflects a decreased familiarity of healthcare providers with available programs to assist with such costs and a possible shortage of such programs, which are almost certainly predominantly philanthropic.

Exhibit 7: Challenges Associated with Helping Patients with Financial Issues



Source: Neuromuscular Disease Healthcare Provider Survey, Jun 2018
Notes: Based on 38 respondents.

- Health insurance-related issues are generally ranked as less challenging to help with when all neuromuscular diseases are considered together, although this assessment may change as treatment options shift away from generics towards new high-cost disease-modifying treatment options that may be subject to prior authorization controls and/or have significant co-pays.

Families and caregivers frequently seek support and guidance from healthcare providers, advocacy groups or patient assistance programs to manage, and help them navigate, the growing costs they face. Anecdotally, providers frequently mention that substantial time is spent within a multidisciplinary clinic visit to discuss the nonmedical needs that arise for patients and their caregivers. One study found that early-onset SMA (diagnosed before age three) was associated with the highest annual nonmedical costs of $51,665, driven by the need for full-time intensive care of the patient at home.[38] Other neuromuscular diseases were associated with notable nonmedical costs, including $12,939 for DMD and $17,880 for ALS, driven primarily by home modification needs and costs associated with food and travel.[38] The additional indirect costs associated with neuromuscular diseases pertain to loss of income for families with a person affected by a neuromuscular disease. The weighted loss of income for families affected by a neuromuscular disease is highest for early-onset SMA at $17,759, followed by $15,481 for DMD and $14,682 for ALS.[38] As expected, indirect costs are higher in cases when more than one family member is affected by a neuromuscular disease, the duration of disease, and when the primary earner is affected by the disease.

Current and evolving approaches to care

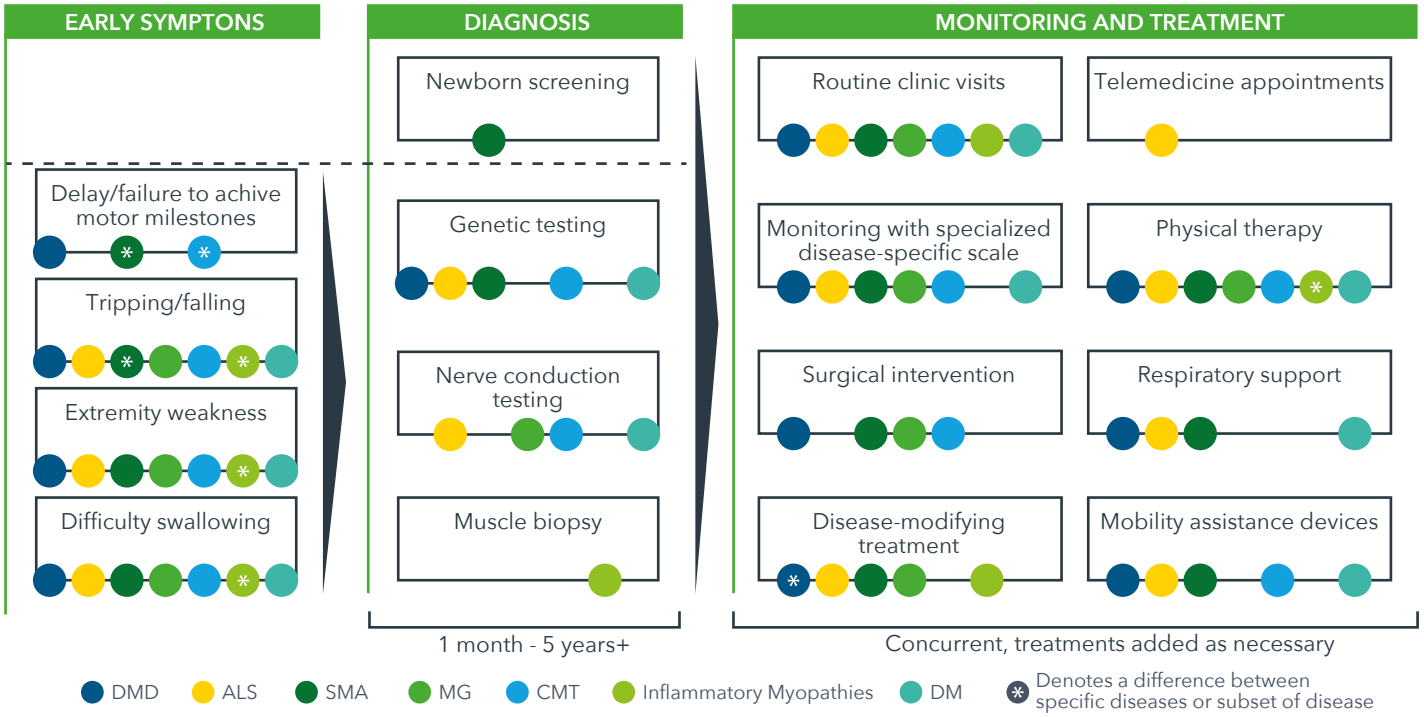
- The lag between a patient's manifestation of symptoms and their diagnosis with a neuromuscular disease is often more than a year.
- Advances in genetic testing have transformed diagnosis for many conditions and is employed consistently by neurologists for BMD, DMD, LGMD and SMA.
- A multidisciplinary care team approach is usually used for disease management due to the range of symptoms involved.
- Care approach is often variable with clinicians leveraging a range of information sources and expertise to inform their treatment decisions.
- Official care guidelines are only available for a subset of diseases and are not universally employed.
- Psychological issues stand out as a prevalent problem; more than 90% of Neuromuscular Disease Healthcare Provider Survey respondents recognize high unmet need in this area and more than 50% find access to a mental health professional extremely challenging.
- Insurance restrictions pose the largest issue for the initiation of disease-modifying therapy, with more than 70% of Neuromuscular Disease Healthcare Provider Survey respondents reporting it is often a barrier.

VARIATION IN THE NEUROMUSCULAR PATIENT JOURNEY

The health journey of a neuromuscular disease patient varies by disease and by individual, with differences in the time from first symptom appearance to diagnosis, as well as the approach taken to diagnose, treat and monitor their condition (see Exhibit 8). Genetic screening is an option for many neuromuscular diseases. Newborn screening is also recommended for a handful of neuromuscular diseases. Pompe disease, spinal muscular atrophy (SMA), and carnitine palmitoyltransferase deficiency (a metabolic myopathy), are all included on a national core panel of diseases for which testing is recommended for newborns in the United States (Recommended Uniform Screening Panel, RUSP). Within these diseases, diagnosis may therefore occur very early, with disease management spanning the patient's lifetime. However, even for these conditions testing does not always occur. The RUSP serves only as a recommendation and individual states ultimately make their own choice about whether to screen for recommended diseases. For the remainder of the neuromuscular diseases, diagnosis is frequently delayed, as early symptoms such as delayed development (childhood-onset), tripping and falling, or muscle cramps (adult-onset), may not immediately be recognized as unusual.

Following diagnosis, care management and treatment strategies again vary by disease and by individual. Diversity in treatment approach is caused by many factors including disease subtype, inter-individual variability in symptom or disease progression, ambiguity in treatment guidelines and differences in patient access to care. Most, but not all, neuromuscular diseases are

Exhibit 8: Patient Journey from Symptom Presentation Through Disease Monitoring



Source: Neuromuscular Disease Healthcare Provider Survey, Jun 2018; NIH Genetics Home References, NIH Factsheets, MDA Disease Information
Notes: Number of respondents to this question varies by disease: n = 10–31. Information is exemplary of a typical patient journey and is not intended to be exhaustive in nature. DMD = Duchenne muscular dystrophy; ALS = amyotrophic lateral sclerosis; SMA = spinal muscular atrophy; MG = myasthenia gravis; CMT = Charcot-Marie-Tooth disease; DM = myotonic dystrophy. Diseases included span the subset of diseases included in the Neuromuscular Disease Healthcare Provider Survey and are not comprehensive.

progressive, and treatments and interventions are modified or added as symptoms require.

THE DIAGNOSTIC ODYSSEY

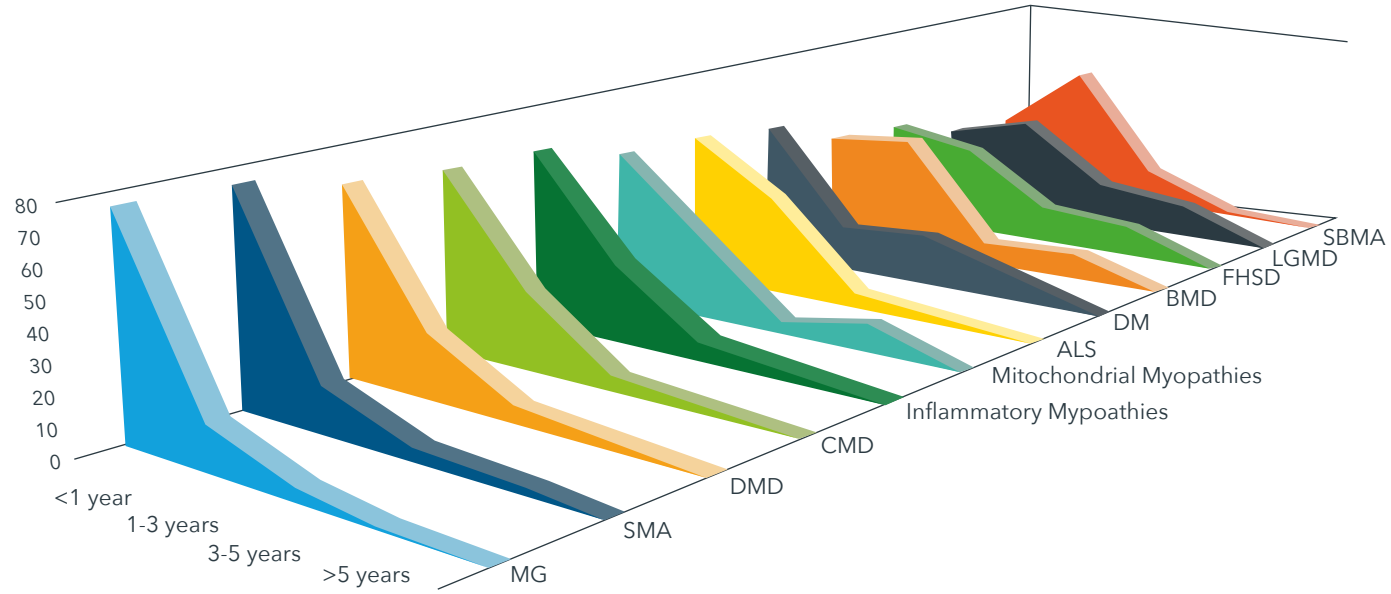
Confirming a diagnosis of a neuromuscular disease can be challenging given the variations in genotypes and clinical manifestation. It may take time to rule out other conditions that can cause patient symptoms such as weakness and fatigue. For some individuals, a definitive diagnosis is never established.

Reflecting these challenges, the Neuromuscular Disease Healthcare Provider Survey respondents indicated a lag between initial symptoms and diagnosis (see Exhibit 9):

- Variation exists in the speed of diagnosis, both between diseases and within a disease area, with it often taking years before a definitive diagnosis is made.
- MG and SMA are the most rapidly diagnosed diseases, with 75% of patients being diagnosed within one year following initial symptom appearance.
- The existence of a diagnostic genetic test does not always lead to more rapid diagnosis; 25% of patients with FSHD and LGMD are diagnosed only after three or more years.
- Notably, for every disease covered by the Neuromuscular Disease Healthcare Provider Survey, at least a small percentage of cases were estimated to take more than five years to diagnose.

Exhibit 9: Average Time between Initial Symptoms and Diagnosis

How much time elapses on average between initial symptoms of the disease and the confirmation of diagnosis by your practice?



Source: Neuromuscular Disease Healthcare Provider Survey, Jun 2018
Notes: Number of respondents to this question varies by disease: n = 10–31. MG = Myasthenia gravis; SMA = spinal muscular atrophy; DMD = Duchenne muscular dystrophy; CMD = congenital muscular dystrophies; ALS = amyotrophic lateral sclerosis; DM = myotonic dystrophy; BMD = Becker muscular dystrophy; FHSD = facioscapulohumeral muscular dystrophy; LGMD =limb-girdle muscular dystrophy; SBMA = Spinal-bulbar muscular atrophy.

Survey findings align with existing literature regarding difficulties in neuromuscular disease diagnosis. A recent study found that 48% of patients with a mitochondrial disease consulted more than five physicians before receiving a diagnosis. Further, over 50% of these patients were misdiagnosed initially, with a psychiatric disorder, fibromyalgia, chronic fatigue syndrome or other non-mitochondrial diagnoses.[52] Similarly, neurologists responding to the Neuromuscular Disease Healthcare Provider Survey indicated that approximately 45% of patients were referred from another specialist, and that over 30% of patients had had no diagnostic test performed prior to referral.

Once a neuromuscular disease is suspected, several steps are involved in confirming a diagnosis. Initially, patients are evaluated on physical exam and serum enzyme tests are conducted. These are blood tests used to measure levels of specific enzymes, such as serum creatine kinase in DMD, which can indicate whether muscle damage is occurring. Electrodiagnostic studies, which record the electrical activity in muscle cells (electromyography) or nerve cells (nerve conduction studies), are used to distinguish between myopathies, neuropathies and neuromuscular junction diseases based on the location and circumstances of abnormal electrical activity.[53] Distinguishing features can also be found with muscle biopsies, although diagnostic value can be limited in disorders with an underlying genetic component. In those cases, if physical exam and blood tests suggest a neuromuscular disease, clinical guidelines recommend targeted genetic testing to confirm diagnosis.[54,55] However, despite advancements in the understanding of genetic contributors to disease, and declining costs for both genetic testing and genome sequencing, these tests have not been universally adopted.

Overall, the Neuromuscular Disease Healthcare Provider Survey found that, in addition to variations in the time to reach a definitive diagnosis, there is also considerable variation in the approach providers take to reach a diagnosis, with respondents almost always employing several techniques to triangulate in on a diagnosis:

- One hundred percent of surveyed neurologists who self-identify as BMD, DMD, LGMD or SMA experts employ genetic testing for diagnosis. This falls to 94% for CMT and 85% for DM1.
- Additional diagnostic techniques, such as blood tests and nerve conduction studies, are consistently used in conjunction with genetic testing, reflecting a need to understand disease progression and severity that cannot be inferred directly from genetic results.
- Approach to diagnosis of diseases lacking consistent genetic causes are often varied. For example, in the diagnosis of DM, a large range of diagnostic techniques (genetic testing, nerve conduction studies, muscle biopsy, blood tests, nerve biopsy) are employed by at least one responding neurologist, but all are employed by fewer than 80%.

CURRENT CARE MANAGEMENT APPROACHES

Once diagnosed, a patient is managed by a neurologist and a care team that includes a wide range of specialists. This team typically manages the varied clinical features and multiple organ involvement typically seen with neuromuscular diseases. Historically, the bulk of care for neuromuscular diseases centered on the treatment and minimization of symptoms, maintaining patient function and comfort as long as possible.

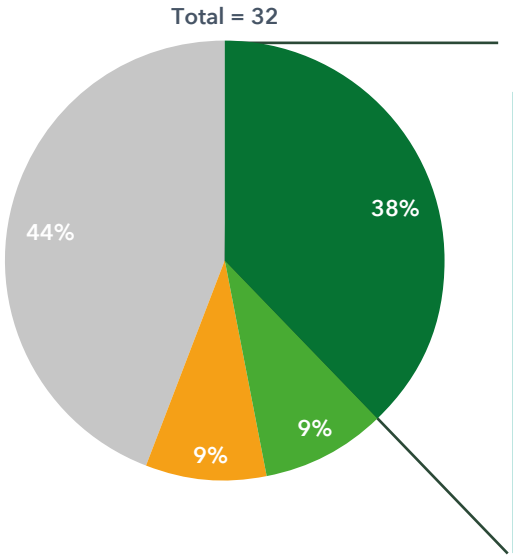
Increasingly, care for neuromuscular disease patients is facilitated through a multidisciplinary care team approach, delivered through specialized multidisciplinary care clinics,[56] which allows patients to consolidate visits to a range of specialists, often within one day. These approaches now represent the standard of care and have support from professional organizations in SMA[57], ALS[58] and muscular dystrophies.[59,60,61] These recommendations reflect findings that care in multidisciplinary clinics has benefits for patients including improved quality of life,[62] extended overall survival[63] and better health outcomes, including reduced hospital visits.[64]

The Neuromuscular Disease Healthcare Provider Survey showed that the factors that influence approach to care for a given disease vary across respondents and across diseases:

- Severity of disease progression is the most highly ranked as a factor influencing care approach overall, however, at the disease level this varied; 92% of healthcare providers included disease severity among the top three factors influencing their care approach to inflammatory myopathies compared to 57% for LGMD.
- Other factors consistently ranked as highly influential include ambulation status, past experiences with other patients and patient age, although the influence of these factors vary by specific disease.
- Although disease diagnosis (based on clinical and/or genetic features) is generally considered to be important for determining care approach, genetic diagnosis is not consistently ranked among the top three influencers – even for diseases with consistent genetic causes. For DMD and SMA, only 42% and 52% of providers, respectively, rank genetic diagnosis among their top three influencers.

Despite similarities in patient symptoms across various diseases, appropriate symptom-assessment approaches and specific care recommendations for a given patient are, in part, informed by the patient's genotype and an understanding of its associated relative risk, highlighting the importance of gaining an accurate genetic diagnosis as early as possible.

Exhibit 10: Guidelines for the Care of Neuromuscular Disease Patients



DISEASE	YEAR UPDATED
Amyotrophic lateral sclerosis (ALS)	2009
Andersen-Tawil syndrome	2017
Congenital muscular dystrophies (CMD)	2015
Duchenne muscular dystrophy (DMD)	2018
Facioscapulohumeral muscular dystrophy (FSHD)	2015
Friedreich's ataxia (FA)	2014
Hyperkalemic periodic paralysis	2017
Hypokalemic periodic paralysis	2017
Lambert-Eaton myasthenic syndrome (LEMS)	2010
Limb-girdle muscular dystrophies (LGMD)	2014
Myasthenia gravis (MG)	2016
Spinal muscular atrophy (SMA)	2018

Official Guidelines Available | Published Guidelines Available, Not Consensus | Reviews Indicate Insufficient Evidence for Recommendations | No Standardized Guidelines Available

Source: See Endnotes 20, 26-27, 29-38

In the future, genetic diagnosis may become more important for healthcare providers in determining care approach as the use of therapies targeted to a genetic subpopulation becomes more routine.

In addition to the factors influencing care approaches highlighted by the Neuromuscular Disease Healthcare Provider Study, published care guidelines provide recommendations to providers for the management of a growing number of neuromuscular diseases (see Exhibit 10). For a subset of diseases, specialized scales for symptom tracking have also been developed.[27,54,55,65-73] The increasing availability and use of such care guidelines and symptom scales reflect efforts to standardize care based on the best available evidence and thereby reduce morbidity and mortality associated with these disorders.

Within the multidisciplinary care team approach to the management of neuromuscular diseases, patients are monitored periodically to measure disease progression and quality of life, and to update symptom management strategies. On average, patients are seen every six months, but frequency depends on the disorder and its severity, with ALS patients evaluated every three months. Overall, Neuromuscular Disease Healthcare Provider Survey respondents estimate that patients attend clinic visits once less per year than they consider ideal. Increasing use of emerging technologies for remote care monitoring may facilitate an increased cadence of care, especially for patients for whom travel is long-distance or especially difficult and is discussed in 'Future Prospects'.

Visit duration varies depending on the disease and its severity, with visits lasting an average of two to three hours but ranging up to a full day (eight hours), and for which patients may travel hundreds of miles. Although the multidisciplinary care approach has been shown to improve quality of care and outcomes for patients, the length of the typical clinic visit is a challenge for both the clinic as well as patients and their families. Tests and assessments recommended in care guidelines are contributors to a lengthy clinic visit. The time burden of following care guidelines is an important consideration

for both patient and clinician, especially as quality of care provided may be benchmarked against whether all guidelines are followed.

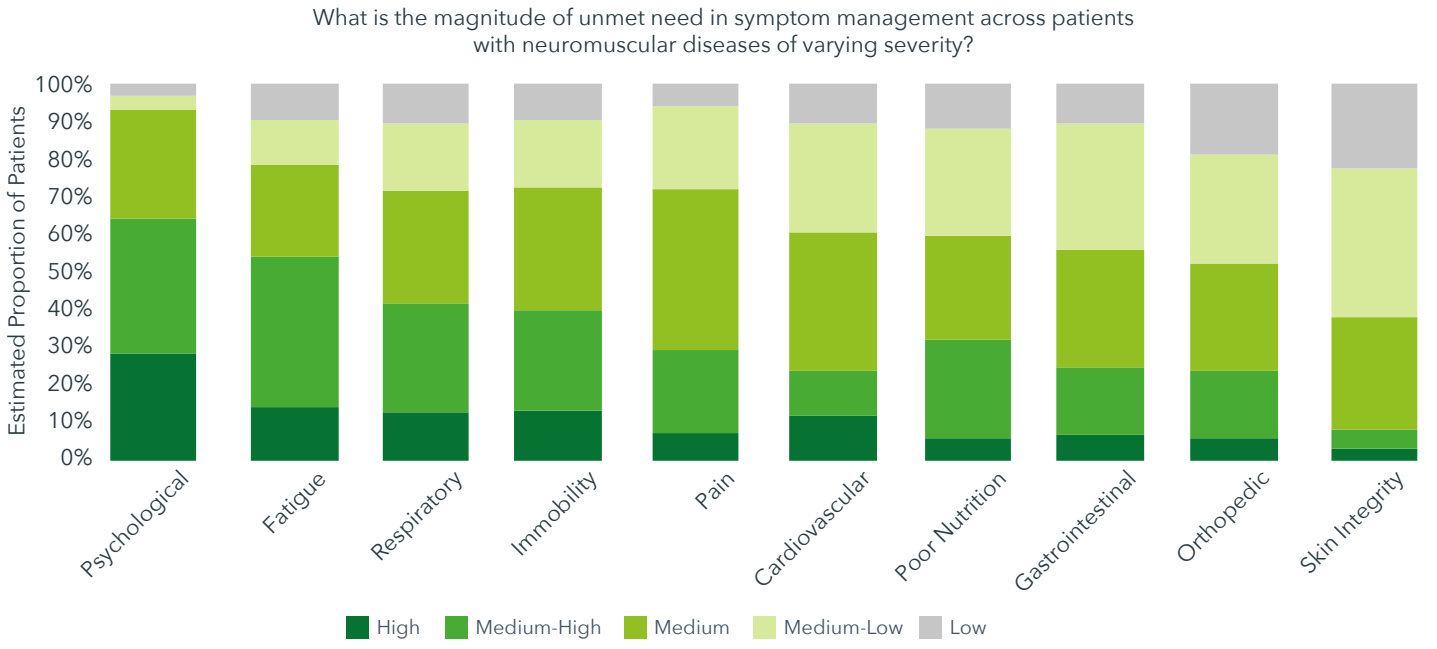
> *"If all assessments recommended in the guidelines were completed, a clinic visit would last for eight hours. We need to shift the focus back towards the patient and their immediate needs*
>
> *Katherine D. Mathews, MD*
> *Director, Iowa Neuromuscular Program*
> *Director, Muscular Dystrophy Clinic,*
> *University of Iowa Health Care*

In addition to their roles in disease management, care centers also play a significant role in providing support to families and reducing caregiver burden through the provision of genetic counseling, family support groups and other wrap-around services. Networks of dedicated multidisciplinary clinics provide a substantial infrastructure for patients diagnosed with neuromuscular disease[56] as do a multitude of non-profit organizations. These range in size and coverage from disease-specific or local support groups to larger, national, umbrella organizations that cover a large group of neuromuscular diseases, providing patients and caregivers with many options.

KEY CHALLENGES IN NEUROMUSCULAR DISEASE CARE

The complex symptoms of neuromuscular disease and incomplete standardization of guidelines can make patient care challenging, even for experts in the field. At a high level, unmet needs in symptom management map closely to the prevalence of those symptoms in the neuromuscular disease population (see Exhibit 11), with

Exhibit 11: Unmet Needs in the Management of Neuromuscular Disease Symptoms



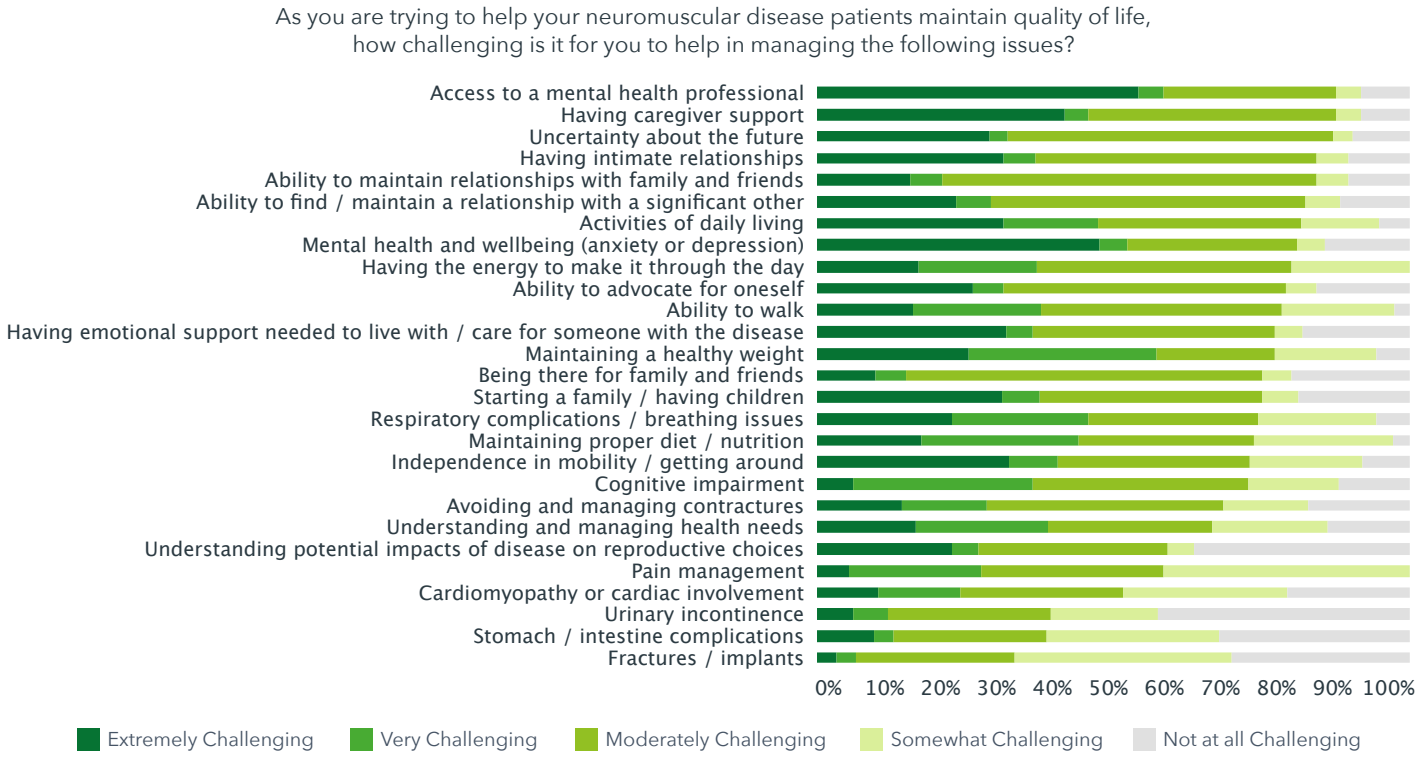
Source: Neuromuscular Disease Healthcare Provider Survey, Jun 2018
Notes: Number of respondents to this question n=84.

respondents to the Neuromuscular Disease Healthcare Provider Survey again highlighting that many patients struggle with psychological symptoms and fatigue.

At a more granular level, the physical and social/emotional challenges in patient care (see Exhibit 12) were also revealed. The most prominent challenges again map closely to the symptoms considered to have the highest unmet needs apart from several nutrition and weight issues, and to helping patients maintain appropriate physical and emotional support:

- Over 50% of Neuromuscular Disease Healthcare Provider Survey respondents reported it very or extremely challenging to help in managing mental health (anxiety or depression) for neuromuscular disease patients in their care, and close to 60% reported similar challenges exist in helping patients with access to a mental health professional.
- Both maintaining a healthy weight and maintaining proper diet/nutrition were rated among the most challenging issues, despite a low ranking of unmet need in this area. This finding may reflect provider assessment of relative severity of weight/nutrition issues when compared with other symptoms, or it may be indicative of a discrepancy between the existence of better care (e.g., through a nutritionist) and a patient's ability to access that care (i.e., coverage and patient tolerance for out-of-pocket costs for nutritionists may be lower than for other specialists).
- Despite the potential overall impact of respiratory and mobility problems, less than 50% of providers ranked managing these issues as extremely or very challenging, which may be reflective of the available equipment and standardized approaches to treating these problems at each stage of disease.

Exhibit 12: Current Challenges in Caring for Patients with Neuromuscular Disease



Source: Neuromuscular Disease Healthcare Provider Survey, Jun 2018
Notes: Based on 38 respondents.

MENTAL HEALTH IN NEUROMUSCULAR DISEASE

Psychological issues/mental health was consistently highlighted within the Neuromuscular Disease Healthcare Provider Survey as being a key issue in the care of neuromuscular disease.

The diagnosis and treatment of mental health issues is complex even for patients without comorbid physical illness, however, the situation is likely to be even more challenging where other, more visible, symptoms may be prioritized. Guidelines for the care of DMD recommend that a patient's mental health be surveilled and monitored throughout the course of their disease,[27] and similar recommendations regarding the active management of psychosocial health are seen for other neuromuscular diseases. However, symptoms of depression or anxiety may overlap with primary symptoms of neuromuscular disease (e.g., fatigue, breathlessness) making them potentially difficult to diagnose. A psychologist or psychiatrist is rarely part of the multidisciplinary team coordinating patient care, suggesting that early warning signs of these issues may be missed.

Research publications considering mental health difficulties and their management specifically in neuromuscular disease patients are extremely limited, although the Neuromuscular Disease Healthcare Provider Survey finding that mental health issues are prevalent among neuromuscular disease patients is in alignment with some recent studies in DMD,[74] SMA,[75] ALS,[76] and neuromuscular disease overall.[77]

Mental health issues have typically been observed to be more severe for individuals with slowly progressing degenerative diseases than those with rapid progression, suggesting that mental health issues may become even more important to consider for neuromuscular disease patients in light of improving care and treatment paradigms if disease progression is successfully slowed.

An interesting insight from rankings of challenges in neuromuscular disease management in the Neuromuscular Disease Healthcare Provider Survey is that top challenges (e.g., mental health, nutrition) are issues that are minimally covered by current guidelines and seem to be under-represented in active research.

OPPORTUNITIES TO UNDERSTAND DISEASE PROGRESSION

Despite recent advances in monitoring and treatment, there is still a limited understanding of disease progression for many neuromuscular diseases, in part due to the heterogeneity in disease severity and speed of progression. Predictors of disease progression are not fully understood, although the specific genetic mutation underlying the disease is known to be an important factor. This suggests that improving diagnostics will facilitate the gathering of subgroup-specific progression insights.

Careful monitoring of disease progression within a genetic subpopulation by tracking symptoms over time is a promising strategy. However, the usual cadence of visits, estimated at two to three times per year for most patients by Neuromuscular Disease Healthcare Provider Survey respondents, limits the quantity and resolution of information that can be gathered, and the ability to detect inflections in patient health. Currently, it is difficult for healthcare providers to comprehensively monitor patients outside of the clinic, such as through mobile symptom monitoring, wearables and telemedicine.

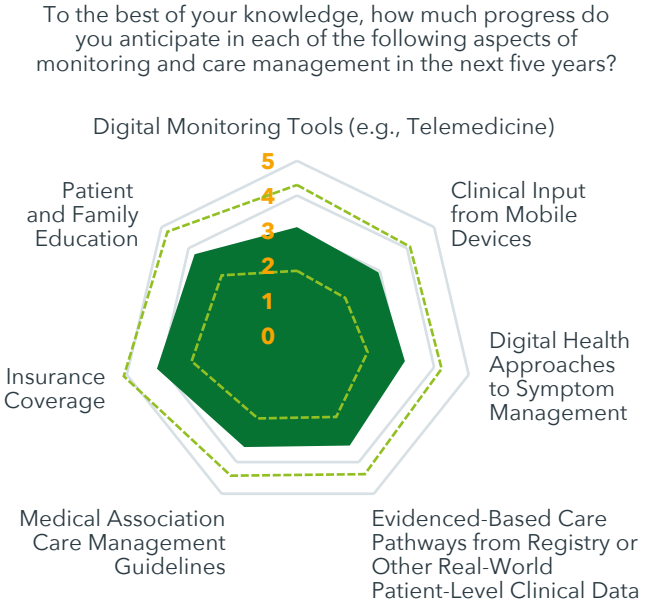
CURRENT AND EVOLVING APPROACHES TO CARE

As technologies improve, there are opportunities to positively impact monitoring and care in neuromuscular disease. Integration of home monitoring into regular practice could enable healthcare providers to remotely conduct more of the measurements traditionally made in the clinic (e.g., heart function, gait and even muscle strength). Real-time remote monitoring of these indicators of disease progression, such as through digital health apps and wearables,[78] will both inform an understanding of the natural history of different neuromuscular diseases, as well as facilitating better tailoring of treatment approach to the individual. In addition, efforts are underway in many diseases to enable self-tracking of symptoms through standardized Patient-Reported Outcomes (PRO) tools.[79,80]

Neuromuscular Disease Healthcare Provider Survey respondents were moderately hopeful about the ability of technology advancements to have an impact on their neuromuscular disease within the next five years, but see more potential impact from overcoming current challenges in insurance coverage and care standardization (see Exhibit 13):

- Respondents noted that the highest-level of progress could come from changes in insurance coverage, likely reflecting both the changing healthcare system overall and the impact of disease-modifying therapies.
- Improved education of patients and their families is expected to have a moderate impact on monitoring and care, potentially indicating current challenges in providing patients and caregivers with accurate information in a timely manner.
- Drawing attention to the inconsistencies and challenges of currently available care guidelines, providers say that there is a potential to positively impact care through the development of evidenced-based care pathways or medical association-endorsed care guidelines.
- Despite general hype regarding the potential for technological advancements (e.g., mobile symptom monitoring, telemedicine) to better understand and manage symptoms, providers are least hopeful that these advances will have notable impact on overall patient monitoring and care within the next five years.

Exhibit 13: Expected Impact of Advances in Monitoring and Care Within the Next Five Years



Source: Neuromuscular Disease Healthcare Provider Survey, Jun 2018
Notes: Rated 1–5 where 1 is 'No impact" and 5 is "High impact" to improving diagnosis of patients in that HCP's practice. Dotted lines denote deviation around average rating. Based on 85 respondents.

OPPORTUNITIES TO INTEGRATE CLINICAL RESEARCH

An increasingly important consideration for neuromuscular disease patients is the monitoring required during their participation in clinical research. The time and effort required by clinical research studies vary. While questionnaires and blood draws may consume minimal time and effort, other trial endpoints can have a larger impact, and need to be balanced with routine monitoring to minimize drain on patient time and other resources.

Metrics employed by trials may not be part of standard clinical or regulatory guidelines (e.g., the 6-minute walk test), and some providers and clinics are not equipped to perform the measurement, which may preclude some patients from participating in a trial. For some clinics, their internal regulations stipulate that the panel of tests and assessments required for clinical research must be performed separately from a patient's routine check-in, creating an additional burden for both patient and healthcare provider.

Alternatively, some clinicians indicate that new metrics may be adopted into general care because of a desire to have better longitudinal data against which to compare trial findings, and thereby understand the significance of the endpoints used to assess the efficacy of new medications. Some thought leaders are also considering the potential to rely more on patient-reported outcome measures (PROMs) and caregiver assessments in care monitoring and decisions, in addition to their use in clinical trials.[81]

THE DAWN OF DISEASE-MODIFYING TREATMENT OPTIONS

There remains a lack of curative treatments for neuromuscular disease, however, a few recently approved therapies in DMD, SMA, ALS and MG have demonstrated the ability to slow or delay disease progression (see Focus Point: New Treatments in NMD). These advances expand upon previously existing disease-modifying treatment for a very limited subset of neuromuscular diseases, such as enzyme replacement therapy for Pompe disease and hormone replacement therapy for hypothyroid myopathy. While these new therapies are promising potential improvements to the care of some patients, they are associated with several key limitations.

First, annual price per patient is considerable, with estimates for ranging from around $145,000 [edaravone (Radicava)] to more than $750,000‡ (nusinersen, eteplirsen). As a result, access to these new therapies is often limited by payer restrictions, including prior authorization requirements. Clinics need to dedicate substantial time to submitting letters to insurers to push for patient access – a time consuming process – and not all clinics have the budget available to hire someone for this full-time role. Such restrictions can also delay treatment, with some patients having to apply multiple times across a period of months. New treatments have generally been shown to be most efficacious when administered early in disease progression, highlighting the need to decrease time spent on both the diagnosis process and applications for access. Finally, some new therapies have methods of administration that require dedicated training time for caregivers – such as the intravenous administration of nusinersen or eteplirsen – or additional coordination with departments not traditionally involved in routine patient care (e.g., for intrathecal administration of nusinersen). Training, booking of additional appointments, inter-departmental correspondence and requirements to communicate with specialty pharmacies all add to the administrative burden of healthcare providers.

‡ Costs reach up to $750,000 for the first year of nusinersen treatment due to additional loading doses, and are also calculated to be approximately $750,000 or higher for eteplirsen for older patients who may require a higher weight-based dose, including those in the original clinical trial cohort

FOCUS POINT: NEW TREATMENTS IN NEUROMUSCULAR DISEASE

Within the last two years, several new disease-altering therapies have been approved for the treatment of neuromuscular disease:

Nusinersen (Spinraza) was approved in 2016 for the treatment of SMA after clinical trials demonstrated improved achievement of motor milestones and maintenance of motor function in patients with infantile and later-onset disease.

Eculizumab (Soliris) was approved in 2017 for the treatment of MG that has progressed to generalized muscle weakness and is refractory to treatment with immunosuppressive therapies. Eculizumab was approved after clinical trial data showed that it decreased muscle weakness and led to an improvement in the daily function of MG patients.

Edaravone (Radicava) was approved in 2017 for the treatment of ALS, based on clinical trial data that demonstrated a slowing in the decline of function associated with disease progression.[§]

Eteplirsen (Exondys 51) received conditional, accelerated approval in 2016 for the treatment of DMD that is amenable to exon 51 skipping, a segment that accounts for approximately 13% of DMD patients. The medication received accelerated approval based on statistically significant increases in dystrophin levels in clinical trials. Clinical benefit (e.g., delay to loss of ambulation, retention of upper limb function) is yet to be firmly established,[82] but supporting clinical trials are ongoing.

Given the challenges associated with these new therapies, Neuromuscular Disease Healthcare Provider Survey respondents were asked to identify issues that posed a barrier to initiating disease-modifying treatments (see Exhibit 14). Their responses solidified concerns about payer restrictions and therapy prices, as well as hinting at an apparent lack of ubiquitous faith in the promise of the disease-modifying treatment options:

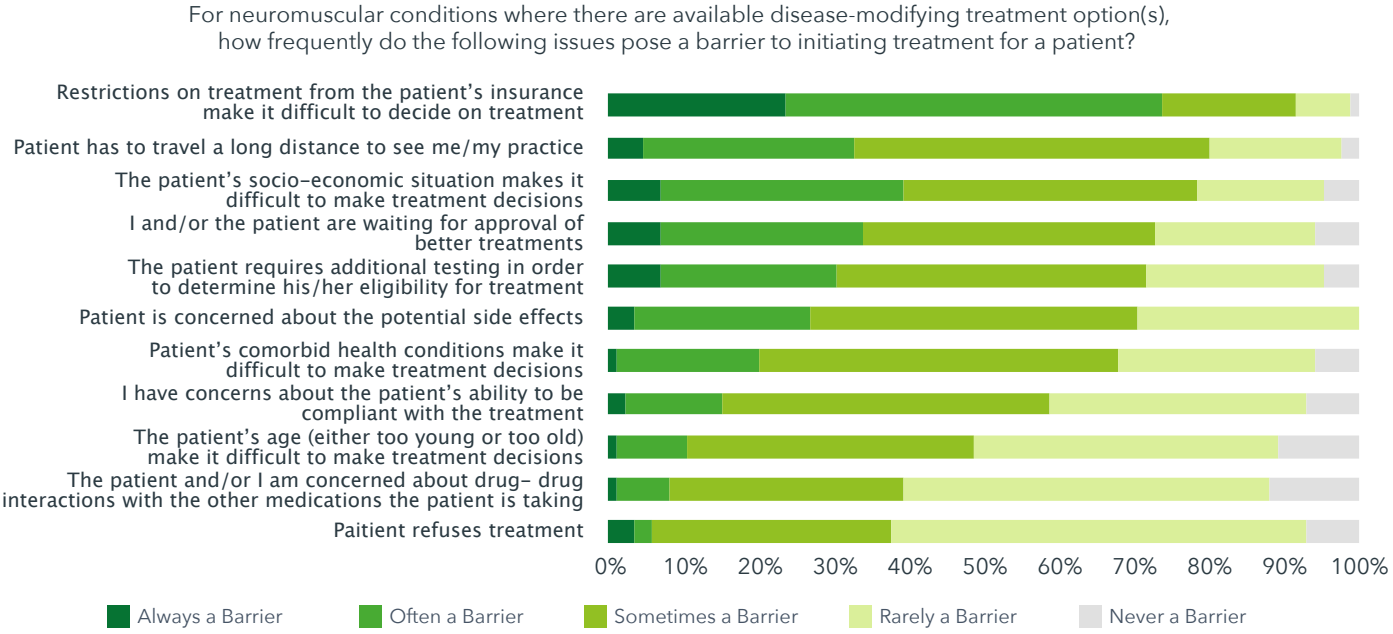
- Restrictions on patient insurance is by far the biggest issue highlighted by neuromuscular disease healthcare providers, with more than 70% reporting that it is always or often a barrier.
- Direct costs to the patient are considered a consistent barrier by approximately 40% of respondents; this concern is likely lower than expected as a result of the considerable patient-assistance programs provided by the manufacturers of high-cost modifying treatments.
- Of note, over 30% of healthcare providers said either they or the patient are waiting for the approval of better treatments, potentially indicating concerns with the efficacy and/or side effects of novel therapies.

CHALLENGES IN REIMBURSEMENT FOR CARE

As treatment paradigms shift for many neuromuscular diseases, associated financial challenges also arise for patients, providers and society. For providers working in disease areas that were previously treated almost exclusively by generic products with minimal access restrictions, navigating prior authorizations and insurance paperwork is a new burden on already stretched resources. However, to support the staffing of full-time patient services coordinators required to handle the workload, some clinics have turned to non-profit sources for funding.

§ Approval of edaravone was somewhat unique as all submitted clinical trial data was generated ex-United States

Exhibit 14: Barriers to Initiating Disease-Modifying Treatments



Source: Neuromuscular Disease Healthcare Provider Survey, Jun 2018
Notes: Based on 84 respondents.

Insurance and cost considerations stretch beyond new therapies. Challenges associated with the multi-disciplinary care model may shift financial burden to the patient. For instance, a standard clinic visit may include time with specialists (e.g., physiotherapists) that a patient also sees regularly outside the clinic, but patients may not have insurance coverage for an additional visit with that doctor in a clinic setting. This may place the financial burden for part of a comprehensive clinic visit entirely on the patient, or occasionally on philanthropic funding sources. Specialists also report that patients decline some care perceived as non-essential (e.g., nutritionists) as a consequence of high out-of-pocket costs – a challenge not unique to neuromuscular diseases.

Options to address the rising cost to patients associated with both the advent of disease-modifying therapies and the redistribution of cost-responsibility occurring in the U.S. healthcare system are still uncertain. Companies releasing new orphan products now routinely invest heavily in providing wraparound support for patients, including case managers who can help them interface with insurance companies, and copay assistance that may offset out-of-pocket expense. A more extreme, and likely unsustainable, option is the provision of the therapy free-of-cost through compassionate use programs, with pharmaceutical companies picking up the tab when insurance companies refuse access.

In summary, the care paradigm for many neuromuscular diseases is experiencing a period of rapid change, with associated challenges for patients, providers and society. Despite these challenges, as our understanding of disease subtypes and associated prognoses improves, targeted therapies will continue to transition from the pipeline to the clinic, improving treatment options, and opportunities to optimize treatment through personalized approaches will increase. Efforts to systematically benchmark approaches and outcomes, both within and outside of clinical trials, will set the groundwork to better develop prognoses for individual patients, and provide a baseline understanding on which to layer differences between patient segments, as well as to smooth patient experience across multiple facets of care.

Therapeutics in the pipeline

- One hundred and sixty-five companies are actively investing in the development of therapies for neuromuscular disease, including seven of the largest 15 pharmaceutical companies.
- More than 275 clinical trials are ongoing globally for over 190 molecules in development for neuromuscular disease.
- Research and development activity is heavily focused on ALS and DMD, with promising candidates targeting specific genetic subgroups.
- Fifty products in development are 'next-generation' antisense oligonucleotides, gene therapies or cell therapies, with strong potential to improve outcomes, alter care paradigms and increase therapeutic treatment costs across neuromuscular diseases.

A ROBUST PIPELINE

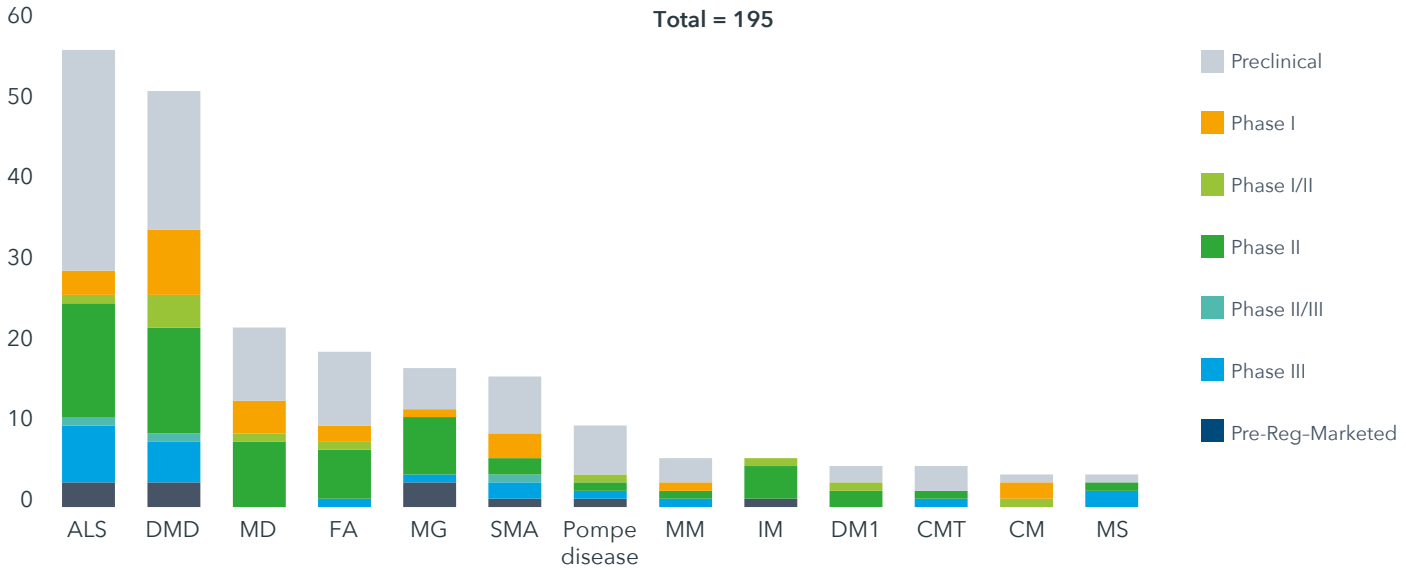
A broad drug-development pipeline is emerging across neuromuscular diseases. Promising drug targets have been identified as the result of a growing understanding of the underlying genetic components and molecular pathways of many disorders, and research and development (R&D) activity in this space has grown rapidly in the last five years. The number of molecules in clinical development increased five-fold from approximately 20 in 2013[83] to the approximately 100 seen in this analysis in 2018. With several clinical trials demonstrating reduced decline in strength and function in patients, and robust preclinical activity, impactful disease-modifying therapies are on the horizon. Globally, over 190 unique candidates are being evaluated for neuromuscular diseases, with R&D activity heavily concentrated in ALS and DMD (see Exhibit 15).

A RANGE OF MOLECULE TYPES

A combination of improvements in the genetic understanding of neuromuscular diseases and technological advances are driving a surge in the number of product types being pursued and the diversity of their mechanisms of action. Almost 200 molecules are currently in preclinical or clinical development. A large minority of pipeline activity is still centered on small molecules, which account for 43% of products in development (see Exhibit 16). The small molecules in development have a variety of mechanisms of action, including receptor modulation, epigenetic reprogramming and antioxidant activity, reflecting the myriad cellular mechanisms implicated in neuromuscular diseases. In addition, a range of other therapy types are also well represented.

Gene therapies, which aim to replace damaged or mutated genes and their non-functional protein products, make up a notable minority of products. The accessibility of muscle and the potential for its cells to amplify the impact of nuclear-targeted therapies due to their being multinucleate,[84] make it an attractive target for gene therapy and novel genome editing technologies. Additionally, breakthroughs in targeting the motor neurons of the central nervous system have also accelerated gene therapy efforts for these diseases.[85] As of August 2018, the gene therapy furthest along in clinical development is AVXS-101 for SMA, which recently started Phase III trials and is being developed by AveXis, recently acquired by Novartis. AVXS-101 is a one-time

Exhibit 15: Number of Products in the Therapeutic Pipeline by Disease Area and Phase of Development

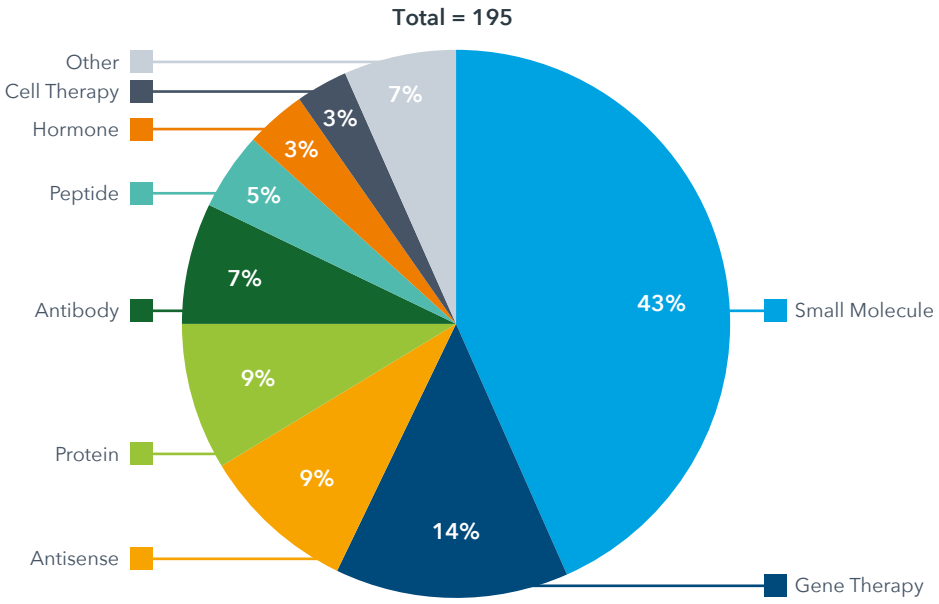


Source: IQVIA Pipeline Analytics, R&D Focus data, Apr 2018
Notes: Products indicated for >1 disease area are represented multiple times. ALS = amyotrophic lateral sclerosis; DMD = Duchenne muscular dystrophy; SMA = spinal muscular atrophy; FA = Friedreich's ataxia; MD = Other muscular dystrophies (Becker muscular dystrophy, congenital muscular dystrophy, facioscapulohumeral muscular dystrophy, limb girdle muscular dystrophy, oculopharyngeal muscular dystrophy); MG = myasthenia gravis; IM = inflammatory myopathies (dermatomyositis, polymyositis, inclusion-body myositis); CMT = Charcot-Marie-Tooth disease; CM = congenital myopathies; MM = mitochondrial myopathy; DM1 = myotonic dystrophy type 1, CM = congenital myopathies, MS = other myasthenic syndromes (LEMS, congenital myasthenic syndrome).

intravenous administration of an SMN transgene (i.e., transferred gene sequence) in a recombinant adeno-associated virus (AAV) vector shell. AveXis is also developing similar products for familial ALS.

Antisense oligonucleotides are a third notable category of products; not least because newly approved eteplirsen and nusinersen fall into this category. These therapies (which block the typical splicing and/or translation of

Exhibit 16: Therapeutic Pipeline by Therapy Type



Source: IQVIA Pipeline Analytics, R&D Focus data, Apr 2018
Notes: Other includes undisclosed, vaccine and oligonucleotide agonists.

PIPELINE STRATEGIES BY DISEASE AREA

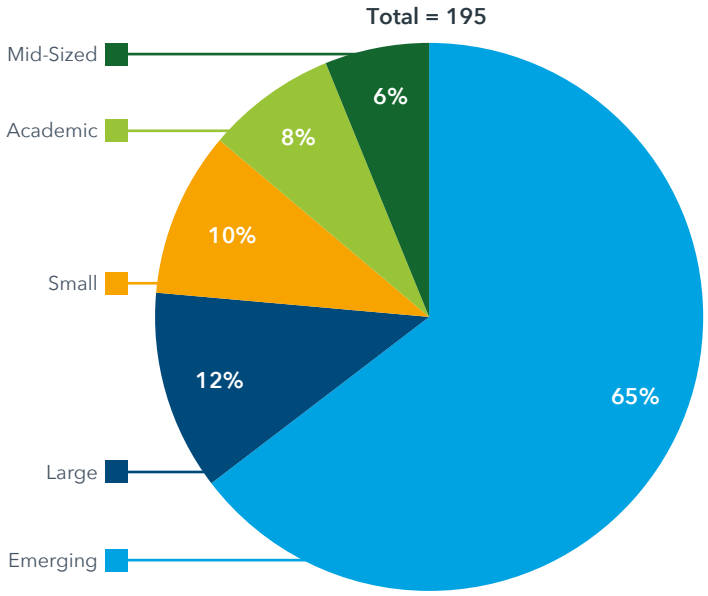
Most therapies in development for DMD aim to correct for the loss of the protein dystrophin by improving membrane stability or alter signaling pathways in affected muscles.[87] Antisense oligonucleotides are prevalent in the DMD pipeline; these molecules work by causing targeted exon skipping (the skipping of a portion of genes, or exons, to remove damaged sections and thereby prevent the creation of dysfunctional proteins) in regions with common mutations. Exon 51 has received the most attention to date as it is relevant for approximately 13% of DMD patients, and eteplirsen, which targets this exon, is the first antisense product to receive conditional approval from the FDA for DMD. Molecules focused on exons 45 and 53 are also in clinical development. The objective of next-generation DMD medicines is to get closer to curing the disease by restoring muscle cell function through microdystrophin gene therapy. This therapy generates a partially functional dystrophin substitute and recent data from a small Phase I/IIa trial has shown promise.[88] Among small molecule approaches, ataluren (Translarna) takes a stop-codon readthrough approach that ignores erroneous stop signals (i.e., nonsense mutations) that occur in the messenger RNA of 15% of DMD patients and prevent the dystrophin protein from being successfully created/translated. According to PTC Therapeutics, ataluren may interact with the ribosome (which builds proteins) to allow it to read through premature nonsense stop signals, allowing for translation of fully functional proteins. Ataluren was approved by the European Medicines Agency and recent Phase III data may support re-submission in the United States.

For other muscular dystrophies, R&D activity is more limited than for DMD. However, there are a number of gene therapies in Phase I trials targeting BMD and LGMD. These therapies leverage the adeno-associated virus (AAV) system to deliver genes for follistatin or sarcoglycans, respectively, to skeletal muscle. Also notable in this disease area is ACE-083, which, according to Acceleron, binds to and inhibits select proteins in the TGF-beta protein superfamily, which can negatively regulate (reduce) muscle growth. Acceleron recently received orphan drug and fast-track designations from the FDA for treatment of FSHD with ACE-083, and this drug is also being tested in CMT. For FSHD and LGMD, an immunomodulatory protein, ATYR1940 (Resolaris), is currently in Phase I/II trials.[86]

Development of therapies for ALS is an area of heavy investment and is widely supported by patient advocacy groups. The complex genetic nature of ALS and an incomplete understanding of its etiology has historically made it challenging to know which molecular pathways present the most promising drug targets. Current pipeline strategies focus on the targeting of subtypes of ALS with gene therapies, neuroprotection and modulation of neuroinflammation and oxidative stress pathways. Anti-oxidant activity is also believed to be the mechanism of action of recently approved ALS medication edaravone, which has been shown to modestly slow disease progression. Phase III trials are also underway for the cell therapy NurOwn in which neurotrophic factor-secreting mesenchymal stem cells aim to slow disease progression.

Pipeline products to treat SMA either endeavor to replace or upregulate production of SMN1 or 2, like newly approved nusinersen, or target SMN-independent pathways to increase muscle strength and function. Approaches to treat FA include the replacement of frataxin protein (under-expressed in the disease) with cell-permeable proteins or through gene therapy, or by promoting expression of endogenous frataxin using epigenetic modifiers or mimics of endogenous upregulators (e.g., erythropoietin). The pipeline also contains a range of small molecules that may protect against the detrimental effects of mitochondrial dysfunction caused by inadequate frataxin, such as the generation of free radical species.

Exhibit 17: Therapeutic Pipeline by Company Size



Source: IQVIA Pipeline Analytics, R&D Focus data, Apr 2018

Notes: Molecules are represented uniquely within one therapy type without duplication. Data shows size of lead company associated with each unique product identified in the neuromuscular disease pipeline. Companies associated with more than one pipeline product will be represented multiple times. Company categories: Emerging = <$100Mn revenue per year or <$200Mn in R&D expenditures per year; Small = >$100Mn and <$1Bn in revenue per year; Mid-Sized = >$1Bn and <$20Bn in revenue per year; Large = >$20Bn in revenue per year. Total may not sum to 100% due to rounding.

nucleotides in order to make proteins) aim either to decrease levels of damaged or dysfunctional proteins, or to modify related proteins in such a way that they become better replacements for mutated counterparts. Around half of molecules in this category are antisense products that target different genetic subpopulations of DMD patients (see sidebar, Pipeline Strategies by Disease Area), many of which are being developed by eteplirsen manufacturer, Sarepta Therapeutics.[86]

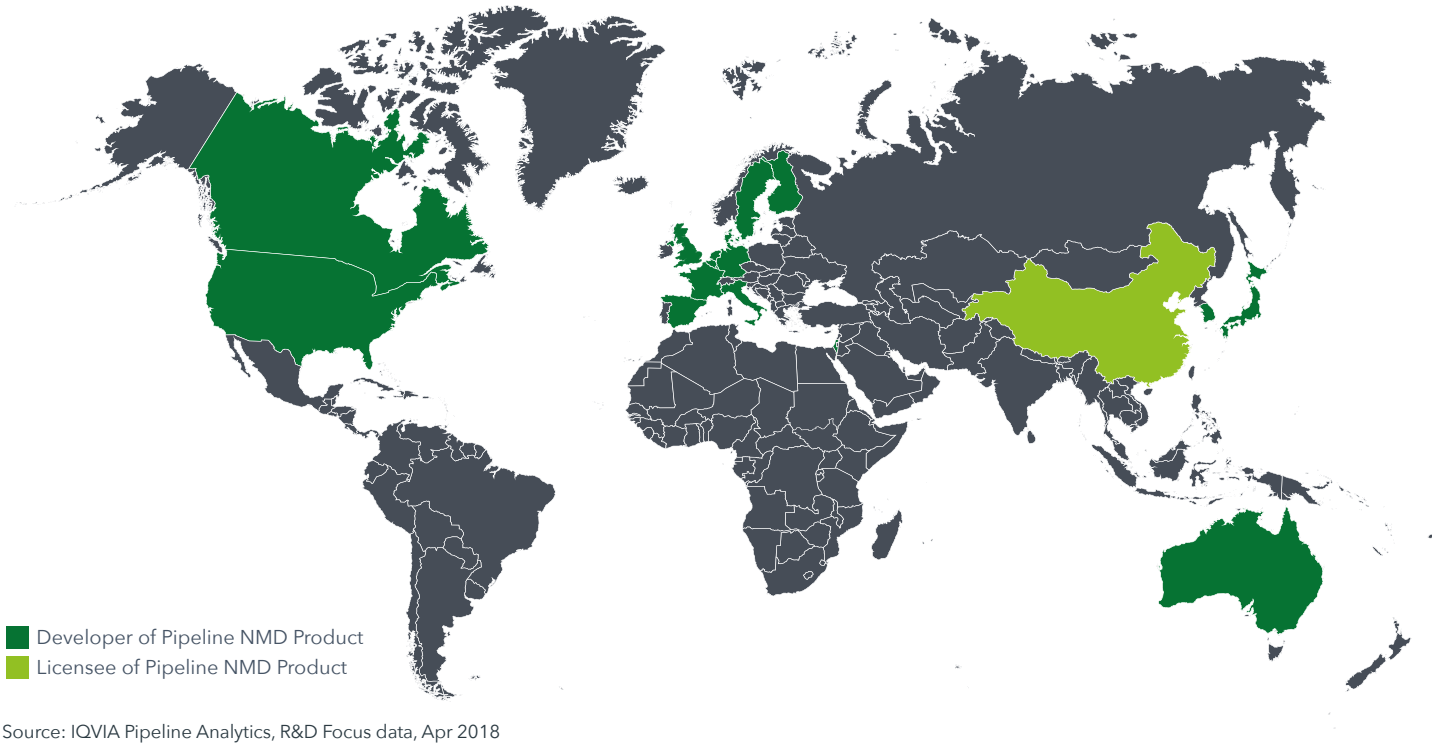
Around 14% of the pipeline is made up of protein or peptide molecules. Some protein products have a mechanism of action that mirrors the aims of gene therapies, namely to provide replacement protein products derived from damaged genes, albeit in a less permanent manner. Other proteins or peptides modulate the activity of enzymes or receptors involved in a range of diseases, including ALS and FA (see sidebar, Pipeline Strategies by Disease Area).

A SPECTRUM OF COMPANIES ACROSS THE GLOBE

Therapies for neuromuscular disease are being developed by a broad range of company types, indicative of wide-reaching interest in this field (see Exhibit 17). One hundred and sixty-five companies globally are involved in drug research and development programs associated with more than 275 clinical trials worldwide.[90] Of those, more than 20 companies are pursuing candidates in more than one disease area.

Ninety-seven emerging biopharma companies lead the majority of development in this area, with 126 drugs in development, accounting for 65% of the pipeline. At the other end of the spectrum are large pharmaceutical companies, including seven of the top 15 globally (by sales), which either have products for neuromuscular disease in the pipeline, and/or are investing in this area by providing early venture-capital support to other companies through early stage investment initiatives (e.g., Novo Seeds, Roche Venture Fund).

Exhibit 18: Map of Companies with R&D Activity in Neuromuscular Diseases



Source: IQVIA Pipeline Analytics, R&D Focus data, Apr 2018

Notes: Countries with both developers and licensees of pipeline products are labeled as developers: Canada, Germany, Italy, Japan, Netherlands, South Korea, Switzerland, United Kingdom and United States; NMD = Neuromuscular disease.

A notable, mid-size company investing in neuromuscular disease R&D is Biogen, which has a product marketed for SMA and has molecules in development for the treatment of ALS. Biogen has recently expanded their collaboration with Ionis Pharmaceuticals, from whom they licensed nusinersen, to develop treatments for a range of disease areas, including neuromuscular disease.

In addition to their diversity in size and presence, companies investing in neuromuscular disease also vary in location. The United States remains a core center of development, home to over 100 unique companies, but 19 countries host the headquarters of at least one company involved in neuromuscular disease development (see Exhibit 18). Notably, 11 companies are headquartered in Japan, eight in Switzerland, seven in France and six in the United Kingdom. The large number of companies and countries involved in product development for the treatment of neuromuscular disease demonstrates a growing momentum occurring due to both advances in disease understanding and novel therapeutic technologies that offer new potential options for treatment.

PIPELINE IMPLICATIONS

Despite heterogeneity across neuromuscular diseases, it is evident that there are some strategies to maintain muscle function, prevent damage or replace missing genes/proteins that are being tried across multiple disease areas (see Exhibit 19). As drug candidates are assessed in one disease area, a variety of different findings may potentially be applicable to other neuromuscular diseases, including the identification of appropriate biomarkers, early indicators of safety concerns or regulatory pathways used to bring these new therapies to the market. In this way, advances in drug development for the diseases that are, at present, highly represented in the pipeline, may have broader beneficial effects in other diseases.

Exhibit 19: Common Therapeutic Strategies in the Neuromuscular Disease Pipeline

	DECREASE INFLAMMATION	INCREASE MUSCLE MASS	GENE THERAPY	ANTISENSE OLIGONUCLEOTIDES	NEURO-PROTECTION	ENHANCE MUSCLE CONTRACTION
ALS	✓		✓	✓	✓✓	✓
CMT		✓	✓	✓		
DMD	✓✓	✓	✓	✓✓*		
FSHD	✓	✓		✓		
LGMD	✓	✓	✓			
MG	✓✓					
SMA		✓	✓	✓✓	✓	✓

✓✓ Approved therapy ✓Ongoing trial

Source: IQVIA Pipeline Analytics, R&D Focus data, Apr 2018

Notes: Asterisk denotes accelerated approval status with ongoing monitoring. Treatment strategies with both approved and trial therapies are denoted only with a tick. ALS = amyotrophic lateral sclerosis; CMT = Charcot-Marie-Tooth syndrome; DMD = Duchenne muscular dystrophy; FSHD = facioscapulohumeral muscular dystrophy; LGMD = limb-girdle muscular dystrophy; MG = myasthenia gravis; SMA =spinal muscular atrophy.

The current pipeline has the potential to transform how neuromuscular diseases are managed, providing novel disease-modifying treatments that will improve upon existing therapies and potentially offer cures for some diseases. A number of obstacles will need to be overcome in order to support the clinical pipeline for neuromuscular diseases:

- Lack of previously validated clinical trial endpoints for many disease areas increases the difficulty of designing trials that are able to identify meaningful changes in disease progression, patient function or quality of life. Timely input from regulatory authorities about the perceived relevance of selected endpoints will be critical, especially given the lack of guidelines for almost all neuromuscular disorders from organizations such as the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). Notably, the FDA only released final guidelines for the development of drugs for dystrophinopathies (e.g., DMD, BMD) – and a draft guidance for ALS – in February 2018.[91,92]
- Identification of a sufficient number of patients to participate in clinical trials can be challenging, given the rarity of many neuromuscular diseases. For example, in ALS, the currently-listed clinical trials in the United States are aiming to enroll approximately 14% of the total estimated ALS population, and clinical trials for DMD have a target enrollment in the United States of 675, which may be 5–10% of the total DMD population.** Required numbers of patients for potential future Phase III trials may be expected to be even higher, suggesting that new strategies for patient enrollment, novel trial designs or generating adequate insights from lower enrollment numbers may be required.
- Recruiting trial-site requirements for trial participation that include unfamiliar measurements, procedures that may be technically challenging or significant time and energy commitments. These, in effect, limit the pool of clinics/treatment centers that are willing or able to host clinical trials.

** Based on estimates of 13,000 ALS patients and 8–12,000 DMD patients in the United States

Presuming eventual trial success, the approval of novel disease-modifying therapies will lead to new treatment paradigms for providers, especially in disease areas where current therapy options are extremely limited. The approval of nusinersen has required considerable changes to the way in which care of SMA patients is managed, including the expansion of multidisciplinary teams to include novel personnel, such as specialized nurses to inject the drug intrathecally in the cerebrospinal fluid, and the addition of time to a patient's schedule to anesthetize them for the spinal cord injections.

Coupled to the changing treatment paradigm are likely new challenges in access and affordability. New therapies coming out of the pipeline are likely to be expensive and pose financial challenges for payers, hospital systems and patients themselves. The current system that links many patients to new disease-modifying treatment options can be a complex network of prior authorizations, case managers, and even manufacturers covering the cost of treatment as a stopgap measure.[93]

Use of real-world evidence studies to demonstrate patient or economic impact – such as quality of life improvements or decreased healthcare utilization – may be beneficial to help clarify the value of these therapies.

Additionally, following initial approval, regulatory authorities are likely to require continued clinical studies for therapies approved on the basis of trials with small study populations and/or surrogate endpoints, as indicated by the requirement placed on eteplirsen to demonstrate further clinical benefit in a post-launch clinical trial.[94] It is likely that regulatory bodies will require such post-marketing surveillance, particularly for therapies leveraging new technologies (e.g., antisense oligonucleotides, gene therapies, etc.), which may add to the overall administrative and cost burden.

Ultimately, excitement around the growing pipeline of potential treatments for neuromuscular diseases needs to be balanced with practical support through careful development of solutions for these associated challenges.

Opportunities to accelerate advancements in neuromuscular disease care

- Employing effective newborn screening programs will enable patients to be diagnosed sooner and lead to a broader understanding of disease characteristics within the general population.
- Increasing use of patient registries/data hubs and improving longitudinal data will improve understanding of the natural history of these diseases.
- Adopting emerging technologies for remote appointments and real-time monitoring will improve overall access and care management.
- A better understanding of patient populations and trial site preparation will streamline future clinical trials.
- Improvements in etiological understanding of neuromuscular diseases and emerging therapeutic advances will improve available care options.
- Designing innovative approaches to pricing and reimbursement for new medications can help tackle rising costs for patients.

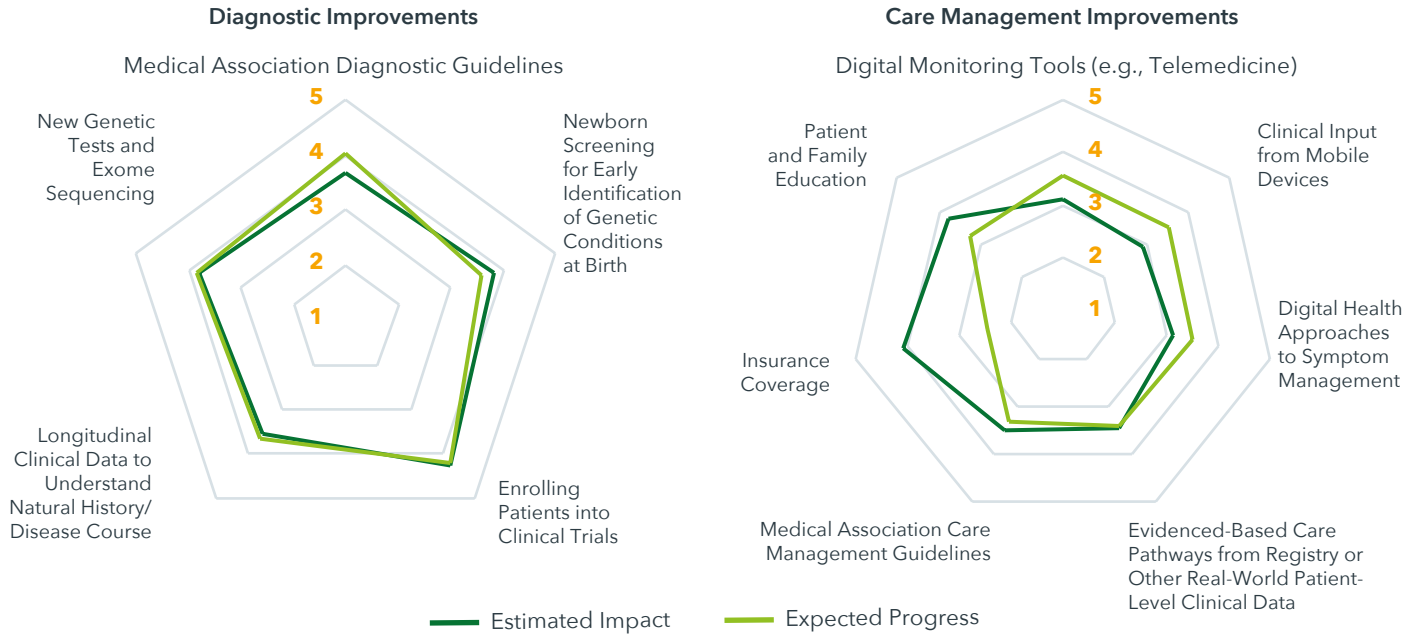
An improved understanding of disease and advances in technology have invigorated the drug development pipeline for neuromuscular disease, offering the potential to transform care within the next decade. Respondents to the Neuromuscular Disease Healthcare Provider Survey recognized the potential for improvements in both diagnosis and care management as a result of the advancements discussed in this report (see Exhibit 20) and ranked both the expected progress and expected impact of each development as 'medium-high'. However, attaining optimal patient outcomes in the shortest possible timeframe likely requires a concerted effort by multiple stakeholders to capitalize on opportunities and maximize the effect of recent advances.

WIDENING USE OF GENETIC TESTING

Use of genetic testing to make a definitive diagnosis is already broadening across the neuromuscular diseases. Over 800 disease subtypes with monogenic origins have been associated with over 400 genes.[95] Bringing genetic testing into the diagnostic algorithm earlier, whenever possible, will reduce risk of misdiagnosis and decrease the current long delays to confirm a neuromuscular disease diagnosis. Additionally, new insights from the discovery of de novo mutations are redefining our historical understanding of the mechanism of disease for some subpopulations of patients and demonstrate how a clear genetic picture may optimize treatment choices.

In some cases, targeted analysis of specific genes is sufficient to identify mutations, if the disease is known to affect the patient's family tree. However, additional genetic information, such as the number of gene variants, can be critical in determining treatment eligibility as well as likely disease progression and treatment response. For example, deletions or loss-of-function mutations in SMN1 leading to SMA can be offset by residual expression of an alternative gene, SMN2, and patients with more copies of SMN2 typically have less severe disease. In trinucleotide repeat expansion diseases such as FA, the length of

Exhibit 20: Estimates of Progress from Diagnosis and Care Management Changes and Their Expected Impact in the Next Five Years



Source: Neuromuscular Disease Healthcare Provider Survey, Jun 2018
Notes: Rated 1–5 where 1 is 'None" and 5 is "High", with reference specifically to HCP's practice for Impact. Number of respondents to this question n=84.

the expansion correlates with the age of diagnosis and influences disease severity.[96]

For disease-modifying therapies, muscle function is likely to be best maintained if patients are treated early in the disease course, ideally before noticeable symptoms. Early genetic screening is key to ensure the best outlook for patients. Newborn screening can have enormous implications on time to diagnosis and intervention, however, these tests need to have high specificity and sensitivity and also be cost-effective given the large population to be tested. These factors were taken into consideration by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, which manages the list of diseases found on the RUSP.[97] Newborn screening programs are implemented at the state-level, requiring local advocates for policy changes and implementation across states. However, the Department of Health and Human Services recommends conditions that should be added to state screening panels based on evidence that screening is achievable (i.e., a suitable test exists) and that there is an available effective treatment. Pompe disease was added to the central list of recommended conditions in 2015 and SMA in 2018 following the approval of nusinersen. An overwhelming majority of parents of patients with DMD, BMD and SMA support newborn screening programs (95.9%), as well as 92.6% of expectant parents.[98]

Newborn screening may take a variety of paths with multiple testing steps. For DMD, suggestions have been made to conduct dried blood spot testing in all newborns for elevated creatine kinase, a biomarker of muscle dysfunction, and follow up with targeted genetic sequencing for individuals who test positive for elevation, mirroring the strategy for testing for Pompe disease. Blood spot testing is a lower-cost, general screen compared with genetic testing, and this strategy has been shown to have good sensitivity in pilot studies.[99]

It is inevitable that more genetic markers will be

discovered as gene sequencing continues to decrease in cost. The price of sequencing an entire human exome or genome has plummeted in the last decade to just over $1,000,[100] making it an increasingly viable option for patients for whom targeted gene sequencing is insufficient. The diagnosis rate from whole exome sequencing for patients with neuromuscular disease who had already undergone extensive targeted testing has been reported as approximately 13%,[101] potentially due to incremental contributions of multiple gene variants, or pathological alterations in genes with poorly defined function. However, the authors highlight that integration of more comprehensive genome-wide panels earlier in the diagnostic process would also have identified many patients who underwent one or single gene sequencing tests and advocate for this strategy to shorten the diagnostic odyssey.

Moving from analysis of single target genes to exome sequencing and finally to full genome sequencing will also lead to substantial increases in the amount of information available. Consequently, the understanding of underlying genetic components of neuromuscular diseases will continue to expand beyond causal variants; there are likely to be myriad modifier genes that influence neuromuscular disease progression and severity that are yet to be discovered. Wider use of genetic testing will therefore both contribute to understanding these influences and subsequently help with disease prognosis and care decisions.

New genetic tests and improving longitudinal data were both ranked as being likely to progress and likely to have an impact within their practice by participants in the Neuromuscular Disease Healthcare Provider Survey (see Exhibit 20), indicating that the implications of evolving genetic technologies are widely recognized.

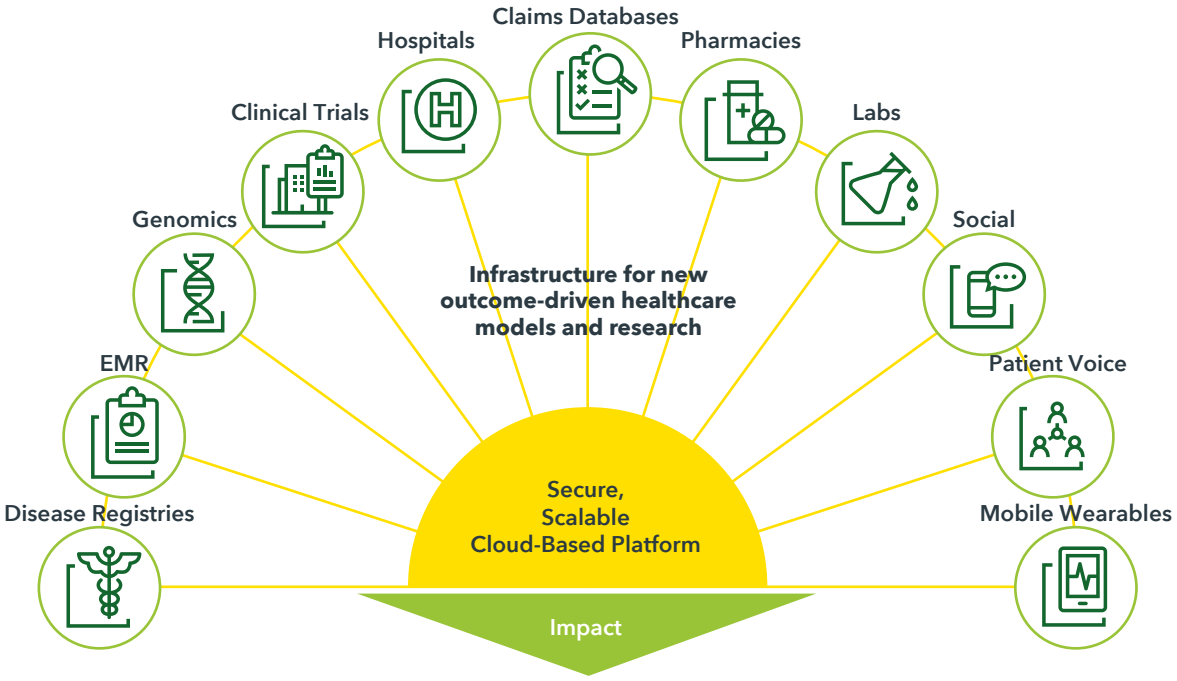
DEVELOPMENT OF DATA HUBS

For neuromuscular diseases, patient registries are effective tools for understanding the prevalence and natural history of disease, measuring quality of care, identifying patients for clinical trials and assessing the safety and effectiveness of new treatments. These tools are particularly applicable in the rare disease space, where sufficient populations of patients to draw conclusions may be geographically dispersed and difficult to track.

Neuromuscular disease registries have existed for over a decade and have evolved over that time. Initial databases of patient diagnoses and basic information have been, and are still being added to or redesigned, to capture many additional details: treatments, outcomes, expenses, comorbidities, family history and even patient-reported outcomes and real-world measurements collected from wearables or smart phones. These newer 'data hubs', such as the Muscular Dystrophy Association's MOVR (neuroMuscular ObserVational Research) hub, aim to drive improved clinical outcomes through identifying best care practices and facilitate optimization of care improvement and drug development (see Exhibit 21).

Through building up databases of de-identified patient records that are linked together, registries can gather cumulative longitudinal data of patients with a given neuromuscular disease. Analysis of these data will help improve understanding of disease manifestation, progression and unique attributes of the population that are not widely understood today. Of particular interest may be the longitudinal tracking of emerging clinical trial metrics (e.g., the 6-minute walk test, expression levels of proteins of interest) in larger patient populations, in order to provide a more comprehensive understanding of their usual trajectories and to establish potential historical patient cohorts as trial controls. In addition, there is potential for the complex datasets to help identify novel biomarkers. Data could also be leveraged to validate proposed outcome measures and determine clinical trial endpoints, better establishing clinical trial readiness in diseases where there is not a robust history of previous pipeline studies. This range of diverse

Exhibit 21: Data Hubs as a Means to Accelerate Advancements in Neuromuscular Disease Care



Source: IQVIA, Jul 2018

uses provide findings that will be relevant to a variety of stakeholders including healthcare providers, drug developers and regulatory authorities.

Registries are also increasingly serving a more direct role in drug development through providing a centralized source for patient identification for clinical trials. Many registries can directly reach out to patients with details about clinical trials for which they are eligible, based on information already available within the registry database. In this scenario, the registry is acting something like air traffic control, optimizing engagement of patients with clinical trials and streamlining their recruitment. As numbers of clinical trials in the neuromuscular disease space grow, this service is likely to become more important as patient recruitment becomes an increasing challenge, leading to trial delays due to low patient enrollment.

In addition to recruitment, registry data can be leveraged to optimize trial design. Feasibility checks against registered patient populations will help drug developers to understand the best inclusion/exclusion criteria for trial, optimal endpoints to quantify efficacy of drug and potential additional considerations, such as the proportion of patients who have a relevant comorbidity.

Following approval of new medications, the data capture infrastructure of registries is likely to be useful for post-marketing studies, which can leverage these services to track patient responses to new treatments over time, assessing long-term safety and effectiveness. An additional consideration is that longitudinal tracking of patient expenses over time may help understand the true financial implications of novel therapies and their knock-on effects on other healthcare expenses.

In addition to logging metrics of disease progression and optimizing clinical trials, registries can also be used to better understand the quality of care typically received by patients with a given neuromuscular disease and to track outcomes that are associated with particular care decisions. This information can be leveraged to identify quality of care challenges and opportunities to

improve care, potentially informing the recommended standard of care and treatment paradigm.

Improving ability to more completely distinguish subpopulations of patients on the basis of genetics (described above) will also contribute to the value of patient registries by helping to parse out the influence of genetics to disease progression and treatment response. In this manner, improving genetic diagnosis and patient registries work hand-in-hand to advance understanding and care.

LEVERAGING DIGITAL TECHNOLOGY ADVANCES

Advances in digital technologies are likely to continue to improve patient monitoring and enable a better understanding of disease progression to optimize care.

One strategy for leveraging technology to ease patient burden is the use of telemedicine, especially for those patients with neuromuscular disease for whom travel to appointments is particularly burdensome. This may be due to the distance they need to travel to a specialized clinic; for example, 25% of individuals with ALS are reported to live more than 100 miles from the nearest specialized ALS center.[102] Patients with neuromuscular disease may also encounter travel difficulties due to disease progression or lack of access to accessible transportation options. Telemedicine appointments vary in nature; they could entail a one-to-one consultation by video, a team consultation with a patient, or performance of tests and assessments at a patient's local facility that are then reviewed by a specialist team elsewhere. Despite early adoption of telemedicine services by the neurology community in general, use in the treatment of neuromuscular disease has been less consistent. Historically, there have been several general barriers associated with the use of telehealth services, such as legal concerns, particularly across state boundaries, and reimbursement uncertainties.[103] However, federal legislation passed in February 2018 are likely to loosen restrictions and expand coverage of telehealth services,[104] especially for the approximately 15–25% of patients covered by Medicare.[29] Additional barriers to more widespread use of telemedicine in the neuromuscular patient population include the multi-disciplinary care model and the longer-term care management required, especially for childhood-onset diseases.

The applicability and specialization of available telemedicine services vary by disease area and is usually considered to be most appropriate for routine appointments following diagnosis confirmation. Providers indicate that the resource may be especially appropriate for patients with ALS, who have the highest number of annual visits among neuromuscular diseases,[29] and where exam focus is more centered on patient functionality and ability to perform daily tasks. Replacement of traditional ALS clinic visits with remote appointments has been shown to lead to no significant difference in disease progression.[105,106] Although ALS has been almost an exclusive pilot area for the use of telemedicine in the treatment of neuromuscular disease, a small study recently showed similar trends of decreased anxiety and hospitalizations for patients with FSHD utilizing telemedicine support.[107] Telemedicine programs also have the potential to improve access to psychological support services for patients with neuromuscular disease, a current area of need.[29]

In addition to traditional telemedicine appointments, the use of innovative digital health approaches for monitoring, measuring and patient support may also impact neuromuscular disease care. Instruments for home-based monitoring of respiratory parameters have existed for a decade but have been mainly employed in ALS.[106] Proposed technologies that could be applied to neuromuscular disease include use of gaming sensors to assess motion and leveraging personal devices to track ambulation parameters and even gait. Ultimately, linkage of readouts from such tools to a patient's electronic medical records (EMR) could be valuable for disease monitoring and treatment decisions. In the near

term, real-time monitoring may be able to give insights into which patients could benefit from additional care (e.g., multiple falls, nocturnal hypoventilation readings). Further in the future, a combination of real-time data and improved understanding of disease trajectory may facilitate early recognition of warning signs or patterns so that alerts can be sent to medical personnel and imminent issues can be averted. However, new devices still need to demonstrate adequate accuracy, reliability and safety before their use becomes routine, and respondents to the Neuromuscular Disease Healthcare Provider Survey are lukewarm in their expectations of the impact of digital health on their practice within the next five years.

Outside of the integration of digital technologies within the healthcare context, the widespread availability of touchscreen technologies and personal devices is improving social network, ability to function and information access among patients.

PREPARING THE WAY FOR SUCCESSFUL CLINICAL TRIALS

As more therapies make their way towards the clinic, it is also important to consider how the neuromuscular disease community can work together to help clinical trials to be successful.

There are two areas of difficulty in which opportunities exist to capitalize on registries or data hubs to smooth the trial process. The first consideration is to facilitate the identification of trial participants, which is often a challenge for trials in rare diseases. Sites that participate in patient registries could be leveraged to increase the ability of trial coordinators to identify and reach out to patients and sites who may be interested in upcoming trials.

Secondly, collated patient information from data hubs will improve understanding of characteristics of the patient pool and important subpopulations. These data will be useful in improving the design of clinical trials by allowing both better understanding of the implications of inclusion/exclusion criteria on eligible patient population (e.g., comorbidities), and improving assumptions about baseline (control) population performance and inter-patient variability against endpoint measures.

> *"The way I envision [the future of digital monitoring] is that I should come in, log into my EMR and there should be names flashing up of patients who really need attention. Ideally, because they're approaching a milestone where we can prevent problems."*
>
> *James Berry, M.D., M.P.H.*
> *Massachusetts General Hospital, Neuromuscular Division*

Outside of improving data, an opportunity exists to decrease barriers to clinical trial setup by equipping interested sites now with the capabilities and equipment to participate as a trial location. This would both increase the geographical coverage of capable trial sites and potentially decrease time to initiate future trials. As it becomes more established which endpoints should be used to evaluate new therapies, sites can prepare by acquiring the needed equipment or training. This is likely to require a financial and time investment and may be an area where non-profit organizations have the opportunity to invest in creating a trial-friendly ecosystem that will have long-term payoff for the patients they represent. These expenses could be shared through collaboration with interested pharmaceutical companies through a pre-competitive

consortium model, as pioneered by the Multiple Myeloma Research Foundation.[108]

IMPROVING CARE PARADIGMS

As described earlier in this report, there is currently variation in neuromuscular disease care, but there is also the increasing potential to aggregate shared learnings and data across providers to assist in widespread optimization of care approaches. Centralized data hubs aim to gather data from clinics nationwide to gather insights. Providers feel that both open knowledge-sharing and the optimization of treatment pathways are the most valuable benefits derived from a centralized network of care centers.[29] Given the high time-burden to comply fully with current care guidelines for many neuromuscular diseases, a valuable early use for aggregated data may be to prioritize these recommendations to reduce the overall burden of assessments.

An important consideration is the maintenance of a bi-directional communication flow between providers and hub organizers, so that community consensus on insights and recommendations can be achieved, while being conscious of security and privacy concerns associated with the transfer of medical information. It is also increasingly important to minimize provider burden associated with registries and data gathering. With increasing interest in the neuromuscular disease space, providers feel under pressure to provide data – which may be difficult to obtain, anonymize and filter – to many different organizations. Potential options to offset provider burden include reciprocal registries (i.e., registries that provide the ability to share data with multiple organizations) to minimize duplication, and better strategies to glean data directly from EMRs.

How to 'future-proof' current care setups to streamline integration of novel 'game-changing' therapies is another area to consider to optimize care in a growing number of neuromuscular diseases. New medications (e.g., nusinersen, eteplirsen) require both cross-stakeholder collaboration to maximize access and cross-department coordination for administration. For these patients, the boundaries of the specialized clinic model are blurred, requiring considerable investment and reorganization for many care sites. Shared learnings from experiences around these initial therapies are likely to be valuable in establishing a set of best practice guidelines for smooth integration of newly approved therapies, including advice for engagement of new providers or departments and management of reimbursement issues.

LOWERING BARRIERS THROUGH INSURANCE REFORM

A common concern in care of neuromuscular disease is how to pay for multidisciplinary care. Earlier in this report, we discussed some financial barriers to optimal care, including insurance limitations on appointment numbers with some types of provider, and patient copay responsibilities. Recently, some organizations have been exploring whether bundled payments are a viable strategy to consolidate payment for a set continuum of healthcare services for a specific condition. The Centers for Medicare and Medicaid launched a bundled payment program in 2015 which covered 48 'types' of care episode,[109] although proposed mandatory participation requirements were recently revised to allow additional time to engage stakeholders and validate value-based care models. For commercial payers, bundled payment uptake has been inconsistent and minimal, with estimates of current commercial payments that are through bundled billing as low as <2%, despite evidence of cost savings in pilot programs.[110] Little precedent exists for bundled billing for outpatient neuromuscular disease care, but with more conversations ongoing about the benefits of value-based care approaches, opportunity may exist for patient advocacy organizations to act collaboratively to bring about change in how multidisciplinary care is paid for across these diseases.

The high costs of current and future disease-modifying therapies are also a topic of concern across stakeholders, especially as growing numbers of expensive medications for small populations accumulate on the market. As discussed more fully in the report Orphan Drugs in the United States,[111] drugs for orphan diseases account for a small but growing fraction of healthcare expenditure. However, the prices of new drugs for neuromuscular diseases (e.g., eculizumab nusinersen, eteplirsen) fall in the top 10% of orphan products. Payer strategies to offset rising costs to date have included options that increase barriers to the patient (e.g., limiting access to the patients most likely to benefit through stratification with biomarkers, shifting more responsibility for payment to the patient) and those that attempt to lower price (e.g., consolidation to increase negotiation power). The former is often countered through the provision of patient support services by manufacturers, including Biogen (SMA360° for nusinersen) and Sarepta (SareptAssist for eteplirsen). However, sustainable solutions are likely to look different than any of these options.

Notes on sources

This report is based on the IQVIA services detailed below.

IQVIA Pipeline Intelligence™ is a drug pipeline database containing up-to-date R&D information on over 39,000 drugs in development worldwide. The database captures the full process of R&D, covering activity from discovery stage through preclinical and clinical development, to approval and launch. The information in Ark R&D Intelligence is manually curated by a team of scientifically trained analysts to ensure quality and relevance.

U.S. National Sales Perspectives (NSP)™ measures revenue within the U.S. pharmaceutical market by pharmacies, clinics, hospitals and other healthcare providers. NSP reports 100% coverage of the retail and non-retail channels for national pharmaceutical sales at actual transaction prices. The prices do not reflect off-invoice price concessions that reduce the net amount received by manufacturers.

National Disease and Therapeutic Index (NDTI)™ is a database of de-identified patient contacts with office-based physicians projected from a panel of physicians in the United States who report on all patient contacts for two consecutive workdays each quarter. Information collected includes patient demographics, diagnosis and treatment information, and physician demographics.

National Prescription Audit (NPA)™ is a suite of services that provides the industry standard source of national prescription activity for all products and markets.

IQVIA Real-World Data is a suite of services that provides near census level coverage of dispensed prescription information at a prescriber and insurance plan level and tracks de-identified anonymous patient records over time to analyze distinct usage patterns.

IQVIA Professional Medical Claims Data is a component of IQVIA's Real World Data that includes patient level diagnosis, procedures and in-office treatments and drug administrations as billed by healthcare providers, ambulatory and general healthcare sites.

Appendix

Appendix Exhibit A: Point Prevalence Estimates for Neuromuscular Diseases

Disease	Per 100K	Type	Location	Reference
ALS	4.7	Prevalence	Ireland	Traynor BJ et al. Amyotrophic Lateral Sclerosis Mimic Syndromes. Arch Neurol. 2000.
ALS	4.34	Prevalence	Northern Europe	Brooks BR. Clinical Epidemiology of Amyotrophic Lateral Sclerosis. Neurologic Clinics. 1996
ALS	4	Prevalence	Global	Hirtz D et al. How Common are the 'Common' Neurologic Disorders?" Neurology. 2007.
ALS	3.9	Prevalence	United States	Mehta, P. et al. Prevalence of Amyotrophic Lateral Sclerosis - United States, 2012–2013. Surv. Summ. 2016.
ALS	3.85	Prevalence	Global	Orphanet Report Series - Prevalence of rare diseases: Bibliographic data - June 2018
BMD	7.29	Prevalence	England	Norwood FLM et al; "Prevalence of Genetic Muscle Disease in Northern England: In-Depth Analysis of a Muscle Clinic Population." Brain. 2009
BMD	2	Prevalence (male)	North America	Romitti PA et al; "Prevalence of Duchenne and Becker Muscular Dystrophies in the United States." Pediatrics;
BMD	1.53	Prevalence (male)	Global	Mah JK et al; "A Systematic Review and Meta-Analysis on the Epidemiology of Duchenne and Becker Muscular Dystrophy." Neuromuscular Disorders
BMD	1.53	Prevalence	Global	Orphanet Report Series - Prevalence of rare diseases: Bibliographic data - June 2018
CMD	0.99	Prevalence	Global	Mah, Jk. Et al. A Systematic Review and Meta-analysis on the Epidemiology of the Muscular Dystrophies. Can J Neurol Sci. 2016.
CMD	0.89	Prevalence	England	Norwood FLM et al; "Prevalence of Genetic Muscle Disease in Northern England: In-Depth Analysis of a Muscle Clinic Population." Brain. 2009
CMD	0.33	Prevalence	Global	Orphanet Report Series - Prevalence of rare diseases: Bibliographic data - June 2018
CMT	40	Prevalence	Global	McCorquodale D et al; "Management of Charcot-Marie-Tooth Disease: Improving Long-Term Care with a Multidisciplinary Approach." Journal of Multidisciplinary Healthcare; V.9; 1/19/16;
CMT	25	Prevalence	Global	Orphanet Report Series - Prevalence of rare diseases: Bibliographic data - June 2018
CMT	17	Prevalence	Global	Nicolaou P et al; "Charcot-Marie-Tooth Disease in Cyprus: Epidemiological, Clinical and Genetic Characteristics." Neuroepidemiology; V.35; 2010; p171; DOI:10.1159/000314351)
CMT	9.8	Prevalence	England	Bargiela D et al; "Prevalence of Neurogenetic Disorders in the North of England." Neurology; V.85; No.14; 10/6/15;
CMT	5.4	Prevalence	USA	Nicolaou P et al; "Charcot-Marie-Tooth Disease in Cyprus: Epidemiological, Clinical and Genetic Characteristics." Neuroepidemiology; V.35; 2010; p171; DOI:10.1159/000314351)
Congenital Myopathies	1.37	Prevalence	England	Norwood FLM et al; "Prevalence of Genetic Muscle Disease in Northern England: In-Depth Analysis of a Muscle Clinic Population." Brain. 2009
DMD	15	Prevalence (male 5–24)	United States	CDC. Prevalence of Duchenne/Becker Muscular Dystrophy Among Males Aged 5–24 Years. Four States). Morbidity and Mortality Weekly Report. 2007
DMD	8.29	Prevalence (male)	Global	Norwood FLM et al; "Prevalence of Genetic Muscle Disease in Northern England: In-Depth Analysis of a Muscle Clinic Population." Brain. 2009
DMD	7	Prevalence (male)	North America	Romitti PA et al; "Prevalence of Duchenne and Becker Muscular Dystrophies in the United States." Pediatrics;
DMD	6	Prevalence (males)	Global	Beynon RP et al; "Cardiac Involvement in Muscular Dystrophies." Q J Med. 2008
DMD	4.8	Prevalence (male)	Global	Mah JK et al; "A Systematic Review and Meta-Analysis on the Epidemiology of Duchenne and Becker Muscular Dystrophy." Neuromuscular Disorders

Disease	Per 100K	Type	Location	Reference
DMD	4.78	Prevalence	Global	Orphanet Report Series - Prevalence of rare diseases: Bibliographic data - June 2018
DMD	4.8	Prevalence (male)	Global	Pringsheim T et al; "The International Incidence and Prevalence of Neurologic Conditions: How Common Are They?" Neurology
DMD	1.5	Prevalence (male, age 5–9)	North America	Romitti PA et al; "Prevalence of Duchenne and Becker Muscular Dystrophies in the United States." Pediatrics;
Emery-Dreifuss	1	Prevalence	Global	Beynon RP et al; "Cardiac Involvement in Muscular Dystrophies." Q J Med. 2008
Emery-Dreifuss	0.13	Prevalence	England	Norwood, F. et al. Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. Brain. 2009
Friedreich's Ataxia	3.5	Prevalence	Europe	Schultz, J.B. et al.Diagnosis and treatment of Friedreich ataxia: a European perspective.Nat Rev Neuro. 2009.
Friedreich's Ataxia	2	Prevalence	Global	Orphanet Report Series - Prevalence of rare diseases: Bibliographic data - June 2018
FSHD	5	Prevalence	Global	Beynon RP et al; "Cardiac Involvement in Muscular Dystrophies." Q J Med. 2008
FSHD	4.5	Prevalence	Global	Orphanet Report Series - Prevalence of rare diseases: Bibliographic data - June 2018
FSHD	3.95	Prevalence	England	Norwood FLM et al; "Prevalence of Genetic Muscle Disease in Northern England: In-Depth Analysis of a Muscle Clinic Population." Brain. 2009
FSHD	3.95	Prevalence	England	Norwood, F. et al. Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. Brain. 2009
LEMS	0.35	Prevalence	Global	Orphanet Report Series - Prevalence of rare diseases: Bibliographic data - June 2018
LGMD	2.6	Prevalence	Global	Orphanet Report Series - Prevalence of rare diseases: Bibliographic data - June 2018
LGMD	2.27	Prevalence	England	Norwood FLM et al; "Prevalence of Genetic Muscle Disease in Northern England: In-Depth Analysis of a Muscle Clinic Population." Brain. 2009
LGMD	2.27	Prevalence	England	Norwood, F. et al. Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. Brain. 2009
LGMD	1.63	Prevalence	Global	Mah, Jk. Et al. A Systematic Review and Meta-analysis on the Epidemiology of the Muscular Dystrophies. Can J Neurol Sci. 2016.
Mitochondrial Myopathies	6.25	Prevalence*	United States	https://mitochondrialdiseasenews.com/2015/08/26/mitochondria-many-disorders-compose-mitochondrial-disease/
Mitochondrial Myopathies	6.1	Prevalence*	England	Schaefer A.M. et al. Prevalence of Mitochondrial DNA Diseasein Adults. Ann. Neurol. 2007
Myasthenia Gravis	20	Prevalence	United States (high))	Howard, J. Clinical Overview of MG. Myasthenia gravis foundation of America
Myasthenia Gravis	15.38	Prevalence	Ireland	Rutledge, S. et al. Myasthenia gravis: a population-based epidemiological study. Ir Med J. 2016
Myasthenia Gravis	14	Prevalence	United States (low)	Howard, J. Clinical Overview of MG. Myasthenia gravis foundation of America
Myasthenia Gravis	7.77	Prevalence	Global	Orphanet Report Series - Prevalence of rare diseases: Bibliographic data - June 2018
Myotonic Dystrophy	12.5	Prevalence	Global	Meola G et al; "Myotonic Dystrophies: An Update on Clinical Aspects, Genetic, Pathology,and Molecular Pathomechanisms." Biochimica et Biophysica Acta
Myotonic Dystrophy	10.6	Prevalence	England	Norwood, F. et al. Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. Brain. 2009
Myotonic Dystrophy	8.36	Prevalence	Global	Mah, Jk. Et al. A Systematic Review and Meta-analysis on the Epidemiology of the Muscular Dystrophies. Can J Neurol Sci. 2016.
Myotonic Dystrophy	6.7	Prevalence	Global	Orphanet Report Series - Prevalence of rare diseases: Bibliographic data - June 2018

Appendix

Disease	Per 100K	Type	Location	Reference
OPMD	0.13	Prevalence	England	Norwood, F. et al. Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. Brain. 2009
SMA	2.9	Prevalence	United States	Lally et al. Indirect estimation of the prevalence of spinal muscular atrophy Type I, II, and III in the United States. Orphanet J. Rare. Dis. 2017.
SMA	2	Prevalence	Global (high)	Verhaart, I.E.C. et al. Prevalence, incidence and carrier frequency of 5q–linked spinal muscular atrophy – a literature review. Orphanet J Raree Dis. 2017.
SMA	1.87	Prevalence	England	Norwood, F. et al. Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. Brain. 2009
SMA	1	Prevalence	Global (low)	Verhaart, I.E.C. et al. Prevalence, incidence and carrier frequency of 5q–linked spinal muscular atrophy – a literature review. Orphanet J Raree Dis. 2017.

*Calculated from population size

Appendix Exhibit B: Per Patient Healthcare Charges by Disease

ICD-10 Disease Diagnosis	Median	10th Percentile	25th Percentile	75th Percentile	90th Percentile
Ion Channel Diseases	**$12,019.26**	**$910.18**	**$3,265.11**	**$44,445.00**	**$163,186.24**
Other Specified Myotonic Disordersa	$15,559.93	$1,068.71	$4,374.68	$52,909.43	$204,607.40
Periodic Paralysis	$12,673.17	$903.94	$3,457.35	$50,625.95	$174,880.62
Myotonia Congenital	$8,300.44	$806.89	$2,624.56	$28,024.40	$111,625.96
Mitochondrial Diseases	**$15,950.06**	**$759.98**	**$4,037.89**	**$65,817.21**	**$259,268.43**
Melas Syndrom[e]	$25,252.62	$1,331.28	$6,535.87	$116,746.34	$527,842.85
Leigh's Disease	$23,416.29	$289.02	$4,495.47	$111,093.11	$453,773.40
Mitochondrial Myopathy, Not Elsewhere Classified[b]	$20,659.00	$1,637.83	$6,050.00	$77,753.70	$298,026.04
Kearns-Sayre Syndrome, Unspecified Eye	$19,836.45	$1,229.50	$5,305.63	$87,571.34	$388,859.65
Mitochondrial Metabolism Disorder, Unspecified	$19,648.87	$1,294.93	$5,138.32	$82,537.88	$305,950.27
Merrf Syndrome	$19,295.19	$566.95	$3,800.36	$105,782.13	$372,284.90
Other Mitochondrial Metabolism Disorders[c]	$18,612.88	$589.92	$3,982.29	$84,080.06	$324,095.68
Kearns-Sayre Syndrome, Right Eye	$15,306.72	$1,004.45	$5,588.05	$61,544.70	$302,367.87
Progressive External Ophthalmoplegia, Right Eye	$15,225.26	$1,381.87	$4,385.25	$65,629.35	$268,542.63
Mitochondrial Metabolism Disorders	$15,054.39	$281.41	$3,642.55	$34,003.63	$79,058.46
Progressive External Ophthalmoplegia, Left Eye	$14,322.24	$1,259.01	$3,821.96	$63,388.12	$238,615.96
Kearns-Sayre Syndrome, Bilateral	$14,292.80	$1,316.93	$3,941.00	$39,001.41	$171,937.20
Progressive External Ophthalmoplegia, Unspecified Eye	$12,513.13	$1,072.99	$3,675.74	$52,891.85	$211,218.47
Early-Onset Cerebellar Ataxia	$12,133.03	$432.20	$3,126.58	$47,235.99	$188,242.75
Progressive External Ophthalmoplegia, Bilateral	$11,655.19	$1,292.93	$3,572.81	$40,989.79	$139,679.02
Kearns-Sayre Syndrome, Left Eye	$10,490.99	$746.19	$2,242.73	$40,229.64	$62,995.67

ICD-10 Disease Diagnosis	Median	10th Percentile	25th Percentile	75th Percentile	90th Percentile
Motor Neuron Diseases	**$17,878.78**	**$490.60**	**$4,478.75**	**$61,816.63**	**$235,017.46**
Motor Neuron Disease, Unspecified	$24,848.90	$2,072.00	$8,000.08	$77,764.30	$283,493.86
Other Motor Neuron Diseases[d]	$19,461.28	$1,264.83	$5,686.27	$66,199.68	$266,294.35
Spinal Muscular Atrophy, Unspecified	$20,629.29	$1,076.16	$7,400.70	$52,628.10	$178,823.55
Progressive Bulbar Palsy	$23,497.60	$1,058.95	$6,358.97	$98,052.42	$414,477.27
Other Spinal Muscular Atrophies And Related Syndromes[e]	$18,860.78	$898.74	$4,883.52	$74,499.94	$277,941.51
Infantile Spinal Muscular Atrophy, Type I [Werdnig-Hoffman]	$36,329.00	$681.76	$5,676.00	$198,887.01	$722,553.71
Other Inherited Spinal Muscular Atrophy[f]	$16,877.24	$320.10	$3,228.54	$78,811.95	$332,215.20
Amyotrophic Lateral Sclerosis	$14,811.83	$153.25	$3,263.20	$54,138.49	$205,769.36
Muscular Dystrophies	**$10,096.61**	**$255.69**	**$2,315.47**	**$41,403.49**	**$181,634.40**
Myotonic Muscular Dystrophy	$9,834.40	$506.83	$2,677.72	$38,764.33	$173,040.89
Muscular Dystrophy	$9,577.69	$177.69	$2,094.51	$39,913.30	$175,372.95
Myopathies	**$3,161.28**	**$0.00**	**$0.00**	**$19,894.59**	**$94,916.59**
Polymyositis with Respiratory Involvement	$31,464.78	$3,248.84	$9,700.37	$114,577.28	$508,839.16
Dermatopolymyositis, Unspecified with Respiratory Involvement	$31,451.73	$3,162.77	$9,913.97	$119,379.60	$476,217.96
Myopathy in Diseases Classified Elsewhere	$24,713.90	$2,108.51	$7,146.37	$93,770.14	$333,370.78
Dermato(Poly)Myositis in Neoplastic Disease	$23,131.78	$1,825.75	$6,157.73	$134,613.56	$557,856.27
Polymyositis with Other Organ Involvement	$21,672.72	$2,502.80	$7,138.38	$80,251.18	$412,077.81
Other Dermatomyositis with Respiratory Involvement[g]	$21,517.47	$2,974.94	$8,344.54	$105,865.74	$519,119.91
Polymyositis with Myopathy	$20,365.02	$2,226.96	$6,814.42	$70,678.38	$282,404.26
Juvenile Dermatomyositis with Other Organ Involvement	$19,853.44	$1,750.48	$5,145.53	$114,230.41	$397,489.75
Polymyositis, Organ Involvement Unspecified	$19,216.26	$1,887.66	$6,191.72	$69,113.54	$271,558.30
Pompe Disease	$19,145.14	$335.05	$3,391.99	$143,748.68	$664,080.69
Other Primary Disorders of Muscles[h]	$18,499.61	$1,388.15	$5,689.18	$61,673.63	$275,813.52
Polymyositis	$18,443.11	$4,940.39	$7,424.19	$83,332.87	$292,674.99
Other Dermatomyositis with Other Organ Involvement	$18,409.85	$2,242.68	$6,392.78	$76,876.62	$328,041.40
Ruvalcaba-Myhre-Smith Syndrome	$17,212.21	$1,235.33	$3,982.40	$76,507.82	$211,928.28
Dermatopolymyositis, Unspecified with Myopathy	$17,067.08	$1,824.20	$5,657.65	$64,938.77	$278,478.72
Juvenile Dermatomyositis with Respiratory Involvement	$16,798.99	$1,394.39	$4,425.10	$65,700.35	$272,104.22
Other Glycogen Storage Disease[i]	$16,754.08	$826.75	$3,603.32	$79,177.65	$323,692.55

Appendix

ICD-10 Disease Diagnosis	Median	10th Percentile	25th Percentile	75th Percentile	90th Percentile
Iatrogenic Carnitine Deficiency	$16,405.24	$351.36	$3,478.75	$53,354.83	$183,508.36
Other Dermatomyositis with Myopathy	$15,822.48	$2,010.38	$5,407.03	$47,669.00	$176,697.90
Anemia Due to Disorders of Glycolytic Enzymes	$15,348.62	$862.09	$3,675.09	$61,463.00	$220,037.98
Other Dermatomyositis, Organ Involvement Unspecified	$15,205.97	$2,182.74	$5,383.25	$53,083.60	$233,915.55
Dermatopolymyositis, Unspecified with Other Organ Involvement	$14,222.30	$1,543.94	$4,378.74	$59,016.89	$246,765.48
Dermatopolymyositis, Unspecified, Organ Involvement Unspecified	$13,926.20	$1,508.76	$4,593.76	$47,858.17	$194,841.07
Dermatopolymyositis, Unspecified	$13,587.97	$1,530.08	$5,663.47	$50,895.40	$185,838.35
Congenital Myopathies	$13,243.78	$215.30	$2,624.57	$61,730.70	$260,210.54
Disorders of Pyruvate Metabolism and Gluconeogenesis	$13,189.06	$579.46	$3,037.75	$67,438.89	$308,744.27
Inclusion Body Myositis [Ibm]	$12,463.94	$850.25	$3,748.46	$43,316.99	$169,415.19
Juvenile Dermatomyositis, Organ Involvement Unspecified	$11,856.59	$881.47	$3,257.80	$47,634.71	$224,804.31
Primary Carnitine Deficiency	$11,756.70	$247.93	$2,609.43	$28,300.12	$69,288.87
McArdle Disease	$11,068.37	$966.15	$3,148.20	$48,881.68	$196,806.58
Myoadenylate Deaminase Deficiency	$10,941.56	$875.35	$3,347.50	$29,324.17	$126,925.28
Disorder Of Carnitine Metabolism, Unspecified	$10,772.26	$702.40	$2,850.78	$37,528.79	$147,466.02
Muscle Carnitine Palmitoyltransferase Deficiency	$10,189.34	$291.18	$2,014.94	$48,980.33	$160,789.89
Juvenile Dermatomyositis with Myopathy	$9,454.75	$679.26	$2,803.00	$35,517.67	$183,183.54
Cori Disease	$9,387.00	$57.47	$2,000.34	$38,410.00	$144,178.68
Other Secondary Carnitine Deficiency[j]	$9,233.32	$185.08	$1,887.32	$35,894.75	$103,218.38
Carnitine Deficiency Due to Inborn Errors of Metabolism	$886.00	$0.00	$0.00	$8,597.40	$52,761.89
Neuromuscular Junction Diseases	**$19,037.98**	**$1,716.28**	**$5,791.15**	**$75,476.36**	**$315,682.89**
Toxic Myoneural Disorders	$130,632.48	$11,540.42	$37,603.99	$295,257.06	$597,026.08
Lambert-Eaton Syndrome in Disease Classified Elsewhere	$76,129.82	$4,080.67	$13,790.47	$364,412.10	$1,138,001.00
Other Specified Myoneural Disorders[k]	$32,160.64	$2,602.24	$9,732.40	$121,988.09	$512,890.38
Myasthenia Gravis with (Acute) Exacerbation	$31,803.72	$2,528.07	$9,075.94	$149,996.91	$608,790.07
Myoneural Disorder, Unspecified	$30,416.38	$2,078.31	$8,132.44	$123,144.57	$448,896.28
Myasthenia Gravis	$27,007.27	$2,597.50	$6,523.26	$110,922.29	$493,841.72
Lambert-Eaton Syndrome, Unspecified	$25,301.80	$1,864.34	$6,617.56	$122,782.27	$527,385.52
Congenital and Developmental Myasthenia	$16,366.21	$1,111.63	$4,992.26	$68,628.67	$303,924.10
Myasthenia Gravis without (Acute) Exacerbation	$14,921.21	$1,487.00	$4,796.00	$51,037.39	$213,128.78

ICD-10 Disease Diagnosis	Median	10th Percentile	25th Percentile	75th Percentile	90th Percentile
Peripheral Nerve Diseases	**$16,624.94**	**$1,707.99**	**$5,613.46**	**$47,697.48**	**$149,584.37**
Other Hereditary and Idiopathic Neuropathies[l]	$18,577.05	$2,320.35	$6,754.27	$50,618.51	$151,703.40
Hereditary Motor and Sensory Neuropathy	$12,556.81	$987.05	$3,772.62	$40,264.32	$141,628.52

Source: IQVIA Advanced Analytics, Aug 2018

Notes: ICD = International Classification of Diseases. See Methods. Data shown in Appendix Exhibit B for individual diseases represents ICD-10 diagnosis codes only with the exception of Diagnosis Group categories. Diagnoses for which there were <15 patients in our data are not shown.

The official guidelines for ICD-10-includes codes titled "other," "other specified," or "not elsewhere classified". These codes represent specific disease entities for which no specific code exists. The "Other" line items within Appendix Exhibit B represent include the following ICD codes:

a. G71.19: Applicable to: Myotonia fluctuans; Myotonia permanens; Neuromyotonia [Isaacs]; Paramyotonia congenita (of von Eulenburg); Pseudomyotonia; Symptomatic myotonia. Approximate Synonyms: Bilateral myotonic cataract; Left myotonic cataract; Myotonic cataract; Myotonic disorder; Paramyotonia congenita; Right myotonic cataract

b. G71.3: Approximate synonyms: Mitochondrial myopathy; Mitochondrial ocular myopathy; Myopathy, mitochondrial

c. E88.49: Approximate synonyms: Disorder of mitochondrial respiratory chain complexes; Mitochondrial disorder, respiratory chain

d. G12.29: Approximate synonyms: Anterior horn cell disease; Paralysis, supranuclear; Primary lateral sclerosis; Pseudobulbar palsy; Supranuclear paralysis

e. G12.8: No approximate synonyms listed

f. G12.1: Applicable To: Adult form spinal muscular atrophy; Childhood form, type II spinal muscular atrophy; Distal spinal muscular atrophy; Juvenile form, type III spinal muscular atrophy [Kugelberg-Welander]; Progressive bulbar palsy of childhood [Fazio-Londe]; Scapuloperoneal form spinal muscular atrophy. Approximate Synonyms: Adult spinal muscular atrophy; Atrophy, spinal muscular, juvenile; Kugelberg-Welander disease; Spinal muscular atrophy; Spinal muscular atrophy, adult; Spinal muscular atrophy, type 2; Spinal muscular atrophy, type ii

g. M33.11: No approximate synonyms listed

h. G71.8: Approximate synonyms: Benign monomelic amyotrophy; Monomelic amyotrophy

i. E74.09: Applicable to: Andersen disease; Hers disease; Tauri disease; Glycogen storage disease, types 0, IV, VI-XI; Liver phosphorylase deficiency; Muscle phosphofructokinase deficiency

j. E71.44: No approximate synonyms listed

k. G70.89: No approximate synonyms listed

l. G60.8: Applicable to: Dominantly inherited sensory neuropathy; Morvan's disease; Nelaton's syndrome; Recessively inherited sensory neuropathy. Approximate Synonyms: Idiopathic small fiber peripheral neuropathy; Neuropathy (nerve damage), hereditary sensory; Notalgia paresthetica

Methodology

IQVIA REAL-WORLD DATA ANALYSIS

IQVIA Real-World Data, including medical claims and prescription information, was used to assess the annual healthcare charges associated with an ICD-9 or ICD-10 neuromuscular disease diagnosis code across myopathies, peripheral nerve diseases, neuromuscular junction diseases, motor neuron diseases, muscular dystrophies, mitochondrial diseases and ion channel diseases. Amounts shown represent pre-adjudicated healthcare claims charges and are not projected to the national level. Records of charges were pulled for all patients with a neuromuscular disease diagnosis code in the time frame July 2015–June 2017. Charges were obtained at the per-patient total charges level and rolled up.

Average total annual medical charges represent the sum of inpatient charges, visit charges and prescription charges, calculated for the timeframes July 2015–June 2016 and July 2016–June 2017 and then averaged. This is additionally calculated for each individual patient group, based on the diagnoses that fall into each disease grouping. When analyzing the range of charges per disease group, means were seen to greatly exceed medians in certain groups due to very high charges among a subset of patients. Outlier values including zero values and extremely high values were included in the analysis.

Un-projected medical claims data are estimated to represent 60% of patients in the United States, while prescription charges are estimated to represent 90.2% of the U.S. market across retail, mail, and long-term care channels of distribution. While national charges are likely underestimated, unadjudicated charges (as used in this analysis) conversely exceed the amount reimbursed by payers, and therefore overestimate health system costs by between 40–60% depending on payer type according to several published sources.[113,114]

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About the IQVIA Institute

The IQVIA Institute for Human Data Science contributes to the advancement of human health globally through timely research, insightful analysis and scientific expertise applied to granular non-identified patient-level data.

Fulfilling an essential need within healthcare, the Institute delivers objective, relevant insights and research that accelerate understanding and innovation critical to sound decision making and improved human outcomes. With access to IQVIA's institutional knowledge, advanced analytics, technology and unparalleled data the Institute works in tandem with a broad set of healthcare stakeholders to drive a research agenda focused on Human Data Science including, including government agencies, academic institutions, the life sciences industry and payers.

Research Agenda

The research agenda for the Institute centers on 5 areas considered vital to contributing to the advancement of human health globally:

- Improving decision-making across health systems through the effective use of advanced analytics and methodologies applied to timely, relevant data.
- Addressing opportunities to improve clinical development productivity focused on innovative treatments that advance healthcare globally.
- Optimizing the performance of health systems by focusing on patient centricity, precision medicine and better understanding disease causes, treatment consequences and measures to improve quality and cost of healthcare delivered to patients.
- Understanding the future role for biopharmaceuticals in human health, market dynamics, and implications for manufacturers, public and private payers, providers, patients, pharmacists and distributors.
- Researching the role of technology in health system products, processes and delivery systems and the business and policy systems that drive innovation.

Guiding Principles

The Institute operates from a set of Guiding Principles:

- Healthcare solutions of the future require fact based scientific evidence, expert analysis of information, technology, ingenuity and a focus on individuals.
- Rigorous analysis must be applied to vast amounts of timely, high quality and relevant data to provide value and move healthcare forward.
- Collaboration across all stakeholders in the public and private sectors is critical to advancing healthcare solutions.
- Insights gained from information and analysis should be made widely available to healthcare stakeholders.
- Protecting individual privacy is essential, so research will be based on the use of non-identified patient information and provider information will be aggregated.
- Information will be used responsibly to advance research, inform discourse, achieve better healthcare and improve the health of all people.

The IMS Institute is now the IQVIA™ INSTITUTE for Human Data Science

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