CAREGIVER PERCEPTIONS AND ADOLESCENT QUALITY OF LIFE IN DUCHENNE MUSCULAR DYSTROPHY

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ABSTRACT

Duchenne muscular dystrophy (DMD) is a rare neuromuscular disorder characterized by early proximal muscle weakness and progressive loss of muscle function that primarily affects males. Although there is currently no cure for the disease, there is ongoing research into treatments to slow the disease progression, which could impact overall quality of life (QoL) for boys and men with DMD. Many early studies on QoL in DMD were conducted using parent-proxy reports but more recent research has suggested that boys with DMD might perceive their QoL differently than their caregivers. The purpose of this study was to determine if parents of adolescents with DMD perceive their child's QoL the same as the boys perceive their own QoL and to determine if specific aspects of DMD (glucocorticoid use, loss of ambulation, noninvasive respiratory support, and inability to self-feed) affect these perceptions. This study analyzed data from PedsQL^{TM} 4.0 Generic Core Scale surveys and the PedsQL^{TM} 3.0 Neuromuscular Module administered to participants ages 11-17 years old and their caregivers through the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS). Overall, parents reported lower physical QoL scores ($p<0.003$) and higher emotional ($p=0.049$), social ($p<0.001$), and school-functioning ($p<0.022$) QoL scores compared to their sons. Older participants and their caregivers both reported higher physical QoL scores than younger participant/parent-proxy reports ($p=0.017$, $p=0.035$). Participants taking glucocorticoids reported lower physical QoL than participants not taking glucocorticoids ($p<0.001$). There was no

difference in participant reported total QoL before and after both loss of ambulation and starting non-invasive respiratory support. The results suggest that adolescents with DMD have more positive perceptions regarding their physical QoL and more negative perceptions regarding their psychosocial QoL when compared to their parents, indicating a difference between adolescent experiences and parent perceptions. The results also suggest that the PedsQL^{TM} 4.0 survey may not appropriately capture physical QoL in adolescents with DMD. Improving population health and QoL is an important public health goal, and the results of this study provides information that may help guide interventions to improve the QoL for adolescents with DMD.

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PREFACE

There are a multitude of people who I would like to thank for their contribution and support of this project. First and foremost, I would like to extend my sincerest gratitude to my thesis committee members Lauren Morgenroth, MS, CGC, Robin Grubs, PhD, LCGC, John Shaffer, PhD, and Paula Clemens, MD for taking the time out of their incredibly busy lives to support the development of my thesis project. Their insightful feedback and guidance was vital to the success of this project, and I have very much enjoyed collaborating with them throughout this process. I would also like to give a special thank you to my committee chair Lauren, without whom this project would not have been possible. Words fail to accurately express just how grateful I am to have worked with such a talented, passionate role model for the past year and a half, and I could not have asked for a better person to chair my committee.

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1.0 INTRODUCTION

Duchenne muscular dystrophy (DMD) is an X-linked neuromuscular disease causing progressive loss of muscle function primarily in boys[1]. It is caused by mutations in the *DMD* gene which codes for the dystrophin protein, an important protein in muscle function[2,3]. Without intervention, boys with DMD experience loss of ambulation during early adolescence and premature death in early adulthood, often due to cardiomyopathy or respiratory failure[1,4,5]. Current interventions, such as glucocorticoid use and respiratory support, can delay the onset of significant disease milestones and increase the lifespan for boys with DMD. Although there is currently no cure, there is ongoing research into pharmaceuticals and other interventions that might slow disease progression, increase life-span, and improve overall quality of life (QoL).[4,6]

The World Health Organization (WHO) defines QoL as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns."[7,8] In recent years, pharmaceutical and clinical research on DMD have become increasingly interested in assessing health-related quality of life (HrQoL)—the subset of quality of life due to one's state of health.[9] Given the significant impact of DMD on overall health, it is important to assess how boys with DMD perceive their own HrQoL to determine if new interventions impact HrQoL for boys and men with DMD, and to determine new potential approaches to improve HrQoL. Early research on this topic depended on parent-proxy reports to assess QoL in DMD. However, more recent research suggests that children with

DMD perceive their own QoL differently than their parents perceive it.[10–16] This project is intended to help determine what differences, if any, exist between child and parent-perceived QoL in DMD. The specific aims are as follows:

1. To determine if caregivers of boys with DMD perceive their child's QoL the same as the children perceive their own QoL.
2. To determine if steroid use, time at loss of ambulation (LoA), utilization of non-invasive respiratory support, and inability to self-feed:
    - correlate with perceived QoL for boys with DMD in this study cohort.
    - correlate with caregiver perceptions of QoL of boys with DMD.
    - correlate with differences between caregiver and participant reported QoL (if any).

We hypothesized that there would be differences between participant and parent-proxy reported HrQoL. We also hypothesized that there would be differences in both participant and parent-proxy reported QoL before and after participants reached specific disease milestones, and that participants using steroids would report higher HrQoL than participants not taking steroids.

This project analyzed data related to HrQoL collected as part of the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS). CINRG is an academic network of sites around the world who have partnered together to research neuromuscular diseases and improve patient QoL.[17,18] The CINRG DNHS is the most extensive DMD natural history study to date. From 2006-2016, the network recruited and followed over 400 boys and men ages 2-30 with DMD from eight different countries and collected phenotypic, genotypic, and biomarker data.[5] Along with physical assessments, participants in the study completed multiple age-specific, validated QoL surveys to assess QoL in DMD. One such survey

was the Pediatric Quality of Life Questionnaire (PedsQL™) 4.0 General Core Scale.[5,19,20] This scale was administered to adolescents ages 11-17 at every study visit. Caregivers of these adolescents simultaneously completed a parent-proxy version of the form to report their perception of their child's QoL.[5] Starting in 2012, the PedsQL™ 3.0 Neuromuscular Module (NMM) was also administered to adolescents ages 11-17 and their parents.[5] This project compares the participant and parent-proxy results of the PedsQL™ Versions 3.0 and 4.0 both overall and at significant disease milestones (LoA, inability to self-feed) to determine if there are differences between participant and parent-proxy reported QoL and to determine factors that might affect perceived QoL.

This project is one of the few to analyze QoL in adolescents with DMD. Most studies investigating QoL in DMD have either focused on children or have grouped adolescents with children ages 10 years of age and younger in the analysis, and only a handful of studies have isolated adolescents for analysis.[11,21,22] Consequently, there is limited data regarding QoL in adolescents with DMD. This project will help elucidate how adolescents with DMD perceive their own QoL and how their perceptions compare to caregiver perceptions. This study also investigated QoL before and after the onset of disease milestones. There is limited research regarding the impact of disease milestones on QoL in DMD. The research thus far has primarily compared boys who had reached the milestone by the time of survey completion to boys who had not reached the milestone.[11,23–25] The longitudinal nature of the data collected through the CINRG DNHS allows this study to analyze QoL immediately before and after the onset of each milestone which provides a more direct examination of the impact of disease milestones on QoL in DMD. The results of this study may help health professionals and genetic counselors better educate parents of children with

DMD regarding current and future QoL concerns and will provide useful information for rare-disease researchers wanting to incorporate QoL as an endpoint in their clinical research trials.

2.0 LITERATURE REVIEW

2.1 DUCHENNE MUSCULAR DYSTROPHY (DMD)

DMD is a rare neuromuscular disorder categorized by early, proximal muscle weakness and progressive loss of muscle function that primarily occurs in males.[1] It occurs in approximately 1/5100 to 1/9330 live births, making it the most common cause of muscular dystrophy.[6,26]

DMD is caused by mutations in the *DMD* gene located on the X-chromosome.[2,3,27] The *DMD* gene codes for the dystrophin protein, a protein that is involved in stabilizing the skeletal muscles.[2,3] Mutations that lead to a truncated dystrophin protein, such as large deletions and frameshift mutations leading to premature stop codons, cause DMD.[28,29] Other mutations in the *DMD* gene that do not lead to a truncated protein can cause a similar neuromuscular disease, Becker muscular dystrophy (BMD).[30,31] BMD is also characterized by progressive proximal muscle weakness, but the clinical course of disease is slower and less severe than that of DMD.[32,33]

2.1.1 Clinical Course of DMD

DMD usually presents in boys between 3-5 years of age.[1,30] Initial symptoms include delayed motor milestones, clumsiness, abnormal gait, and difficulty keeping up with peers. [1,30] Other early signs of DMD include elevated serum creatine kinase (CK) levels, calf hypertrophy, and a Gower sign.[1,30] The Gower maneuver involves first getting on one's hands and feet and then walking the hands up the legs to stand. Because boys with DMD experience proximal muscle weakness, they use this unique position to stand from sitting on the floor.[4,6] After DMD is

suspected in an individual, the diagnosis can be confirmed with *DMD* deletion/duplication testing followed by gene sequencing if a large deletion or duplication is not identified. If DMD is strongly suspected but genetic testing does not identify a mutation, then a muscle biopsy can be performed to assess dystrophin protein levels.[4,6]

As boys with DMD age, they experience progressive loss of proximal muscle function. They begin to have difficulty walking followed by reduced arm strength and mobility.[1] Over time, they eventually lose ambulation and require a wheelchair. If left untreated, most boys transition to the wheelchair during their early teenage years.[5,6,27] Current treatment and management options can delay loss of ambulation, but do not prevent it.[4,27]

Boys with DMD have variable intellectual delays and may also fall on the autism spectrum. Many also have behavior concerns such as hyperactivity and attention deficit disorder.[34] Other symptoms of DMD include pulmonary, cardiac, and musculoskeletal complications, as well as swallowing difficulties.[6,35] Almost all boys with DMD develop restrictive lung disease which can later cause respiratory insufficiency.[1] Obstructive sleep apnea is another pulmonary complication associated with DMD, affecting up to 63% of boys by young adulthood.[36–38] Along with pulmonary complications, boys with DMD develop cardiac concerns, such tachycardia, arrhythmias, and dilated cardiomyopathy.[1,39,40] Musculoskeletal complications include joint contractures, bone fractures, and scoliosis. As the disease progresses, boys with DMD can experience difficulties chewing and swallowing, which can affect nutrition if not managed appropriately.[6] Death occurs between the second and fourth decades of life, most often due to respiratory failure or cardiac arrest.[4,5]

2.1.1.1 Significant Disease Milestones

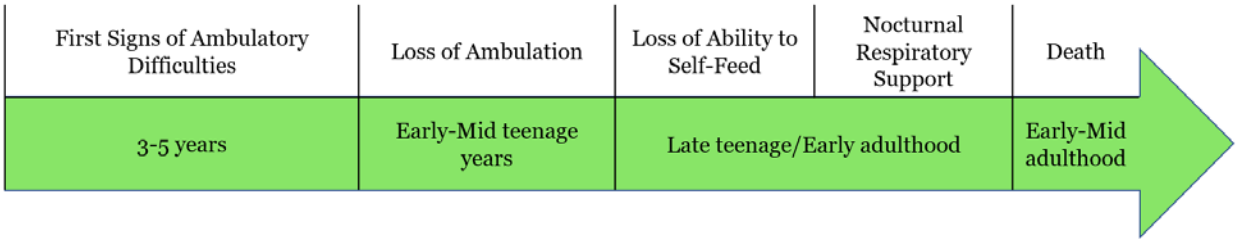


Figure 1: *Timeline of Disease Milestones in DMD with Glucocorticoid Treatment*

As boys with DMD age, they experience significant clinical milestones—points that mark disease progression. Figure 1 outlines the timing of some of these important milestones as they occur today where glucocorticoid treatment is the standard of care for boys with DMD.[4,27,41] Ambulation milestones include the inability to stand up from the floor, the inability to climb stairs, and the complete loss of ambulation.[5,27] Another major milestone is the inability to self-feed. This occurs in early adulthood when the individual loses the ability to lift their arms to feed themselves.[5] At or shortly after losing the ability to self-feed, boys with DMD require use of non-invasive nocturnal ventilation as respiratory complications progress.[5,27] The last disease milestone is, unfortunately, early death.

2.1.2 Treatment and Management

2.1.2.1 Glucocorticoids

Glucocorticoids are a type of steroid hormone that are used to slow the progression of DMD-related symptoms and are considered standard of care for DMD. Prednisone and Deflazacort are two types of glucocorticoids commonly used to treat boys with DMD. In February of 2017, Deflazacort was approved by the Food and Drug Administration (FDA), making it the first and

only FDA approved glucocorticoid to treat DMD in the United States.[42] A number of studies have consistently demonstrated that glucocorticoids increase the time to loss of ambulation, reduce disease symptoms (such as scoliosis, muscle weakness, and respiratory symptoms), delay the onset of other disease milestones, and prolong life.[41,43,44] However, boys using glucocorticoid treatment also experience significant side effects, including obesity, reflux, osteoporosis, vertebral fractures, delayed puberty, growth restriction, immunosuppression and cataracts.[27,45–47] Behavioral problems such as aggression, hyperactivity, mood-swings, and depression are also frequent.[46,47] Given the side-effects, it is recommended that boys do not begin steroids until their motor skills plateau although some clinicians have studied early use of steroids.[6,27,48]

2.1.2.2 Symptom Management

Aside from glucocorticoids, several other options are available for managing the symptoms of DMD. Assistive devices, such as shoe inserts, braces, and supportive standing devices, help boys continue to ambulate as their muscles weaken.[6] Eventually, wheelchairs are used for mobility. Physical therapy helps to retain full range of motion in the joints and prevent joint contractures. Surgery may be considered to treat certain joint contractures, but recent management guidelines recommend surgery only on an individual basis.[6] To manage cardiac symptoms, boys with DMD can take heart failure medications, including ACE inhibitors and beta blockers.[4,35] Both non-invasive and invasive ventilation devices may be used to manage respiratory disease and sleep apnea, depending on the severity of disease—although non-invasive devices are preferable.[35,49] Bone health is maintained using Vitamin D and/or Calcium supplements as needed.[35] Boys with DMD follow with a multidisciplinary team to manage and treat their symptoms.

2.1.2.3 New Therapeutics

There are several active clinical trials and research studies investigating novel therapeutics for DMD. A number of these research drugs will not be curative, but aim to reduce the severity of disease to that of a BMD phenotype.[4] Examples of experimental therapeutics include exon-skipping, nonsense suppressor, and muscle regeneration therapies.[4] Exon-skipping therapeutics block translation of particular exons in the *DMD* gene to allow the production of a functional, albeit incomplete, dystrophin protein.[50,51] Although the resulting protein is shortened, it is predicted to function well enough to slow down the natural course of disease. In September 2016, Eteplirsen became the first exon-skipping drug approved by the United States FDA to treat boys with DMD.[51] This therapeutic is aimed to treat boys whose mutations are amenable to the skipping of exon 51 (approximately 14% of boys with DMD).[51] The FDA granted accelerated approval to Eteplirsen, a decision that has proved to be controversial, particularly given the limited possible efficacy and sample size of the cohort in the Phase II trial.[52] Time and monitoring will provide more evidence regarding the effectiveness of this drug.

Another active area of research for DMD treatment is gene therapy using vectors to deliver functional DMD genes to muscle cells. The cells can theoretically incorporate the functional gene into their genome and begin to produce a normal dystrophin protein. Early research studies were complicated by adverse immune responses to the vectors used to deliver the functional dystrophin gene, .[52,53] Despite these initial set-backs, gene-therapy has now entered into clinical trials, and in January 2018, the first dose of gene therapy was administered to a boy with DMD. If successful, gene therapy has the potential to cure DMD.

There are a wide array of other therapeutics under investigation that are intended to treat boys with DMD regardless of mutation status. Some of these therapeutics are posed as an

alternative to glucocorticoids and claim to slow disease progression without the significant side-effects of current steroid treatment.[6,54] Other interventions aim to upregulate utrophin—a dystrophin paralogue expressed primarily in fetal development.[4,6,55] Since utrophin has a similar structure and function to dystrophin, increasing utrophin expression could help compensate for the lack of dystrophin protein and reduce the severity of disease.[55]

2.2 THE COOPERATIVE INTERNATIONAL NEUROMUSCULAR RESEARCH GROUP DUCHENNE NATURAL HISTORY STUDY

2.2.1 The Cooperative International Neuromuscular Research Group (CINRG)

CINRG is a network of over 20 academic and research sites across the world who have partnered together to perform clinical research trials for neuromuscular disorders and improve the quality of life for individuals with these diseases.[17,18] Given the rarity of neuromuscular diseases and the need for increased sample sizes to properly research therapeutics, the CINRG network was established in 2000 to allow for multi-site involvement in the study of promising new treatment options for neuromuscular disorders. So far, the network has recruited over 1,300 participants in over 20 studies, which has resulted in over 25 publications.[18]

2.2.2 Duchenne Natural History Study (DNHS)

The CINRG DNHS is a prospective, longitudinal research study performed by the CINRG network to study the natural history of DMD.[5] From 2006 to 2016, CINRG sites across the world

recruited and followed over 400 boys with DMD. The enrollment number and length of the study make it the most extensive DMD natural history study to date.[5] A subset of data collected through the CINRG DNHS was analyzed to conduct this thesis project.

2.2.2.1 Purposes

The CINRG DNHS gathered phenotypic, genotypic, and biomarker outcomes data to explore the natural history of the disease, study the effects of long-term glucocorticoid use, and assess the impact that DMD has on individuals and families. The study also aimed to investigate genetic modifiers of DMD, assess novel outcome measures, and identify new serum biomarkers for the disease.[5] The phenotypic data collected through this study created a normative data set that could be used as a "control group" in future clinical research trials.[5]

2.2.2.2 Study Enrollment and Timeline

Enrollment for the CINRG DNHS began in 2006 and the study closed in 2016. Over this 10-year timespan, more than 400 boys ages 2-30 years old with DMD were enrolled from eight different countries: Argentina, Australia, Canada, India, Israel, Italy, Sweden, and the United States.[5,18]

Boys were eligible to participate in the study if they were between 2-30 years old and had a definitive diagnosis of DMD. A definitive diagnosis was defined as the presence of one of the following: 1) clinical features of the disease and immunofluorescence or immunoblot test demonstrating complete lack of dystrophin protein, 2) genetic confirmation of an out-of-frame single or multi-exon deletion in the *DMD* gene, 3) clinical features of the disease and genetic confirmation of a small variant (point mutation, insertion, etc.) that likely produces a truncated protein, or 4) clinical features of the disease and an older brother with a confirmed diagnosis of

DMD. Boys ages 5-30 were also eligible for enrollment if they had clinical features of DMD and evidence supporting a dystrophinopathy. Acceptable evidence included: 1) a *DMD* gene mutation, 2) a muscle biopsy showing reduced or absent dystrophin protein, or 3) CK levels elevated five times higher than normal and an X-linked family member (maternal uncle, maternal cousin, etc.) with a confirmed diagnosis of DMD.[5]

Boys were excluded from the study if: 1) they were ambulatory after their 13th birthday and had never used steroids, 2) they were ambulatory after their 16th birthday while using steroids, or 3) they demonstrated noncompliance with the study protocol.[5] The first two exclusion criteria were included to ensure that boys with BMD or milder forms of DMD were not included in the study.

Upon enrollment, all study participants completed a baseline assessment and had follow-up assessments at months 6, 12, 18, and 24. Ambulatory participants completed two extra study visits at months 3 and 9. After the 24-month visit, participants returned annually for continued assessments, culminating in at least 5 years of follow-up data per participant some with 10 years.[5]

2.2.2.3 Measurements

A variety of measurements and medical history were taken at each study visit, including general health status, muscle strength and function, pulmonary function, cardiac function, and HrQoL measures.[5] Assessments from this study were used to determine when participants began using glucocorticoids and reached the disease milestones assessed in this project (LoA, loss of self-feeding, and use of non-invasive respiratory support). Details regarding every measurement used in this study is outlined in McDonald et al. 2013. Surveys administered through this study were also used to assess participant and caregiver perceptions of participant QoL. For more information on the HrQoL measures, see Section 2.3.2.1.

Glucocorticoid use, LoA, and use of non-invasive respiratory support were established using health status data. Health status was assessed at each study visit with a physical exam and review of medical information as provided by the participant or the caregiver of the participant. Along with demographic and molecular diagnostic information, information about the participant's medical history was collected. This information included history of glucocorticoid (steroid) use, specialty medical services, use of assistive devices, and school support received by the participant.[5]

Muscle strength and function were measured using both timed and untimed assessments. One such untimed assessment is the Brooke Upper Extremity Grade.[5,56] The Brooke Upper Extremity Grade is a validated measurement of upper extremity function used to evaluate disease progression in DMD. Function is rated on a scale of 1 to 6, with 1 being no loss of upper extremity function and 6 being complete loss of upper extremity function.[56] Data from this scale was used to quantify inability to self-feed in this project.

2.3 QUALITY OF LIFE IN DMD

There has been an increased interest within the last decade in assessing QoL in boys with DMD. In 1995, the WHO defined QoL as a person's "perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns."[7,57] In other words, QoL is how an individual feels regarding the way in which they are living. There are many factors that affect overall QoL. One of these factors is one's HrQoL. HrQoL is the perceived quality of life based on one's health status, and is defined by the Center for Disease Control and Prevention (CDC) as one's "perceived physical and mental health

over time."[8] HrQoL captures the domains of the WHO 1984 definition of health that can affect overall quality of life—physical, mental (psychological), and social health.[8,9] HrQoL and general QoL measures are now measured frequently in research and clinical trials, especially those investigating chronic, progressive diseases like DMD, since these measures can capture information that might be lost with clinical markers.[58,59] The FDA even recommends incorporating QoL measures into clinical research trials and supports the use of these measures in DMD research.[58,60] Because of this, QoL has become an important measurement in clinical research on DMD. This thesis project will contribute to the ongoing research of QoL in DMD.

2.3.1 QoL in Pediatric Neuromuscular Disorders Populations

Neuromuscular disorders (NMDs) are diseases that affect both the nervous system and muscular system. Muscular dystrophies like DMD and BMD are one kind of NMD. Other types of NMDs include myopathies, motor neuron diseases (like Spinal Muscular Atrophy), and peripheral nerve diseases (like Charcot Marie Tooth disease).[61]

2.3.1.1 QoL in Pediatric NMDs Compared to Unaffected Peers

Generally, individuals with pediatric NMDs report lower overall QoL compared to healthy peers.[62] Both physical and psychological HrQoL appear to be negatively impacted in this population.[24,62,63] Interestingly, one study found that Dutch children with muscular dystrophies actually reported increased physical HrQoL compared to healthy peers.[64] This study included participants with muscular dystrophies as well as female carriers of DMD or BMD. Although female carriers of these disorders can experience musculoskeletal and cardiac symptoms, they

generally are not as physically affected as males with DMD/BMD.[65,66] This could be one explanation for the unexpected results of that study.

2.3.1.2 QoL in DMD Compared to Other Neuromuscular Disorders

Very few studies have directly compared the QoL for boys with DMD to those with other NMDs. The most comprehensive analysis compared QoL between participants with over 15 different kinds of NMDs. Participants with DMD, BMD, congenital muscular dystrophy, and spinal muscular atrophy reported significantly reduced physical HrQoL compared to participants with other NMDs, although overall QoL was not significantly different between the groups.[24] This implies that boys with DMD are impacted more by their physical manifestations than individuals with most other NMDs. Another study comparing boys with BMD to boys with DMD found that boys with BMD reported increased HrQoL compared to boys with DMD.[64] This provides further evidence that boys with DMD have reduced QoL compared to other NMDs.

2.3.2 Measuring QoL in DMD Populations

2.3.2.1 Validated Surveys

A number of validated surveys that measure QoL and HrQoL in children, adolescents, and adults have been established for use in DMD cohorts. The CINRG DNHS utilized six such surveys: 1) the PedsQL™ Version 4.0 Generic Core Scale[10,19,20], 2) the PedsQL™ Version 3.0 NMM[10], 3) the Pediatric Orthopedic Society of North America (POSNA) Pediatric Musculoskeletal Functional Health Questionnaire (also referred to as the Pediatric Outcomes Data Collection Instrument or PODCI)[67,68], 4) the WHO QoL-BREF[57,69], 5) the Life Satisfaction Scale for Adolescents (LSI-A)[70,71], and 6) the Medical Outcome Study 36-item Short-Form Health

Survey.[5,72] Other commonly used surveys include the KIDSCREEN™-52 questionnaire, the Quality of Life in Neurological Disorders (Neuro-QOL) and the Patient-Reported Outcomes Measurement Information System (PROMIS), all of which were developed to evaluate HrQoL in individuals with chronic illnesses.[73–76] The PedsQL™ Generic Core Scale was developed for use in both healthy and ill children and adolescents. [10,19,20] The PODCI, on the other hand, is more specialized, and assesses HrQoL in relation to musculoskeletal health in children and adolescents.[11] The PedsQL™ Neuromuscular module is another specialized survey for children and adolescents used to analyze HrQoL in relation to neuromuscular health.[10] The WHO-QoL-BREF, the LSI, and the 36-item Short-Form Health Survey were developed to assess QoL in adolescents and adults. [57,69,72] Of all of the QoL surveys available to assess QoL in boys with DMD, the PedsQL™ 4.0 Generic Core Scale is one of the most frequently used surveys, particularly in the United States.[12] This thesis utilized data collected through the PedsQL™ 4.0 Generic Core Scale in the CINRG DNHS so that the results will be comparable to previous research. This project also analyzed data from the PedsQL™ 3.0 NMM since this survey was developed for use in neuromuscular disease population and may better represent QoL in DMD.

2.3.3 DMD QoL Throughout the Lifespan

Within the last decade—as the life expectancy of boys with DMD has risen and clinical research trials have begun incorporating QoL surveys into their trials—researchers have become increasingly interested in how boys with DMD perceive their own QoL.[12] Researchers have sought to compare the QoL of boys with DMD to that of healthy peers. There is also interest in how children with DMD perceive their QoL over time and compared to adolescents and adults with the disease. Although it is easy to assume that individuals with a debilitating disease like DMD would

have reduced QoL that worsens with disease severity, research studies on the subject have produced different results regarding how QoL is impacted in this population.[62,77,78]

2.3.3.1 Pediatric DMD QoL

Many early studies on child QoL in DMD were conducted using parent-proxy reports, which may or may not be an accurate representation of child-perceived QoL (this topic is explored further in Section 2.3.6.).[11,12,79,80] One of the first studies that directly assessed child and adolescent-reported QoL in DMD was completed by Uzark et al. in 2012. They surveyed 117 boys with DMD ages 6-18 years old using the PedsQL™ Versions 3.0 and 4.0 in an effort to assess how the boys perceived their own HrQoL. Their results showed that, on average, children with DMD reported lower QoL compared to data collected from healthy peers.[11] Other studies have replicated the conclusion that overall QoL is reduced in children with DMD compared to healthy controls.[10,22,81] However, recent research contradict these findings and suggest that children with DMD do not perceive a significant difference in QoL compared to healthy children of the same age.[21,82,83]

Particular aspects of HrQoL for children with DMD may be impacted to a greater degree or in different ways than others.[12] HrQoL is often broken down in to three domains: physical, psychological, and social. Studies have repeatedly demonstrated that children with DMD report reduced levels of physical HrQoL compared to healthy peers, even when the average QoL is not significantly impacted.[10,11,21,68,80,82,83] Analysis regarding psychological HrQoL in pediatric DMD participants is less consistent, with some studies concluding that boys with DMD have reduced psychological and HrQoL compared to healthy peers[10,11,21,80] and others concluding that there is no statistical difference for this age group.[82,83] Similar findings exist for social HrQoL. Zamani et al. reported in 2016 that children with DMD report lower HrQoL in regards to “friends” when

compared to healthy controls, although there was no difference in overall reported QoL.[83] Findings from previous studies, however, conflict with this result, and often only demonstrate a reduced social HrQoL in the pediatric DMD population when the overall QoL is also decreased.[11,22,82] If children with DMD do have a lower psychological and social HrQoL when compared to healthy peers, then the difference does not appear to be as large as the physical HrQoL domain.[12]

2.3.3.2 Adolescent and Adult DMD QoL

Adolescents are often grouped with children when investigating overall QoL, and therefore, the research on adolescent QoL conflicts just as described above for pediatric participants. Less is known regarding the general QoL in adults with DMD, perhaps due to the fact that many clinical and research trials currently using QoL surveys do not recruit adults with DMD. A recent study conducted in the Netherlands concluded that adults with DMD have a lower general QoL compared to healthy adults, although 73% of participants rated their overall QoL as either "good" or "very good".[84] This contrasts to a 2005 study performed by Kohler et al. which found that overall QoL was not significantly different between healthy adults and adults with DMD.[23] Landfelt et al. 2016 found that individuals with DMD in later stages of disease reported significantly lower total QoL than those in earlier stages.[16] Since adults with DMD are at a later stage of disease, this could indicate that adults with DMD have reduced QoL compared to children with DMD.

Like their pediatric counterparts, adolescents and adults with DMD also have reduced physical HrQoL compared to healthy peers.[10,11,21,68,80,82–84] Physical HrQoL also correlates with disease severity (and thus age) in DMD.[11,23,82] This is the only domain of HrQoL that consistently correlates with disease severity.

Interestingly, psychological HrQoL does not seem to be negatively impacted by age—adolescents and adults with DMD have even reported higher psychological HrQoL compared to children with DMD.[11,22] Adolescents and adults with DMD also do not differ significantly in this domain compared to healthy controls, suggesting possible improvement of psychological HrQoL over time.[22,84] As boys with DMD age, they start to engage less in social interactions and activities than younger children with DMD. Despite this decrease in social engagement, social HrQoL does not seem to be significantly affected.[21,23]

2.3.4 Factors Affecting QoL

This section provides an overview of some factors that may affect QoL for individuals with DMD. It is important to note that there are a variety of other factors that could also impact QoL but for the purposes of this thesis, the focus will be on physical factors and interventions that correlate with and/or affect the onset of disease milestones since disease milestones mark times of significant physical and medical changes for boys with DMD.

2.3.4.1 Glucocorticoid Use and QoL

As described in Section 2.1.2.1., glucocorticoids reduce DMD disease symptoms and delay the loss of motor ability. Given the fact that glucocorticoids delay severe disease symptoms, and that reduction in disease severity is associated with increased physical HrQoL, it would stand to reason that boys with DMD who are taking glucocorticoids could have increased physical HrQoL compared to boys with DMD of the same age who are not taking glucocorticoids. Only a handful of studies have directly compared child-reported HrQoL between boys with DMD on and off steroids. Bray et al. surveyed boys with DMD using the PedsQL™ General Core Scale and

compared the results between boys taking glucocorticoids and boys not taking glucocorticoids. Boys with DMD who were on glucocorticoids reported significantly increased physical HrQoL compared to the steroid-free group.[14] There was also no difference in psychological HrQoL between the two groups. Uzark et al. compared both parent-proxy and child-reported QoL between children with DMD on and off glucocorticoids. They determined that parents of children with DMD who are taking glucocorticoids report increased child activity levels than parents of children with DMD who are not taking glucocorticoids; however, child self-reports did not replicate this difference.[11] There was also no significant difference in overall psychological HrQoL between the two groups as reported by child or parent-proxy report, although boys taking glucocorticoids reported less worry than boys not taking glucocorticoids.[11]

2.3.4.2 QoL at Disease Milestones

It is hypothesized that QoL may be affected by the onset of significant disease milestones, such as loss of ambulation, use of noninvasive respiratory support, and inability to self-feed. Some studies have investigated possible interactions between these milestones and reported HrQoL in DMD, but no causal relationships have been identified.

Multiple studies have demonstrated that boys with DMD who use wheelchairs (and have thus lost the ability to ambulate independently) report significantly lower physical HrQoL levels than boys who do not require wheelchairs.[10,80] No significant differences in child-reported psychological HrQoL have been identified between these two groups. Although boys using wheelchairs report lower physical HrQoL than ambulatory boys, studies have not determined if the onset of wheelchair use correlates with a reduction in individual HrQoL.

Studies conflict as to whether HrQoL is affected when boys with DMD require noninvasive respiratory support. Mah et al. surveyed children with neuromuscular disorders, including DMD,

using the PedsQL Generic Core Scale to see if at-home respiratory support affected QoL.[24] This study found that individuals with neuromuscular disease who require at-home respiratory care report a significantly lower HrQoL than those with neuromuscular disease who do not require respiratory care.[24] Because other neuromuscular diseases were included in this study, it is unclear whether these results apply specifically to the DMD community. Conversely, Kohler et. al. surveyed boys with DMD using the 36-item Short-Form Health Survey and found that use of respiratory support did not significantly affect the reported HrQoL.[23] Of note, this study surveyed children using a survey developed for adults, so again, it is unclear whether the results provide an accurate assessment of the pediatric DMD population.

Since most of the QoL studies in the DMD population have surveyed children and adolescents, there is little data regarding whether the inability to self-feed affects HrQoL. Houwen-van Opstal et al. analyzed the relationship between HrQoL and the Brooke scale and found no significant correlation between the two.[82] This may suggest that severely reduced upper arm mobility (which would indicate an inability to self-feed) does not correlate with reduced HrQoL.

2.3.4.3 Limitations of DMD HrQoL Studies

One of the primary limitations of studies investigating HrQoL in DMD is reduced sample size.[12] Aside from a study published by Landfelt et al. in 2016 which surveyed over 700 boys and men with DMD, most studies in this area have sample sizes of 100 boys or less.[12,16] DMD is a rare disease, and therefore, it can be difficult to gather adequate sample sizes to perform these studies. Low sample sizes increase effects from random error and can be a possible explanation for some discrepancies between studies. Another significant limitation is the use of different survey methods.[12] Although the variety of available surveys allows for descriptions of different aspects

of HrQoL, it can make it difficult to directly compare study results, especially since surveys do not always include the same items for analysis.[12]

2.3.5 Caregiver Perceptions of DMD QoL

Parent-proxy measures have often been used when evaluating QoL in DMD.[11,12,79,80] These measures consist of asking parents or other primary caregivers to report on how they think their child with DMD perceives his QoL. It is an indirect measure of QoL since the boys themselves are not directly reporting. Although this method is convenient—caregivers are sometimes more willing and able to complete written surveys than children with DMD—there is debate as to whether parent-proxy measures are accurate representations of patient-perceived QoL in DMD.

To assess possible differences between child-reported and caregiver-reported QoL in DMD, researchers administer the same survey to both the child and the caregiver and analyze the responses. The results from these studies reveal that caregivers generally report lower overall HrQoL than the boys do, indicating that caregivers perceive a lower QoL for the boys than the boys themselves perceive.[10–16] The discrepancy between parent and child-reported HrQoL is not consistent, however, with some studies indicating poor agreement[10,11] and others indicating moderate to high agreement.[13,15,16] Interestingly, Cremeens et al. reported very poor agreement between parent-proxy and child-reported QoL, but parents in their study rated their child's QoL significantly higher than the child did, not lower like subsequent studies.[85] One possible explanation for this difference is that this study only analyzed boys with DMD ages 5.5-8.5 years old while other studies have included older children and adolescents in their study population. However, age effects on the concordance between parent-proxy and child-reported QoL have not yet been sufficiently analyzed.

Trends regarding how parent-proxy and child-reported QoL compare among the three core domains of HrQoL (physical, psychological, and social) provide more insight into how caregivers perceive the QoL of their children with DMD. Even when overall concordance is low, parents and their children with DMD generally have moderate to high agreement in regards to the child's physical HrQoL. This is often the most agreed-upon aspect of HrQoL in children with DMD. Agreement regarding psychological and social HrQoL, however, tends to be significantly lower than physical HrQoL with caregivers sometimes underestimating their child's perceived psychological HrQoL and other times overestimating it. These trends suggest that parents are more able to report on domains of HrQoL that they can see than they are able to report on less visible domains. Some studies have found that parent-proxy and child-reported HrQoL have moderate to high agreement when considering the topics of "Daily Activities" and "School Functioning," further supporting the idea that parents of children with DMD are more able to report on aspects of HrQoL they can directly observe.[11,14]

Although there are trends, the agreements between parent-proxy and child-reported QoL in each domain are still inconsistent, particularly in the psychosocial domain. Lim et al. hypothesized that some of these differences could be explained by differences in statistical methods.[13] Most studies use the Student's t-test, Pearson's correlation coefficient, and Interclass Correlation Coefficient (ICC) when analyzing the data, but they can also be analyzed using a Rasch model which can capture both question difficulty and responder ability.[13] Lim et al. surveyed boys with DMD and their caregivers using the PedsQL™ Version 4.0 (Generic Core Scale) and compared these methods of analysis. The results of the Rasch model-analysis indicated that there was less agreement regarding psychosocial HrQoL than physical HrQoL, and that more parents reported their child's QoL lower than the child did.[13] These results are consistent with those using

standard statistical methods. The Rasch model also revealed that 4 out of 23 individual items in the survey were reported differently between caregivers and the boys with DMD.[13] Further use of the Rasch model could provide more information regarding specific differences between parent-proxy and child-reported QoL.

There is a distinct lack in research regarding other factors that may influence caregiver perceptions of QoL in DMD. Social economic status, parent age, child age, and perceived personal QoL may all impact how caregivers of boys with DMD report the QoL of the boys. Future research on these and other factors will allow for a better understanding of the relationship between parent-proxy and child-reported QoL.

In summary, there does seem to be differences between how boys with DMD perceive their QoL and how their parents perceive it, although these differences are not consistent across studies. Parents generally report lower QoL than the boys do. Boys and their parents typically have higher agreement regarding physical QoL compared to psychosocial QoL, suggesting that parents are more able to report on aspects of QoL that they can directly observe. More research is needed to determine factors that affect parent-child agreement of QoL in DMD.

3.0 MANUSCRIPT

3.1 BACKGROUND

Duchenne Muscular Dystrophy (DMD) is an X-linked neuromuscular disorder that causes proximal muscle weakness followed by progressive loss of muscle function.[1] It is the most common genetic cause of muscular dystrophy and occurs in approximately 1/5,100-1/9,300 live births.[6,26] In the current era of treatment, boys with DMD generally lose ambulation in their mid-teenage years and die in early- to mid-adulthood, most often due to respiratory or cardiac complications.[4,5] There is not yet a cure for DMD, but there are substantial clinical research trials investigating pharmaceuticals and other interventions to delay the onset of disease milestones and (potentially) cure DMD.[6] These therapeutics may also impact perceived quality of life (QoL) for boys with DMD.

Within the last decade, as clinical research on DMD has expanded, there has been an increasing interest in assessing QoL for boys with DMD. This research has primarily focused on health-related quality of life (HrQoL), which The Center for Disease Control and Prevention (CDC) defines as the "perceived physical and mental health over time."[8] HrQoL thus consists of physical and psychosocial QoL. Although HrQoL is technically a subset of QoL, the two terms are often used interchangeably.

Many of the early studies on HrQoL in DMD relied on parent-proxy reports to determine how the disease affects QoL. However, more recent research has suggested that parents of boys with DMD may actually underestimate how their children perceive their own QoL, indicating that QoL in DMD is higher than parents perceive.[10–16] Research also suggests poor concordance

between child and parent-proxy reports regarding psychosocial QoL, with parents sometimes reporting lower psychosocial QoL than the children report and other times reporting higher.[10,11,14,85] Physical QoL appears to be more consistent across child and parent proxy reports. Some have suggested that this means parents of boys with DMD are better able to report on aspects of HrQoL that they can directly observe.[12] However, research continues to yield mixed results regarding participant and caregiver-reported QoL, and further analysis is needed to address these differences.

Most of the research on QoL in DMD has focused on younger children with the disease. Although some studies have included adolescents in their cohort, there are very few studies that focus specifically on QoL in adolescent and/or adult populations.[11,14] One study conducted by Uzark et al. separated the results of their study by age-groups. This study concentrated primarily on QoL in DMD compared to healthy individuals, so results between DMD age-groups were not directly assessed. Although these results were not compared statistically, it appears that participants in the 13-18 year age group reported lower physical and higher psychosocial QoL compared to participants in the 8-12 year age group. Caregivers of participants in the 13-18 year age group also reported lower physical health scores compared to the 8-12 year age group; however, unlike the participants, caregivers reported lower psychosocial QoL for the older children than the younger children.[11] These results suggest that there may be age effects on HrQoL and indicate that the results of studies on children with DMD might not apply to adolescents with DMD.

Researchers have also investigated other factors that could affect HrQoL for boys with DMD. Some factors hypothesized to affect QoL include glucocorticoid use, loss of ambulation (LoA), inability to self-feed, and non-invasive respiratory support use. Those last three factors are

considered to be significant disease milestones and may be used as endpoints in clinical research trials. Research has demonstrated improved physical QoL with glucocorticoid use, although it is unclear if this translates to improved total QoL.[11,14,86] Studies also suggest that LoA correlates with reduced physical QoL for boys with DMD but does not correlate with psychosocial QoL.[10,80] There is also conflicting data regarding the use of non-invasive respiratory support, with some research identifying no correlation with QoL and some indicating that non-invasive respiratory support correlates with reduced total QoL.[23,24] Although the interactions between disease milestones and QoL in DMD have been investigated, no causal relationships have been identified.

This study aims to determine if caregivers of boys with DMD perceive their child's QoL the same as the children perceive their own QoL. This study also aims to determine if steroid use, time at LoA, utilization of non-invasive respiratory support, and inability to self-feed: 1) correlate with perceived QoL for boys with DMD in this study cohort, 2) correlate with caregiver perceptions of QoL of boys with DMD, or 3) correlate with differences between caregiver and participant reported QoL (if any). The data for this study was previously collected through the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS). The CINRG DNHS is the most comprehensive DMD natural history study to date. Between 2006-2016, over 400 boys and men with DMD participated in the study. The phenotypic, genotypic, and biomarker data collected through this study has helped to shape the perception and management of DMD.

3.2 METHODS

This study was reviewed and approved as Exempt by the University of Pittsburgh Institutional Review Board (IRB) (Appendix).

3.2.1 Study Population

The data analyzed in this study was previously collected through the CINRG DNHS which recruited over 400 boys ages 2-30 years old with DMD from eight different countries and followed them yearly between 2006-2016. Information on the CINRG DNHS study methods, including study timeline, eligibility criteria, and exclusion criteria, is outlined in detail by McDonald et al. in 2013.[5] The data used in the analysis for this study was chosen based on availability of matching participant and parent-proxy reports. Figure 2 outlines how the data was selected for analysis. Of the 440 participants who participated in the CINRG DNHS, 219 participants ages 11-17 years old completed the Peds™ QL 4.0 Generic Core Scale at least once, and 46 participants ages 11-17 years old completed the Peds™ QL 3.0 Neuromuscular Module (NMM) during at least one study visit. Two participants who completed the PedsQL™ 4.0 survey did not have corresponding parent-proxy surveys and were excluded from analyses. Eight participants who completed the PedsQL™ 3.0 survey did not have corresponding parent-proxy reports and were also excluded from analyses. This left 217 and 38 participant and parent-proxy pairs for the PedsQL™ 4.0 and PedsQL™ 3.0 surveys respectively. Since the surveys were administered at every study visit, most pairs had data from multiple visits. Only the first visit with complete participant and parent-proxy data was used for analysis.

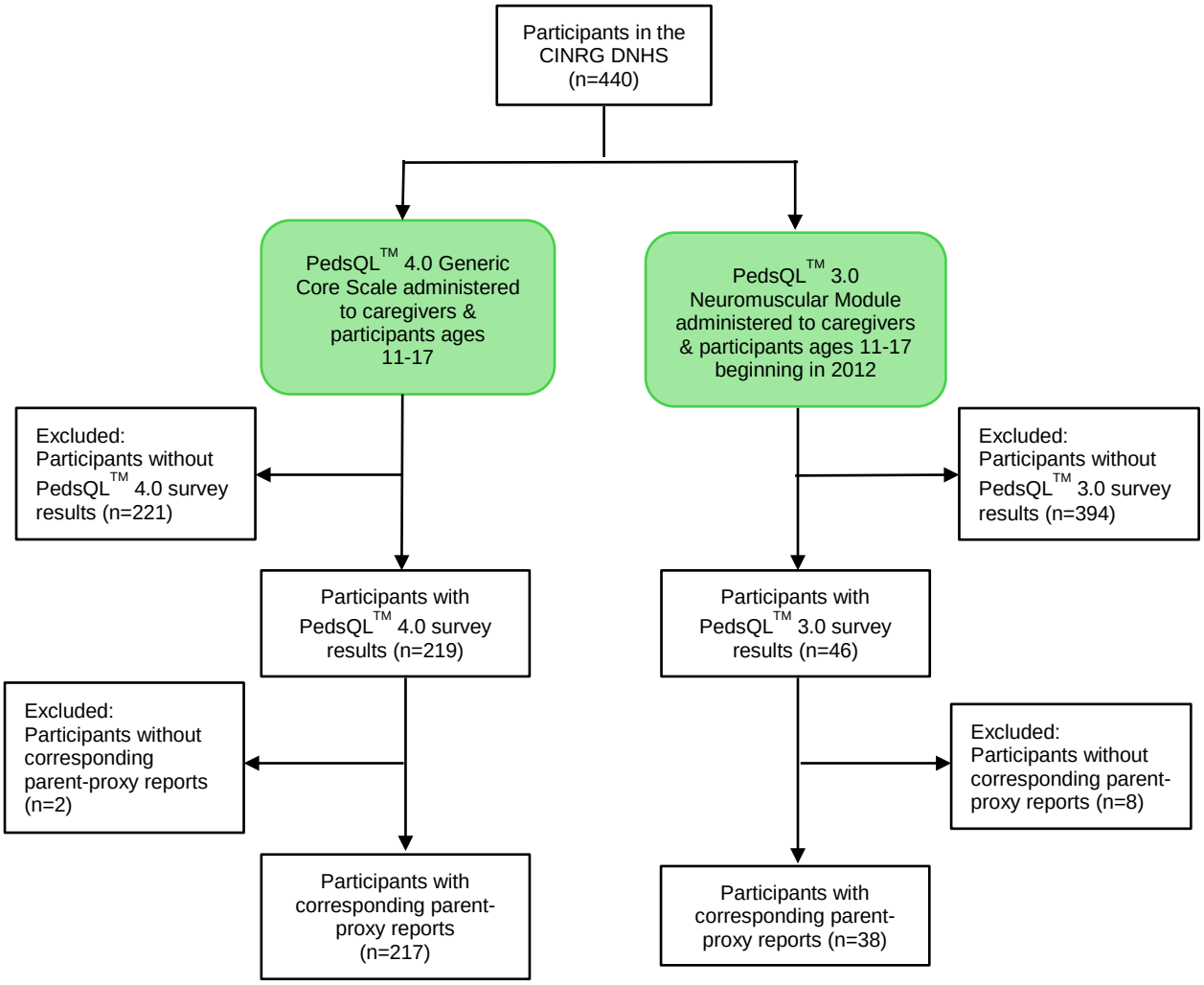


Figure 2: *Process for Selecting Data for Analysis*

The data used to analyze QoL at disease milestones was selected based on participant milestones and survey availability. Participants who reached the milestone during the survey were isolated for analysis. Participants were excluded from analysis if did not have survey data before or after the onset of the disease milestone. Reasons for missing data include: 1) the participant reached the milestone before entering the study, 2) the participant did not reach the milestone during the study, or 3) the surveys were not completed before or after the onset of the milestone.

3.2.2 Data Acquisition

Upon IRB approval, a data request was sent to the team in charge of the CINRG DNHS data. Only the necessary data required for analysis in this study was requested. After the data request was accepted, the statistician compiled the requested data and provided a completely de-identified data set for analysis.

3.2.3 Health-Related Quality of Life Data

The Pediatric Quality of Life Questionnaire (PedsQL^{TM}) Version 4.0 Generic Core Scale and Version 3.0 Neuromuscular Module (NMM) were both used to assess HrQoL in adolescents with DMD. The PedsQL^{TM} 4.0 Generic Core Scale is a 23-question self-report survey that measures four core dimensions of HrQoL: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning.[20] These subscales are combined to reveal Total QoL. The PedsQL^{TM} 3.0 NMM is a 25-question self-report survey that is broken down into three subscales: About my Neuromuscular Disease (NMD), Communication, and Family Resources.[10] These subscales are combined to reveal Total QoL. The questions on both surveys ask how much of a problem certain tasks and activities have been for the participant over the last month. Participants and caregivers rated their responses on a Likert-type scale from 0-4, with 0 indicating that a task is never a problem and 4 indicating that a task is "almost always" a problem.

Participants in the CINRG DNHS aged 11-17 years old competed the PedsQL^{TM} 4.0 self-report at every study visit. Caregivers of participants ages 5-17 simultaneously completed the PedsQL^{TM} 4.0 parent-proxy survey. The PedsQL^{TM} 3.0 NMM was not administered until 2012.

Once added to the study, participants in the CINRG DNHS and their caregivers completed the PedsQL™ 3.0 NMM in the same fashion as the PedsQL™ 4.0 Generic Core Scale.[5]

3.2.4 Disease-Specific Milestones

LoA, inability to self-feed, and use of non-invasive respiratory support were the chosen disease-specific milestones for analysis in this study. Participant and parent-proxy reports were compared before and after the onset of each event. LoA and first-reported use of non-invasive respiratory support were each defined as the visit at which the physical exam or interval medical history first identified the onset of each milestone. Inability to self-feed was defined as a Brooke Upper Extremity Scale score of 5 or 6. The Brooke Upper Extremity Scale is a validated measurement of upper extremity function used to evaluate disease progression in DMD. Function is rated on a scale of 1 to 6, with 1 being no loss of upper extremity function and 6 being complete loss of upper extremity function. A score of 5 is defined as an inability to raise the hands to the face, but continued ability to hold items in the hand.[56] Glucocorticoid use was defined in two ways: 1) use status at the time of the completed HrQoL survey and 2) visit at which the interval medical history first identified glucocorticoid use.

3.2.5 Data Analysis

For the participant and parent-proxy comparisons, only the first visit with complete participant and parent-proxy data was used for analysis. The total scores for each subsection of the survey were compared between participant and parent-proxy reports—responses for individual question on the surveys were not evaluated. There were sporadic missing responses across the

questionnaires which prevented subscales or total scores to be calculated for a few participant and parent-proxy pairs. This caused sample sizes to differ slightly across the subscales of each survey. Responses were also compared based on age (11-13 years old vs 14-17 years old) and glucocorticoid use. The age groups were chosen based on the average age of the study population.

For disease milestones, the survey data collected at the first visit where the event is noted in the physical exam was compared to the data collected at the previous visit, as long as the previous visit occurred within 365 days of the event. The non-invasive respiratory support category is the only exception, with a couple of "before" data points occurring within 2 years (730 days) of the event. This exception was made to ensure a large enough cohort for analysis. There was no significant difference in results when these exceptions were omitted from analysis. Only the results of the PedsQL^{TM} 4.0 survey were analyzed in relation to disease milestones. There were not enough survey responses from the PedsQL^{TM} 3.0 NMM survey to apply to the milestone data.

More caregivers completed the PedsQL^{TM} 4.0 survey than participants, and there were many caregiver survey results surrounding disease milestones that did not have matching participant surveys. For this reason, parent-proxy data was analyzed in two ways for the disease milestones: 1) caregivers of the available participant survey results were analyzed, and 2) all available parent-proxy data was analyzed, regardless of matching participant data.

The data was assessed for normality and outliers. All surveys were compared using two-sided Paired t-tests. Correlation between overall participant and parent-proxy reports was performed using Pearson's correlation.

3.3 RESULTS

3.3.1 Participant Information

The PedsQL™ 4.0 Generic Core Scale and the PedsQL™ 3.0 NMM surveys were administered to participants ages 11-17 years old and their caregivers. Participant demographics are outlined in Table 1. Of the 217 participants who completed the PedsQL™ 4.0, 160 (73.9%) were between the ages of 11-13 years old, and 57 (26.1%) were 14-17 years old at the time of survey completion. 102 (47.0%) of these participants were ambulatory. Of the 38 participants who completed the PedsQL™ 3.0 NMM, 20 (52.6%) were between the ages of 11-13 years old and 18 (47.4%) were 14-17 years old at the time of survey completion. 18 (47.4%) of these participants were ambulatory. Most participants with survey data were using glucocorticoids at the time of survey completion (71.0%, 81.6%). The participants who were using glucocorticoids were taking either prednisone, deflazacort, or prednisolone. The large majority of participants in both the PedsQL™ 4.0 and PedsQL™ 3.0 NMM survey cohorts were Caucasian (70.0%, 81.6%), followed by Asian (18.4%, 10.5%), Black (1.84%, 2.63%) and Pacific Islander (0.09%, 0.00%).

Table 1: *Participant Demographics*

	PedsQL™ 4.0 Generic Core Scale		PedsQL™ 3.0 NMM	
	N=217	%	N=38	%
Race				
Caucasian	152	70.0	31	81.6
Asian	40	18.4	4	10.5
Black	4	1.84	1	2.63
Pacific Islander	2	0.09	0	0.0
Other	19	8.75	2	5.26
Ethnicity				
Non-Hispanic	186	85.3	38	100
Hispanic	31	14.2	0	0.0
Age Range (11-18)				
11-13	160	73.9	20	52.6
14-18	57	26.1	18	47.4
Ambulation				
Ambulatory	102	47.0	18	47.4
Non-ambulatory	115	53.0	20	52.6
Glucocorticoids				
Use	154	71.0	31	81.6
Nonuse	63	29.0	7	19.4

3.3.2 Comparison of Participant and Parent Proxy Reports

Figure 3 shows the participant and parent-proxy results of the PedsQL™ 4.0 Generic Core Scale surveys. Overall, there was no significant difference between the Total QoL reported in the participant and parent-proxy surveys ($p=0.35$). However, participants reported higher Physical Functioning scores ($p=0.003$) and lower Emotional Functioning ($p=0.049$), Social Functioning ($p<0.001$), and School Functioning ($p=0.022$) scores than the parent-proxy reports (Table 2).

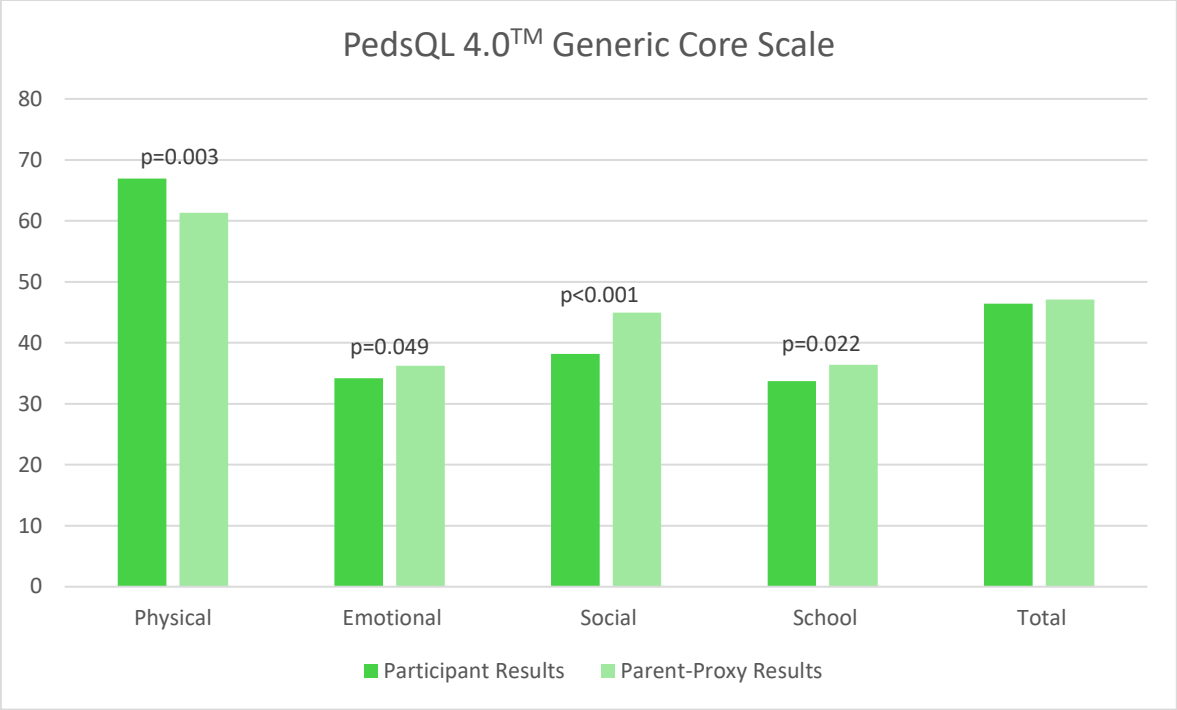


Figure 3**:** *PedsQL™ 4.0: Participant Results Compared to Parent-Proxy Results*

Table 2: *PedsQL™ 4.0 Overall Participant and Parent-Proxy Results*

	Participant Report Average (SD)	Parent-Proxy Report Average (SD)	Difference (SE)	P-value	Correlation (r)
Physical (n=215)	66.91 (23.71)	61.56 (28.91)	5.35 (1.80)	**0.003***	0.51*
Emotional (n=217)	34.09 (19.87)	36.26 (18.90)	2.17 (1.09)	**0.049***	0.66*
Social (n=217)	38.18 (18.84)	44.93 (19.14)	6.75 (1.31)	**<0.001***	0.48*
School (n=208)	33.57 (18.00)	36.36 (19.61)	2.79 (1.21)	**0.022***	0.57*
Total (n=215)	46.36 (15.36)	47.17 (15.04)	0.817 (0.88)	**0.354**	0.64*

SD= Standard Deviation, SE= Standard Error, *= p <0.05

Figure 4 shows the participant and parent-proxy results of the PedsQL™ 3.0 Neuromuscular Module surveys. Participants reported significantly higher Family Resources scores (p=0.005) and Total QoL compared to the parent-proxy reports (p=0.033). There was no significant difference between participant and parent-proxy reports regarding the About My Neuromuscular Disease (NMD) and Communication subscales (Table 3).

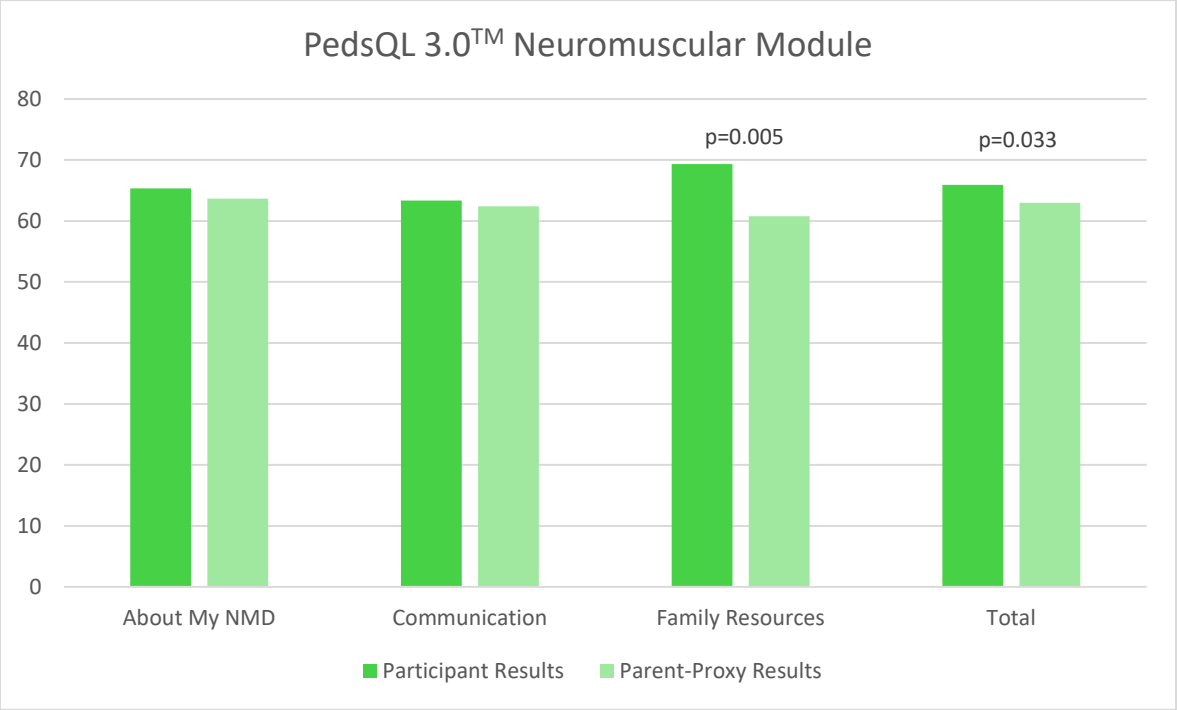


Figure 4: *PedsQL™ 3.0 NMM: Participant Results Compared to Parent-Proxy Results*

Table 3: *PedsQL™- 3.0 NMM Overall Participant and Parent-Proxy Results*

N=38	Participant Report Average (SD)	Parent-Proxy Report Average (SD)	Difference (SE)	P-value	Correlation (r)
About my Neuromuscular Disease	65.36 (16.50)	63.69 (15.95)	1.67 (1.66)	**0.305**	0.82*
Communication	63.37 (25.00)	62.39 (25.31)	0.99 (2.14)	**0.647**	0.86*
Family Resources	69.31 (18.71)	60.79 (22.35)	8.52 (2.88)	**0.005***	0.64*
Total	65.92 (14.63)	62.97 (15.28)	2.95 (1.33)	**0.033***	0.85*

SD= Standard Deviation, SE= Standard Error, *= p <0.05

3.3.3 Participant Age and QoL

Age-effects on reported QoL in the PedsQL™ 4.0 survey are outlined in Table 4. Older participants (14-18) reported higher Physical Functioning scores (p=0.017) and lower Social Functioning scores (p=0.022) than younger participants (11-13). There was no significant difference in participant-reported Total QoL between the age groups. Caregivers, however,

reported higher Total QoL for older participants than for younger participants (p=0.042). Caregivers of older participants also reported higher Physical Functioning scores (p=0.035) than caregivers of younger participants.

Compared to parent-proxy reports, older participants reported lower Total QoL scores (p=0.03). They also reported lower Emotional Functioning (p=0.02), Social Functioning (p=0.004), and School Functioning (p=0.006) scores than their parent-proxies. There was no difference between participant and parent-proxy reported Total QoL for younger participants. However, younger participants, reported higher Physical Functioning scores (p=0.009) and lower Social Functioning (p=0.004) than their parent-proxy reports.

Table 4: *PedsQL™ 4.0 and Participant Age*

	Age Group 11-13 Average (SD) n=160	Age Group 14-18 Average (SD) n=57	Difference (SE)	P-Value
Physical				
Participant Report	64.66 (24.41)	73.46 (20.38)	8.80 (3.67)	**0.017***
Parent-Proxy Report	59.13 (28.31)	68.64 (29.73)	9.51 (4.48)	**0.035***
Difference (SE)	5.53 (2.09)	4.82 (3.54)		
P-Value	**0.009***	**0.180**		
Emotional				
Participant Report	34.14 (20.51)	33.95 (18.12)	0.196 (3.07)	**0.949**
Parent-Proxy Report	35.20 (19.36)	39.25 (17.36)	4.06 (2.91)	**0.164**
Difference (SE)	1.05 (1.25)	5.31 (2.21)		
P-Value	**0.402**	**0.020***		
Social				
Participant Report	39.92 (19.26)	33.29 (16.82)	6.63 (2.88)	**0.022***
Parent-Proxy Report	45.23 (19.00)	44.08 (19.69)	1.15 (2.96)	**0.699**
Difference (SE)	5.30 (1.45)	10.79 (2.83)		
P-Value	**0.004***	**0.004***		
School				
Participant Report	34.06 (19.62)	33.77 (15.29)	0.292 (2.92)	**0.921**
Parent-Proxy Report	35.25 (19.58)	39.58 (19.52)	4.36 (3.09)	**0.161**
Difference (SE)	1.59 (1.43)	6.20 (2.16)		
P-Value	**0.269**	**0.006***		
Total				
Participant Report	46.01 (16.16)	47.08 (12.92)	0.977 (2.39)	**0.683**
Parent-Proxy Report	45.94 (14.87)	50.69 (15.11)	4.75 (2.32)	**0.042***
Difference (SE)	0.336 (1.03)	3.61 (12.58)		
P-Value	**0.745**	**0.036***		

Age effects on the PedsQL™ 3.0 survey are listed in Table 5. There was no significant difference in reported Total QoL between younger and older participants. Caregivers of younger participants reported higher About My NMD scores than caregivers of older participants (p=0.016). Younger participants also reported higher About my NMD scores than older

participants, although this result was not statistically significant (p=0.111). Participants in the 11-13 age group reported significantly higher Family Resources scores than their caregivers (p=0.003). This difference was not seen with participants in the 14-17 age group and their caregivers.

Table 5: *PedsQL™ 3.0 NMM and Participant Age*

	Age Group 11-13 Average (SD) n=20	Age Group 14-17 Average (SD) n=18	Difference (SE)	P-Value
About NMD				
Participant Report	69.42 (14.19)	60.85 (18.08)	8.57 (5.24)	**0.111**
Parent-Proxy Report	69.52 (15.14)	57.23 (14.61)	12.29 (4.84)	**0.016***
Difference (SE)	0.099 (1.75)	3.63 (2.74)		
P-Value	**0.956**	**0.204**		
Communication				
Participant Report	63.75 (17.79)	62.96 (31.73)	0.787 (8.23)	**0.924**
Parent-Proxy Report	61.04 (18.15)	63.89 (31.96)	2.85 (8.32)	**0.734**
Difference (SE)	2.71 (2.67)	0.926 (3.43)		
P-Value	**0.324**	**0.790**		
Family Resources				
Participant Report	73.50 (19.06)	64.65 (17.67)	8.85 (5.98)	**0.158**
Parent-Proxy Report	61.00 (22.10)	60.56 (23.26)	0.44 (7.36)	**0.952**
Difference (SE)	12.50 (12.62)	4.10 (5.09)		
P-Value	**0.003***	**0.432**		
Total				
Participant Report	69.58 (12.05)	61.84 (16.43)	7.74 (4.64)	**0.104**
Parent-Proxy Report	66.80 (13.93)	58.70 (15.95)	8.10 (4.85)	**0.103**
Difference (SE)	2.78 (1.43)	3.14 (2.36)		
P-Value	**0.067**	**0.201**		

3.3.4 Glucocorticoid Use and QoL

Table 6: *QoL and Glucocorticoid Use*

	Glucocorticoid Nonuse (n=63)	Glucocorticoid Use (n=154)	Difference (SE)	P-Value
Physical				
Participant Report	80.24 (18.88)	61.63 (24.0)	18.60 (3.36)	**<0.001***
Parent-Proxy Report	71.98 (31.99)	57.43 (27.06)	14.55 (4.27)	**<0.001***
Difference (SE)	8.26 (3.84)	4.20 (2.00)		
P-Value	**0.036***	**0.037***		
Emotional				
Participant Report	33.17 (21.10)	34.47 (19.40)	1.29 (2.98)	**0.665**
Parent-Proxy Report	33.93 (20.37)	37.22 (18.24)	3.29 (2.82)	**0.246**
Difference (SE)	0.754 (2.43)	2.75 (1.18)		
P-Value	**0.757**	**0.022***		
Social				
Participant Report	37.00 (19.51)	38.66 (18.59)	1.66 (2.82)	**0.558**
Parent-Proxy Report	43.33 (22.02)	45.57 (17.87)	2.24 (2.86)	**0.435**
Difference (SE)	6.32 (2.51)	6.92 (1.54)		
P-Value	**0.014***	**<0.001***		
School				
Participant Report	36.03 (21.56)	33.21 (17.28)	2.83 (2.86)	**0.325**
Parent-Proxy Report	37.55 (23.24)	35.95 (18.17)	1.50 (3.07)	**0.626**
Difference (SE)	2.90 (2.21)	2.75 (1.44)		
P-Value	**0.194**	**0.059**		
Total				
Participant Report	50.86 (14.63)	44.58 (15.32)	6.27 (2.29)	**0.007***
Parent-Proxy Report	50.66 (16.14)	45.80 (14.41)	4.86 (2.26)	**0.033***
Difference (SE)	0.20 (1.62)	1.22 (1.04)		
P-Value	**0.90**	**0.25**		

Analysis of the effects of glucocortiocoid use and QoL was only performed on the data collected through the PedsQL^{TM} 4.0 survey. The majority of the participants who completed the

PedsQL^{TM} NMM were taking glucocorticoids, and there were not enough participants in the non-glucocorticoid group to make an appropriate comparison (n=7).

At the time of survey completion, there was no difference between participant and parent-proxy reports of Total QoL from the PedsQL^{TM} 4.0 survey, regardless of glucocorticoid use status (Table 6). However, both participants and parent-proxy surveys reported improved Total QoL for participants not using glucocorticoids than participants using glucocorticoids (p=0.007, p=0.033). When results were broken down by subscales of QoL, both participant and parent-proxy surveys reported increased Physical Functioning scores for participants not using glucocorticoids than for participants using glucocorticoids at the time of the survey (p<0.001, p<0.001). Over 50% of participants not using glucocorticoids reported a Total QoL score of 80 or above. Participants also reported higher Physical Functioning (p=0.036, p=0.037) and lower Social Functioning (p=0.014, p<0.001) scores than parent-proxy surveys, regardless of glucocorticoid use status. Participants using glucocorticoids reported decreased Emotional Functioning scores compared to parent-proxy reports (p=0.022). This difference was not seen in participants not using glucocorticoids. School Functioning did not differ significantly by glucocorticoid use status.

Table 7: *Parent-Proxy Reports Before and After Glucocorticoid Use*

(n=37)	Average (SD)	Difference (SE)	P-Value
Before	35.74 (15.94)	1.28 (2.27)	**0.577**
After	34.46 (16.17)		

Survey responses were also compared before and after the start of glucocorticoid use (Table 7). There was no significant difference in parent-proxy reported Total QoL before and after starting glucocorticoids. There was insufficient data to analyze participant responses (n=2).

3.3.5 Loss of Ambulation and QoL

Table 8 outlines participant and parent-proxy reported Total QoL before and after LoA. "Parent-Proxy Report" refers to the caregivers of the participants while "All Parent-Proxy Reports" refers to the total available caregiver survey results for this milestone. Average age of LoA was 12.92 years old. Of all the parent proxy surveys collected, caregivers reported increased Total QoL after participants reached LoA compared to before LoA (p=0.045). Participants and their corresponding parent-proxy surveys also generally reported increased Total QoL after LoA, although this difference was not statistically significant. There was no significant difference between participant and parent-proxy reported Total QoL before or after LoA (Table 9).

Table 8: *PedsQL™ 4.0 Total QoL and Loss of Ambulation*

	Average (SD)	Difference (SE)	P-Value
Participant Report (n=25)			
Before	43.52 (12.42)	3.10 (1.95)	**0.125**
After	46.62 (11.73)		
Parent-Proxy Report (n=24)			
Before	44.22 (12.26)	5.03 (3.54)	**0.169**
After	49.25 (15.32)		
All Parent-Proxy Reports (n=59)			
Before	46.07 (11.49)	3.69 (1.80)	**0.045***
After	49.76 (13.18)		

Table 9: *PedsQL™ 4.0 QoL and Loss of Ambulation-Participant and Parent-Proxy Comparison*

	Participant Average (SD)	Parent-Proxy Average (SD)	P-Value
Before (n=24)	43.71 (12.66)	44.22 (12.26)	**0.841**
After (n=24)	46.44 (15.32)	49.25 (15.32)	**0.281**

3.3.6 Loss of Self-Feeding and QoL

Table 10 outlines participant and parent-proxy reported Total QoL before and after the participant lost the ability to self-feed. Average age of loss of self-feeding (Brooke scale of 5 or higher) was 15.58 years old. Interestingly, participants reported improved Total QoL after losing the ability to lift their hands to their face (p=0.044). Parent-proxy reports also generally reported increased Total QoL after this milestone was reached, although these results were not statistically significant. Participants tended to report higher Total QoL than their corresponding parent-proxy surveys, but again this result was not statistically significant (Table 11).

Table 10: *PedsQL™ 4.0 Total QoL and Inability to Self-Feed*

	Average (SD)	Difference (SE)	P-Value
Participant Report (n=29)			
Before	43.70 (14.59)	5.01 (2.38)	**0.044***
After	48.71 (12.79)		
Parent-Proxy Report (n=27)			
Before	41.87 (17.92)	2.97 (2.98)	**0.327**
After	44.8. (19.88)		
All Parent-Proxy Reports (n=38)			
Before	44.60 (17.52)	2.00 (2.15)	**0.367**
After	46.57 (19.65)		

Table 11: *PedsQL™ 4.0 QoL and Inability to Self-Feed-Participant and Parent-Proxy Comparison*

	Participant Average (SD)	Parent-Proxy Average (SD)	Difference (SE)	P-Value
Before (n=29)	44.44 (14.34)	41.37 (17.43)	3.06 (2.67)	**0.261**
After (n=28)	49.48 (12.32)	43.86 (20.19)	5.62 (3.34)	**0.105**

3.3.7 Use of Non-Invasive Respiratory Support and QoL

Table 12 outlines participant and parent-proxy reported Total QoL before and after the participant began using non-invasive respiratory support. There was no significant difference between participant reported Total QoL before and after the onset of non-invasive respiratory support use. The same was true for the parent-proxy reported Total QoL. There was also no significant difference between participant and parent-proxy reported Total QoL before or after the participant began using non-invasive respiratory support (Table 13).

Table 12: *PedsQL™ 4.0 Total QoL and Use of Non-Invasive Respiratory Support*

	Average (SD)	Difference (SE)	P-Value
Participant Report (n=16)			
Before	46.14 (12.72)	1.09 (2.59)	**0.679**
After	47.23 (12.55)		
Parent-Proxy Report (n=16)			
Before	46.84 (15.79)	2.34 (3.48)	**0.511**
After	49.19 (8.48)		
All Parent-Proxy Reports (n=38)			
Before	46.69 (15.04)	2.87 (2.68)	**0.297**
After	49.56 (9.09)		

Table 13: *PedsQL™ 4.0 QoL and Non-Invasive Respiratory Support- Participant and Parent-Proxy Comparison*

	Participant Average (SD)	Parent-Proxy Average (SD)	Difference (SE)	P-Value
Before (n=16)	46.14 (12.72)	48.04 (13.44)	1.90 (2.44)	**0.450**
After (n=16)	47.17 (12.52)	49.15 (8.48)	2.02 (2.37)	**0.408**

3.4 DISCUSSION

3.4.1 QoL in Adolescents with DMD

The two surveys evaluated in this study revealed interesting and sometimes conflicting results. Overall, the responses in every section of the PedsQL™ 4.0 survey were lower than those previously reported by healthy peers.[11] The PedsQL™ 4.0 survey showed no difference between participant and parent-proxy reported Total QoL, suggesting that parents of adolescents with DMD perceive their sons' Total QoL the same as the sons do. However, participants reported significantly higher Total QoL on the PedsQL™ 3.0 NMM survey compared to their caregivers, which contradicts the findings from the other survey. Upon investigation of the survey subscales, it appears the difference in Total QoL reported in the PedsQL™ 3.0 NMM was primarily driven by participant reports regarding family resources. The boys in this population did not perceive as many problems regarding family resources as their parents, which suggests that adolescents with DMD are either less aware of or less concerned with money problems than their parents. This is not unexpected since parents manage household finances and are likely more aware of the costs associated with DMD treatments than their children.

There were also differences in perception regarding the subscales of the PedsQL™ 4.0 survey, with participants reporting higher physical QoL and lower psychosocial QoL in all three domains (emotional, social, and school) than their parents. The physical QoL results are somewhat surprising in the context of previous research, which has indicated that boys with DMD and their caregivers generally have similar perceptions regarding physical QoL.[12] One possible reason for the discordant findings in this study is the age-group of the participants. Most research on QoL in DMD has either been focused on children or has grouped adolescents and children into the same

analysis.[10,12,21,25,64,85] This study focuses on boys ages 11-17, and the experiences of an adolescent may be quite different than the experiences of a child. This could also explain why this study identified that participants reported significantly lower psychosocial QoL when other studies have not.[11,14] Although age effects on QoL have not been sufficiently studied in DMD, it's possible that age could explain these differences in results. Interestingly, there was no significant difference in participant and parent-proxy reports from the "About My Neuromuscular Disease" subsection of the PedsQL™ 3.0 NMM. This section focuses on physical aspects of neuromuscular disorders, so it should theoretically mirror the physical QoL results from the PedsQL™ 4.0 survey. Since the sample size for the PedsQL™ 3.0 NMM was smaller, it is possible that there was not enough data to detect the significant difference seen in the PedsQL™ 4.0 survey. It is also possible that the PedsQL™ 4.0 survey does not accurately address QoL in DMD. The physical QoL questions on the PedsQL™ 3.0 NMM survey were developed specifically for those with neuromuscular disorders and addresses appropriate physical complications such as difficulty using hands or difficulty breathing. In contrary, the physical QoL questions on the PedsQL™ 4.0 survey ask about more general tasks including walking, running, and lifting heavy objects—assessments that are largely inappropriate for non-ambulatory boys with DMD who no longer attempt to perform those tasks. Given that approximately half of this study population was non-ambulatory and boys with DMD generally lose ambulation during adolescence, it is possible that the physical QoL questions on the PedsQL™ 4.0 survey are not appropriate for adolescents with DMD and may not accurately capture physical QoL in this population.

If participants or caregivers perceived a question as being inappropriate or were unable to answer the question, they had the option to leave the question blank. Blank questions could impact the total scores for each section since the total score equals the scores for each question divided by

the total number of questions answered for that section. A brief analysis of the responses to individual questions revealed minimal impact of skipped questions. The physical QoL questions on the PedsQL^{TM} 4.0 survey that participants skipped the most were the two related to walking (4.15%) and running (3.69%). This matches our expectations given DMD disease progression. These two questions were also the most common physical QoL questions skipped by caregivers, although fewer caregivers skipped these two questions than participants (2.76%, 1.84%) It is unlikely that the skipped questions significantly impacted total physical QoL in this study. Further analysis regarding the scores for each question could better elucidate the appropriateness of those measures.

To further assess possible effects of age, data collected from boys ages 11-13 were compared to data collected from boys ages 14-17. Participants in the older age group reported lower social QoL compared to participants in the younger group suggesting that perceived social QoL decreases as age increases for adolescents with DMD. Older participants also reported significantly lower Total QoL on the PedsQL^{TM} 4.0 survey than their caregivers. This seems to have been driven by differences in perceived psychosocial QoL since participants reported lower scores across emotional, social, and school-functioning domains compared to their caregivers, suggesting that older adolescents perceive their psychosocial QoL lower than their parents do. If it is true that the discrepancy between perceived psychosocial QoL exists for older adolescents but not younger adolescents, then this could provide one explanation for the conflicting research regarding participant and caregiver-perceived psychosocial QoL. Younger participants in this study also reported higher physical QoL than their caregivers, suggesting a discrepancy in perceived physical QoL between caregivers and younger adolescents with DMD. This contradicts the previous studies that have identified moderate to high correlations between participant and

parent-proxy reported physical QoL, although, as stated previously, most previous research has included both children and adolescents in analysis, so the differences captured in this study may be unique to adolescents with DMD. [12]

Unlike with the PedsQL™ 4.0 survey, there was no significant difference in Total QoL reported between older and younger participants in the PedsQL™ 3.0 NMM. This could be due to the fact that the PedsQL™ 3.0 NMM emphasizes disease-specific physical effects on QoL (17 of the 25 questions relate to physical QoL) and does not fully assess the social and emotional impacts of disease.

Results from the PedsQL™ 4.0 survey were also separated by glucocorticoid use at the time of the survey completion. Participants using glucocorticoids reported significantly lower emotional QoL compared to parent proxy reports. This difference was not observed with participants who were not using glucocorticoids which could mean that caregivers of boys with DMD perceive that glucocorticoids have a more positive effect on emotional QoL than the boys perceive.

Surprisingly, both participants and caregivers reported that boys using glucocorticoids had lower total QoL compared to boys not using glucocorticoids. Even more surprising, this result seems driven entirely by the physical reports, for which both participants and caregivers reported higher physical QoL for participants not using glucocorticoids than for participants using glucocorticoids. Glucocorticoids are known to delay the onset of disease milestones and are thought to improve physical QoL in DMD.[14,44] The unexpected trend was also observed between the age groups, with both participants and caregivers reporting increased physical QoL on the PedsQL™ 4.0 survey with older ages. Given the progressive nature of DMD, these results seem counterintuitive, especially when research generally shows a negative correlation between physical

QoL and age.[11,14,16] Analysis of the data revealed no significant outliers driving the results. In fact, physical QoL was consistently the highest rated subscale of QoL regardless of age or glucocorticoid use.

One possible explanation for the difference in Total QoL based on glucocorticoid status is that adolescents with DMD who are taking steroids may perceive a burden of treatment not experienced by adolescents who are not taking steroids. Treatment burden is caused by the work needed to maintain the treatment, which includes the burden of patient understanding, time, frequency, and effort required to pursue and manage the treatment.[87] Side-effects of treatment could also be considered in treatment burden. One study conducted in Italy revealed that individuals living with rare diseases are not only impacted by the significant side-effects of treatment, they feel restricted by the consistent need for treatment and perceive that their treatments, although necessary, limit their freedom.[88] Treatment burden has also been identified as a problem with chronic conditions like advanced heart failure.[87] Given the significant side effects and repetitive nature of glucocorticoid therapy, it is possible that the adolescents in this study were negatively impacted by their therapy, and this was reflected in the Total QoL results. Another possibility is that the participants taking glucocorticoids may expect to experience improved physical abilities because they are taking a medicine. However, glucocorticoids merely delay the time to reach disease milestones, so adolescents taking steroids may not perceive a benefit, especially as they continue to lose muscle function. This could lead to disappointment, which could then lead them to perceive worse physical and overall QoL compared to adolescents not taking glucocorticoids.

Another possible explanation for the unexpected physical QoL results for adolescents taking steroids lays in the nature of the PedsQL™ 4.0 survey questions. If it is true that the

PedsQL™ 4.0 survey does not appropriately capture physical QoL for adolescents with DMD, this could have influenced the results related to glucocorticoid use. Unfortunately, analysis of glucocorticoid use and QoL could not be performed using the PedsQL™ 3.0 NMM for comparison since there were too few steroid non-users to perform an appropriate comparison.

Another interesting finding is that participants reported lower social QoL scores than their caregivers regardless of age and glucocorticoid status. Although there was moderate correlation between participant and parent-proxy reports, this was the lowest correlation observed for all scales in the PedsQL™ 4.0 survey. This suggests that adolescents with DMD may experience social deficits that their parents do not perceive, and that interventions targeting social QoL could help improve the total QoL for adolescents with DMD. Previous research comparing social QoL perspectives for boys with DMD ages 5-18 years old has also identified moderate agreement between participant and parent-proxy reports; however, participants in these studies appear to report higher average social QoL than their caregivers.[10,14,25] This trend was even seen in Uzark et al's study which isolated adolescents with DMD for analysis, although the participant and parent-proxy social QoL results were not directly compared so it is unclear if there was a significant difference.[11] The social QoL results in this study are also generally lower than those reported in previous studies using the same survey method.[10,11,14,25] Given that the data used in this study came from an international cohort, it is possible that adolescents in this study have different perceptions regarding their social QoL than those in previous studies.

3.4.2 QoL Results at Disease Milestones

LoA, inability to self-feed, and use of non-invasive respiratory support were the chosen disease milestones for analysis in this study because of their significance within the timeline of

disease progression and effect on medical management. Unfortunately, many of the adolescents who completed the PedsQL^{TM} 4.0 survey had already reached one or more of the disease milestones by the time of their first survey, meaning the before-and-after comparisons could not be performed for these participants. This means the sample sizes for these analyses were smaller and the power to find any differences is reduced.

No significant differences were found for participants reported Total QoL before and after LoA. This finding is congruent with prior studies that have not identified a difference in perceived Total QoL between participants using wheelchairs and those not using wheelchairs.[10,11] These results support the hypothesis that there is not a causal link between QoL and LoA. Caregivers, on the other hand, reported increased QoL after the participants lost ambulation, although this result was not replicated in the subset of caregivers who had comparable participant surveys. Davis et al. 2010 assessed parent-proxy reported QoL and LoA (n=12) and found no effect of wheelchair use on parent-proxy reports. Given the results of this study, it is possible that previous studies have been too small to identify a significant difference.

Surprisingly, participants reported increased QoL after reaching the inability to self-feed compared to before losing this ability. This contradicts previous research which has suggested that the Brooke scale (the scale used to quantify inability to self-feed in this study) does not correlate with perceived QoL in boys with DMD.[82] This finding is also incongruent with discussions held at an advocacy conference hosted by Parent Project Muscular Dystrophy (PPMD) in March of 2018. Surveys administered during “The Duchenne Patient-Focused Compass” session revealed that boys with DMD ages 11-17 years old are significantly impacted by the inability to raise their arms above their head.[89] Survey respondents even reported that if a therapeutic intervention could preserve one ability in this age group, it would be most important to maintain the ability to self-

feed. This sentiment was also expressed by adults with DMD.[89] It is important to note, however, that the adolescent survey responses were completed by both boys with DMD and their caregivers, so the findings may not completely reflect the experiences of the boys. Still, given the opinions expressed at this conference, it is surprising that participants in this study reported higher QoL after losing the ability to self-feed. Although this result may be novel and significant, it could also be a product of the abnormal physical QoL reports observed in this study and may not accurately reflect the experiences of the adolescents. More research is needed to determine if and how the inability to self-feed affects QoL in DMD.

There were no significant differences in participant or parent-proxy reports before and after use of non-invasive respiratory support. This is consistent with the findings of Kohler et al. 2005. However, the Kohler study utilized an adult survey to assess children with DMD, so it is difficult to properly interpret these findings in relation to the current study.[23] Another study has found that non-invasive respiratory support correlates with decreased QoL, but the cohort in this study consisted of children with DMD and children with other neuromuscular disorders, so it is difficult to determine if the results extend to adolescents with DMD. The findings in this study could mean that non-invasive respiratory support use does not impact perceived QoL in DMD.[24] It is also possible that the timespan between the before and after surveys was too short to detect any perceived differences.

3.4.3 Survey Selection

The CINRG DNHS administered multiple different surveys to participants and their caregivers to capture QoL data. The PedsQL™ 4.0 Generic Core Scale was selected for primary analysis in this study because previous research on QoL in DMD has often used the PedsQL™ 4.0

scale. This means the results of this study can be more directly compared to the results of previous studies. One limitation of this survey is it was developed for all children regardless of health status. Other surveys such as the Pediatric Orthopedic Society of North America (POSNA) Pediatric Musculoskeletal Functional Health Questionnaire (also referred to as the Pediatric Outcomes Data Collection Instrument or PODCI)[67,68] and the PedsQL™ 3.0 NMM were developed to assess musculoskeletal and neuromuscular HrQoL. This study also analyzed the results of the PedsQL™ 3.0 NMM to see how responses differed between the two PedsQL™ surveys. Based on the findings outlined earlier in the discussion, it appears as though the PedsQL™ 4.0 has a more robust assessment of psychosocial QoL than the PedsQL™ 3.0 NMM; however, the PedsQL™ 4.0 might not be the most appropriate tool for assessing physical QoL in adolescents with DMD. Previous research has suggested incorporating both of these surveys to gain a more in-depth assessment of QoL in DMD.[10] Given the strengths and weaknesses of these two surveys, it would be reasonable to include both surveys when assessing QoL in DMD as this study has done.

3.4.4 Limitations and Directions for Future Research

Some of the limitations of this study have been outlined already. A number of the outcomes in this study relied on the PedsQL™ 4.0 Generic Core Scale for analysis. Although this scale has been validated for use in DMD cohorts[10], this survey might not be appropriate for analyzing physical QoL for adolescents with DMD, and other survey measures may better capture QoL in this study population. Future research could compare the results from this study to those of other surveys administered during the CINRG DNHS (like the POSNA) to better elucidate how adolescents with DMD and their caregivers perceive the boys' QoL. Future research could also assess differences in responses between participants and caregivers in different geographical

regions. Since the CINRG DNHS was an international study, the overall survey results could be impacted by differing QoL perspectives in different countries. Participants in the CINRG DNHS also completed these surveys at multiple study visits, meaning there is longitudinal data that could be explored. Although the scope of this study does not include a longitudinal analysis, a cursory overview of the PedsQL^{TM} 4.0 survey data suggests that participant and parent-proxy reported Total QoL is inconsistent over time. A robust longitudinal analysis of QoL in DMD has not yet been attempted. This analysis could provide more insight into the conflicting results between QoL in different age-groups.

Results in this study were separated by age-group, but another way to assess QoL over the lifespan in DMD is to break down the results by the participants' ambulatory stages. More recent studies investigating QoL in DMD have separated the results by ambulatory stage.[16,83] Their results clearly identified an inverse correlation between total QoL and ambulatory status.[16,83] Although it is assumed that older boys with DMD are at later ambulatory stages, new and emerging therapeutics are delaying the progression of disease and may blur the lines between age and ambulatory status. Future research could continue to assess how ambulatory stage correlates with total QoL as well as the subscales.

Analysis of disease milestones in this study was also limited by small sample sizes since many participants either reached the milestone(s) before entering the study or did not reach them during their time in the study. This means there was less statistical power to detect differences in survey responses and the data was more prone to random error. Further research is needed to determine what causal effects (if any) the disease milestones analyzed in this study have on QoL. Finally, research on QoL in adolescents with DMD is limited, with most studies grouping

adolescents with children for analysis. The results of this study warrant further investigation into QoL in adolescents with DMD.

3.5 CONCLUSION

This study shows that there are differences between adolescent and caregiver-perceived QoL with DMD. Caregivers may underestimate their child's physical QoL and overestimate their child's psychosocial QoL, suggesting that adolescents with DMD have psychosocial difficulties not noticed by their caregivers. Future research on the topic should continue to ascertain both participant self-report and parent-proxy reports to better understand these perceptions.

This study also suggests that adolescents with DMD have different perceptions regarding their QoL than younger children with DMD, and more research is needed to further assess these differences. Research on adolescents is lacking, and future research could help determine strategies to improve QoL specifically for adolescents with DMD. This study, for example, suggests that interventions aimed at improving social QoL could have a significant impact on QoL for adolescents with DMD. As therapeutics develop and the progression of disease slows, adolescents with DMD may retain more physical abilities than before. This means it will be important to continue to assess QoL in adolescents as their perceptions will likely change over time.

Finally, this study suggests that adolescents taking glucocorticoids may experience burden from the daily medicine and may have more negative perceptions regarding their physical QoL than suggested given previous research. LoA and use of non-invasive respiratory support does not correlate with changes in HrQoL for adolescents with DMD; however, it is possible that the sample sizes were too small to detect a difference, as evidenced by the total caregiver responses at the

time of LoA. Participants in this study also reported increased QoL after losing the ability to self-feed. Although this could suggest that adolescents with DMD perceive reduced burden after losing the ability to feed themselves, this contradicts anecdotal evidence. Further research on the effects of disease milestones on QoL in DMD is needed, and researchers should strive to incorporate larger sample sizes and appropriate surveys to better detect any differences.

4.0 RESEARCH SIGNIFICANCE TO GENETIC COUNSELING AND PUBLIC HEALTH

Although this thesis project focused specifically on adolescents with DMD and their caregivers, the findings of the study have the potential to extend beyond this population. Rare-disease researchers, for example, can use the findings from this study to better inform their own research projects. The FDA states that QoL measures are an important part of clinical research and should continue to be incorporated into research trials, especially those related to chronic and rare-diseases.[58] Given the importance of QoL measures in clinical research, it is crucial that researchers select the most appropriate QoL surveys for their population. This study helps to demonstrate that some QoL surveys may capture more useful information than others. It is important that DMD researchers and investigators studying other rare and/or debilitating diseases utilize appropriate assessments to ensure their QoL measurements reflect the experiences of their participants.

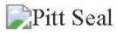
QoL research in DMD and other rare diseases also contributes to the broader field of public health. Public health incorporates ten essential services to improve population health and prevent negative health outcomes.[90] This thesis project applies to many of the core services of public health. The first service is, of course, research. Research is a key component of public health and is incorporated through every step from initial assessment of a public health problem to the final evaluation of the proposed solution. The research in this project contributes to the "Monitor Health" service which is part of the overall assessment of a public health problem. By evaluating QoL in adolescents with DMD, this project helps monitor one aspect of health in DMD and provides information needed to assess the health in individuals with DMD and rare-diseases in general. This project also contributes to the "Diagnose and Investigate" service—the next step in

assessing a health problem. By analyzing the effects of age, glucocorticoid use, and disease milestones on QoL, this study investigates factors that may impact QoL in DMD and contributes to the knowledge needed to propose interventions to improve QoL for boys with DMD. Finally, by comparing the two different survey methods and assessing their use in the DMD population, this project contributes to the "Evaluation" service of public health. This study suggests that the PedsQL^{TM} 4.0 survey might not be the most appropriate measurement to assess physical QoL in DMD and other diseases with a significant physical impact, but the PedsQL^{TM} 3.0 NMM might not capture certain aspects of psychosocial QoL. Choosing the right survey to assess QoL is crucial for developing policies and interventions to improve population health and QoL, and by evaluating these surveys in the context of adolescents with DMD, this study helps to guide proper use of these surveys in DMD and other populations.

Since DMD is a genetic disease, genetic counselors in a variety of specialties may have the opportunity to work with a family impacted by DMD. Some genetic counselors work in neuromuscular clinics where regularly follow families with DMD and other neuromuscular disorders over many years. These counselors have the unique opportunity to help individuals and families cope and adapt to the changes experienced throughout the course of the disease. Genetic counselors can use the findings in this study to educate parents about the QoL for adolescents with DMD. This could help parents of younger children with DMD anticipate the QoL for their child in the future and could help parents of adolescents with DMD better understand their sons' experiences. Genetic counselors who are part of the care team for an adolescent with DMD can also use the information provided in this study to better assess the psychosocial state of the adolescent. For example, genetic counselors could consider asking targeted questions about their patient's social life and, if needed, suggest strategies to improve social QoL.

Not all genetic counselors work with individuals and families impacted by DMD. Still, genetic counselors can use the results from this project to inform their own counseling for different genetic diseases. This study identified that there are significant differences between QoL perceived by the adolescents with DMD and their caregivers. Such differences likely exist for other diseases, and genetic counselors could incorporate this knowledge when working with children and adolescents with various genetic diseases and their parents.

APPENDIX: INSTITUTIONAL REVIEW BOARD APPROVAL LETTER



University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Paula Clemens
From: IRB Office
Date: 10/31/2017
IRB#: PRO17090400
Subject: Caregiver Perceptions of Quality of Life in Boys with Duchenne Muscular Dystrophy

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The above-referenced project has been reviewed by the Institutional Review Board. Based on the information provided, this project meets all the necessary criteria for an exemption, and is hereby designated as "exempt" under section
45 CFR 46.101(b)(4)
There are no items to display

Please note the following information:

- Investigators should consult with the IRB whenever questions arise about whether planned changes to an exempt study might alter the exempt status. Use the "**Send Comments to IRB Staff**" link displayed on study workspace to request a review to ensure it continues to meet the exempt category.
- It is important to close your study when finished by using the "**Study Completed**" link displayed on the study workspace.
- Exempt studies will be archived after 3 years unless you choose to extend the study. If your study is archived, you can continue conducting research activities as the IRB has made the determination that your project met one of the required exempt categories. The only caveat is that no changes can be made to the application. If a change is needed, you will need to submit a NEW Exempt application.

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

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