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THE ROLE OF THE NEUROMUSCULAR MEDICINE SPECIALIST AND PHYSIATRY IN THE MANAGEMENT OF NEUROMUSCULAR DISEASE

Craig M. McDonald, MD [Professor and Chair] and
Department of Physical Medicine and Rehabilitation, Professor of Pediatrics, University of California Davis School of Medicine, Sacramento, CA

William M. Fowler Jr, MD [Professor Emeritus and Founding Chair]
Department of Physical Medicine and Rehabilitation, University of California Davis School of Medicine, Sacramento, CA

Synopsis

The neuromuscular medicine, and physiatry specialists are key health care providers who work cooperatively with a multidisciplinary team to provide coordinated care for persons with Neuromuscular diseases (NMDs). The director or coordinator of the team must be aware of the potential issues specific to NMDs and be able to access the interventions that are the foundations for proper care in NMD. These include health maintenance and proper monitoring of disease progression and complications to provide anticipatory, preventive care and optimum management. Ultimate goals include maximizing health and functional capacities, performing medical monitoring and surveillance to inhibit and prevent complications, and promoting access and full integration into the community in order to optimize quality of life.

This issue of the *Physical Medicine and Rehabilitation Clinics of North America* is intended to provide the reader with a comprehensive over-view of the diagnostic approach, clinical characteristics, and care and management of patients with neuromuscular disease (NMD), with emphasis on the most common hereditary and acquired neuromuscular disorders. Neuromuscular diseases (NMDs), a classification category that describes hereditary and acquired diseases of the peripheral neuromuscular system, includes those that affect anterior horn cells, peripheral nerves, neuromuscular junctions and muscle.

The estimated total prevalence of the most common neuromuscular diseases (NMDs) in the United States is 500,000 (see Appendix – Prevalence Table).[1–7] Combined with all forms of acquired NMDs the prevalence exceeds 4 million which is an impressive figure when compared for example to the prevalence of spinal cord injury, estimated to be between 239,000 to 306,000.[8–11] There is tremendous diversity of etiologies for both acquired and hereditary neuromuscular diseases. Some NMDs are acquired with diverse causes distinct from genetic etiologies such as autoimmune, infectious, metabolic, toxic, or paraneoplastic

Correspondance to: Craig M. Mcdonald, MD, 4860 Y Street, Suite 3850, Sacramento, CA 95817. Phone: 916-734-2923, FAX: 916-734-7838. cmmcdonald@ucdavis.edu.

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(e.g. amyotrophic lateral sclerosis (ALS), myasthenia gravis, lambert eaton syndrome, botulism, Guillain Barre syndrome, or diabetic peripheral neuropathy). There are over 500 distinct NMDs identified to date which have specific genes that have been linked causally to these conditions.[12–14] Limb girdle muscular dystrophy, for example, has over 20 genetically distinct subtypes that have been identified to date. The genetic heterogeneity of hereditary neuromuscular diseases has created challenges for clinicians and researchers.

Although currently incurable, NMDs are not untreatable. The neuromuscular medicine, and physiatry specialists are key health care providers who work cooperatively with a multidisciplinary team to maximize health, maximize functional capacities (including mobility, transfer skills, upper limb function, and self-care skills), inhibit or prevent complications (such as disuses weakness, skeletal deformities, disuses weakness, airway clearance problems, respiratory failure, cardiac insufficiency and dysrhythmias, bone health problems, excessive weight gain or weight loss, metabolic syndrome), and promote access to full integration into the community with optimal quality of life.

The molecular basis of hereditary NMDs has been emerging and coming into sharper focus over the past three decades. Many promising therapeutic strategies have since been developed in animal models. Human trials of these strategies have started, leading to the hope of definitive treatments for many of these currently incurable diseases. Although specific treatments for NMD have not yet reached the clinic, the natural history of these diseases can be changed by the targeting of interventions to known manifestations and complications. Diagnosis can be swiftly reached; the family and patient can be well supported, and individuals who have NMD can reach their full potential in education and employment. In Duchenne muscular dystrophy for example, corticosteroid, respiratory, cardiac, orthopaedic, and rehabilitative interventions have led to improvements in function, quality of life, health, and longevity, with children who are diagnosed today having the possibility of a life expectancy into their fourth decade.[15–28]

Advocacy organizations report variable and inconsistent health care for individuals with NMD. Although anticipatory and preventive clinical management of NMDs is essential, recommendations exist in only a few areas. Addressing the many complications of NMDs in a comprehensive and consistent way is also crucial for planning multicenter trials, as well as for improving care worldwide. The development and implementation of standardized care recommendations have been emphasized by stakeholders in heterogeneous NMD communities including government agencies, clinicians, scientists, academicians, volunteer health agencies, and advocacy organizations. The purpose of this issue is to provide a framework for recognizing the primary manifestations and possible complications and for planning optimum treatment across different specialties with a coordinated multidisciplinary team.

Reported Needs of Persons with Neuromuscular Diseases

The greatest needs of the population of persons with NMDs were recently evaluated by our The NIDRR-funded Rehabilitation Research and Training Center (RRTC) in NMD at the University of California Davis Medical Center. We performed a comprehensive quality of life survey of over 1,000 individuals with neuromuscular diseases.[29, 30] The most frequent problems impacting quality of life in NMD are shown in Table 1. Consumers with NMD reported that the most significant problems impacting their health, function and quality of life were secondary conditions including weakness, fatigue and poor endurance, weight management, sleep disturbances, muscle contractures, and breathing problems. These problems translate into functional issues that consumers with NMD note to be significant,

such as difficulty walking, exercising, controlling weight, and doing activities of daily living.

The Interdisciplinary NMD team

The comprehensive management of all of the varied clinical problems associated with NMDs is a complex task. For this reason, the interdisciplinary approach is critical. It takes advantage of the expertise of many clinicians, rather than placing the burden on one. This interdisciplinary approach to caring for patients with NMD, and participation by committed providers that have NMD disease-specific expertise are key ingredients to the provision of optimal care (figure 1).[31, 32] The patient and family / care providers should actively engage with the medical professional who coordinates clinical care. Depending on the patient's circumstances, such as area/country of residence or insurance status, this role might be served by, but is not limited to, a neurologist or pediatric neurologist, physiatrist / rehabilitation specialist, neurogeneticist, pediatric orthopedist, pediatrician, or primary-care physician. In the U.S. the coordination of care is often done by the Neuromuscular Medicine specialist (ACGME approved fellowships in Neuromuscular Medicine now exist for subspecialty certification within the American Board of Psychiatry and Neurology and the American Board of Physical Medicine and rehabilitation). The director or coordinator of the team must be aware of the potential issues specific to NMDs and be able to access the interventions that are the foundations for proper care in NMD. These include health maintenance and proper monitoring of disease progression and complications to provide anticipatory, preventive care and optimum management.

NMD Management is best carried out by a team consisting of physicians; physical, occupational and speech therapists; social workers; vocational counselors; and psychologists, among others. Ideally, owing to the significant mobility problems associated with most NMDs, the neuromuscular medicine specialist, physiatrist and all the key clinical personnel should be available at each visit. Tertiary care medical centers in larger urban areas usually can provide this type of service. This may be an independent clinic or may be sponsored by one or more of the consumer-driven organizations that sponsor research and clinical care for people with NMDs, including the Muscular Dystrophy Association (MDA), the Amyotrophic Lateral Sclerosis (ALS) Association, the Charcot-Marie-Tooth International and Association groups, and the Fascioscapulohumeral Society, among others. Although the *physiatrist* (Greek for *physis* for "nature" and *iatrikos* for "healing") is well-suited to direct the rehabilitation team and to oversee a comprehensive, goal-oriented treatment plan, physiatrists are co-directors of less than 20% of the MDA clinics in the United States.[33,34] Bach has previously described the many major advances physiatrists have contributed to the care of NMD patients and has pointed out the rather significant need for more physiatric involvement in the care of NMD patients.[34]

Toolkits of Assessments and Interventions for the Interdisciplinary NMD Team

There are varied toolkits of assessments and interventions applicable to NMD management (Table 2).[31] Input from different specialties and the specific assessments, and interventions will change as the NMD progresses. Some measures such as strength assessment, functional grading, timed function measures, and pulmonary function measures are core measures performed at least annually for most NMDs. Others are performed regularly depending on the expected impairments for specific NMDs.

The World Health Organization International Classification of Functioning (ICF) Framework)

Although their degrees and severity can vary, the characteristics or complications of most NMDs include progressive weakness, limb contractures, spine deformity, and decreased pulmonary function; some patients suffer cardiac and intellectual impairment. In determining the severity of impairment and disability, a comprehensive evaluation of patients with NMDs should be done at routine intervals or as clinically indicated. The World Health Organization's International Classification of Functioning, Disability and Health (ICF)[35] provides a useful framework for evaluating the manifestations and complications of NMDs. The bioecological ICF framework[35] incorporates domains covering *body structure and function, individual activities and participation, and environmental factor*s that impact the overall physical and mental health of the individual in a societal context. In this framework ***body structures*** are anatomical parts of the body such as organs, limbs, and their counterparts and ***body functions*** are the physiological functions of body systems (including physiological functions). Impairments are problems in body structure or body function as a significant deviation from normal or loss. ***Activity*** is the execution of a task or action by an individual and activity limitations are difficulties an individual may have in executing activities. ***Participation*** is involvement in a life situation and participation restrictions are problems an individual may have in involvement in life situations. While the ICF framework covers environmental domains such as external barriers to participation, we typically do not include assessments of environmental domains of the ICF framework because of limited ability of therapeutic agents, surgeries or rehabilitation interventions evaluated in clinical trials to impact these domains.

Patient-reported outcomes (PROs) encompass self-perceived or caregiver-proxy perceived concepts of health and well-being defined broadly including such concepts as health-related quality of life, satisfaction, physical functioning, basic mobility and transfers, sports and physical functioning, mobility and ambulation, upper extremity functioning and ADLs, pain, fatigue, quality of sleep, emotional health, social health, depression, anxiety, stigma, etc.

Selected Assessments for NMD

There are diverse assessments that are performed in NMDs for clinical studies, natural history studies, and clinical trials. For example, table 3 summarizes the diverse nature of clinical endpoints and assessments that have been used clinically and in natural history studies involving persons with Duchenne muscular dystrophy (DMD) organized according to a modified ICF framework. Some core measures such as manual muscle testing for strength, ROM, timed function, pulmonary function, and selected cardiac measures are routinely performed annually or more frequently if clinically indicated.

Important clinical data that should be obtained initially on each patient include: gender, birth date, family history, date of disease (symptom) onset, disease duration, dominant limb, weight and height, cardiovascular and pulmonary symptoms and findings, presence of contractures and spine deformity, muscle strength, ambulatory status (including age at cessation of ambulation and years of wheelchair use), and any treatment interventions. When relevant, these data should be updated at each patient visit. In large clinics data can be recorded on a standardized form and entered into a computer database or electronic health record. Records of respiratory and cardiovascular symptoms and findings should be maintained at each clinic visit. The history should include questions relating to shortness of breath with ambulation, at rest, and during sleep; palpitations; dyspnea; and chest pain. A thorough systems review should be made of cardiopulmonary complications, including

pneumonia, prolonged upper respiratory tract infections, respiratory compromise requiring assisted ventilation, and heart failure.

Strength Assessments

Precise measures of strength are important for evaluating clinical progression in NMD as well as assessing the efficacy of any interventions. Strength traditionally has been assessed with manual muscle testing (MMT) using the Medical Research Council (MRC) scale for muscle grading (Table 4), although this is not reliable in muscles that are only mildly affected.[36–42] Care must be exercised for consistent inter-examiner measures of the antigravity muscles.

Quantitative strength measurements are somewhat more labor intensive, but provide more sensitive and reproducible information.[38, 40–42] These include static (isometric) and dynamic (isokinetic) measurements, most often done in selected muscle groups (usually bilateral knee, elbow, shoulder, and neck flexors and extensors) with a force transducer that displays force output through a digital force monitor. Static pinch strength and grip strength also may be measured using a force transducer, and these measurements followed serially at clinic visits. The highest score from three maximal trials usually is recorded. The hand-held dynamometer (HHD) is perhaps the most practical yet reliable way to obtain quantitative strength testing in the clinic. The HHD is a small device equipped with an internal load cell that operates as a force transducer. The HHD is capable of measuring force generated by a subject against the examiner who holds the device firmly against the subject and provides stabilization (counter-resistance). The maximum force is recorded. Although it does not replace formal quantitative strength testing, the HHD has reasonably good reliability in NMD for weaker muscle groups and is a good alternative to MMT.

Dynamic strength may be assessed using an isokinetic dynamometer at a fixed speed (e.g., 30 degrees per second) for both concentric (shortening) and eccentric (lengthening) contractions[40]. Flexors and extensors should be evaluated through a full range of motion. Parameters that can be measured include peak torque, total work, work per repetition, peak torque to body weight ration, joint angle at peak torque, range of motion, and fatigue index (decrement in work performance over the exercise bout).

Range of Motion Assessments

Passive Joint range of motion (PROM measurements) should be done with a standard goniometer following the protocol used by Brooke and colleagues,[4] and Fowler and colleagues.[40] Joints to be evaluated for contractures include elbow and wrist extension, hip adduction for iliotibial band tightness, hip and knee extension, and ankle dorsiflexion. The definition of clinically significant contractures varies according to the joint. In some joints, even as little as a 7° flexion contracture can result in the center of gravity (COG) falling to an unstable plane (e.g., anterior to the hip joint and posterior to the knee center of rotation). Care must be taken to measure the ROM of two-joint muscles in position of function (e.g., ankle ROM measured with the knee fully extended).

Active ROM (AROM) assesses the participant’s ability to recruit muscle strength to perform a muscle contraction through an available ROM. Passive ROM (PROM) is first performed by a clinical evaluator to assess the extensibility of muscle, tendons and ligaments passively through a ROM. This is followed by evaluation of AROM. The assessment of ROM must be performed taking into account what PROM is available due to contracture. AROM and PROM are necessary for appropriate biomechanics in activities such as walking and using the upper extremities for functional activities.

Timed Function Tests

Time to rise from the floor (supine to stand)—The time to rise from the floor from a supine position (in seconds) follows the protocol reported previously by CIDD[36], UC Davis[40], and the Cooperative International Neuromuscular Research Group (CINRG)[42]. The assessment is performed in all ambulatory study participants who can perform the test. For standing from supine the velocity is calculated as 1 divided by the time to complete the task. Subjects are given 30 to 60 seconds to complete the task. A subject who is unable to complete the task is given a score of 99 and a velocity which approaches zero.

Time to climb four stairs—The time to climb 4 standard stairs follows the protocol as described previously by CIDD[36], UC Davis[40], and CINRG[42]. The assessment is performed in children age 2 and older. For the total task of climbing 4 standard stairs, velocity was calculated as 1 divided by the time to complete the task. Subjects are given 30 to 60 seconds to complete the task. A subject who is unable to complete the task are given a score of 99 and a velocity which approaches zero.

Time to walk/run ten meters—The time to walk/run ten meters follows the protocol reported by CIDD[36], and UC Davis for 30 feet[40, 43], and CINRG for 10 meters[42]. The assessment is performed in children age 2 and older. Timed function test velocities were calculated as distance divided by completion time. Velocity for the 10 meter walk/run test is determined by dividing distance (10 meters) by the time to complete the task (in seconds). Subjects are given 30 to 60 seconds to complete the task. A subject who is unable to complete the task are given a score of 99 and a velocity which approaches zero. Other Timed function tests. These may include time to stand from a chair, time to propel a manual wheelchair 10 meters or 30 feet, time to put on a T-shirt, and time to cut out a $3'' \times 3''$ pre-marked square from a piece of paper with safety scissors.

Six-minute Walk Test (6MWT)—We have recently modified the ATS version of the six-minute walt test (6MWT) and validated the test as a clinical endpoint for DMD[44–46]. Subsequently, there has been widespread utilization of this measure and success of the measure as a primary endpoint in multicenter clinical trials. The modified 6MWT utilizes standard video instructions, a safety chaser to assist the subject up in the event of a fall, and constant rather than intermittent encouragement. Subjects walk around two cones placed 25 meters apart. For the CINRG DMD natural history study, the 6MWT is performed in all participants who can be expected to walk at least 75 meters. A subject who is unable to ambulate 10 meters on a 10 meter walk/run test is given a “0” value for the 6MWT. Using this protocol[44], we determined the 6MWT to be reliable and valid in DMD at a single center. The primary variable derived from the 6MWT is the six-minute walk distance (6MWD) in meters. For clinical trials where subjects are tested serially, lower values of 6MWD can be obtained in more marginal ambulators. To account for maturational influences we have described the use of age- and height- based percent predicted values for 6MWT [46]. For the DMD subjects we also measure the number of steps taken during the 6MWT with a tally counter or with a stepwatch activity monitor placed on the right ankle. This allows the calculation of average stride length and cadence. The 6MWT takes approximately 15 minutes to complete.

9-hole peg test (9-HPT)—The 9-HPT is commercially available, easy and quick to administer, portable test that is used to measure upper limb function and dexterity.[47–49] The 9-HPT records the time to pick up 9 pegs from a container, put into the holes, and then returned to the container. The test has been validated in all age groups and has high inter-rater and test-retest validity. The 9-HPT shows concurrent and convergent validity, and the measure appears sensitive to change in adults with neuromuscular and musculoskeletal

disorders [50, 51]. Both adult and pediatric norms are available [48, 49]. It has been chosen by the NIH Toolbox as a measure of dexterity because it is a very viable tool for longitudinal epidemiologic studies and intervention trials (www.nihtoolbox.org). The primary variable derived from the 9-HPT is completion time in seconds. Total time for administration of the 9-HPT is 10 minutes or less.

Disease-specific Functional Rating Scales

Disease specific functional rating systems exist for many NMDs. For example, the ALS Functional Rating scale (ALSFRS) is commonly obtained in ALS patients[52]. In DMD, Functional classifications utilize the upper extremity scale reported by Brooke et al [36] and the lower extremity scales used by Vignos et al.[53,54].

ALS Functional rating Scale-revised (ALSFRS-R)—The ALSFRS-R assesses patients' levels of self-sufficiency in areas of feeding, grooming, ambulation, communication, and respiratory[52]. The assessment determines the degree of impairment in ALS patients' abilities to function independently in activities of daily living, locomotion, communication, and breathing. It consists of 12 items to evaluate bulbar function, motor function and respiratory function and each item is scored from 0 (unable) to 4 (normal). The ALSFRS has been validated both cross-sectionally and longitudinally against muscle strength testing, the Schwab and England ADL rating scale, the Clinical Global Impression of Change (CGIC) scale, and independent assessments of patient's functional status. The ALSFRS-R is an attractive primary outcome measure in clinical trials of ALS because it is validated, easy to administer, minimizes dropout, reduces cost, and correlates with survival. Unlike the other standard outcome measures currently employed, the ALSFRS-R is also a measure of global function[52].

Vignos Lower Extremity Functional Grade—*T*he following functional grade was originally described by Vignos [53, 54]: 1: walks and climbs stairs without assistance; 2: walks and climbs stairs with the aid of a railing; 3: walks and climbs stairs slowly with the aid of a railing (over 12 seconds for 4 standard stairs); 4: walks unassisted and rises from chair but cannot climb stairs; 5: walks unassisted but cannot rise from chair or climb stairs; 6: walks only with the assistance or walks independently with long leg braces; 7: walks in long leg braces but requires assistance for balance; 8: Stands in long leg braces but unable to walk even with assistance; 9: is in a wheelchair; 10: is confined to bed.

Brooke Upper Extremity Functional Grade—The following functional grade was originally described by Brooke et al. [36]: 1: Starting with arms at the sides, the patient can abduct the arms in a full circleuntil they touch above the head; 2: Can raise arms above the head only by flexing the elbow; (i.e. shortening the circumference of the movement or using) or using accessory muscles; 3) Cannot raise hands above head but can raise an 8 ounce glass of water to mouth using both hands if necessary; 4: Can raise hands to mouth but cannot raise an 8-ounce glass of water to mouth; 5: Cannot raise hands to mouth but can use hands to hold pen or pick up pennies from the table; 6: Cannot raise hans to mouth and has no useful function of hands. As an optional measure if the patient has a Brooke Grade of 1 or 2 measured by the therapist, it is determined how many Kg of weight can be placed on a shelf above eye level, using one hand.

North Star Ambulatory Assessment (NSAA)—The NSAA is a clinician rated 17-item functional scale designed for ambulant boys with DMD who are able to stand [55–60]. This evaluation tool assesses functional activities including standing, getting up from the floor, negotiating steps, hopping, and running. The assessment is based on a 3 point rating scale of 2= ability to perform the test normally, 1= Modified method or assistance to perform test,

0=unable to perform the test. Thus, total score can range from 0 (completely non-ambulant) to 34 - no impairment on these assessments. The North Star Ambulatory Assessment is currently also used in several other countries and international clinical trials[61]. NSAA has shown good reliability and validity in multi-center studies as well as good clinical validity through Rasch analysis [56, 58].

Motor Function Measure (MFM)—The MFM is a recently developed instrument to assess motor function in ambulant and non-ambulant patients with neuromuscular diseases (NMD) aged 6–62 years [62]. The scale is comprised of 32 items, in three dimensions: D1: standing position and transfers (13 items), D2: axial and proximal motor function (12 items), and D3: distal motor function (7 items). Each test is scored by the therapist on a 4-point Likert scale. Scores for subscales and the composite total score range from 0= worse to 100%= better. In heterogeneous NMD patients, internal consistency, intra- and inter-rater reliability for the global scale and the subscales was excellent, and face validity, convergent validity and discriminant validity were good [62]. Vuillerot et al. [63] showed that the MFM was able to measure changes in motor function over time in DMD and the total score predicted loss of ambulation. The MFM takes 30–40 minutes to complete.

Egen Klassification (EK2) Scale—The EK2 scale was developed by the Danish Muscular Dystrophy Association as a clinical tool to assess overall functional ability in non-ambulatory patients with DMD [64]. This tool includes assessments comprised of functional ability measuring upper extremity grade, muscle strength measured with the manual muscle test, and forced vital capacity defined as a percentage of normal values (FVC%). The construct is based on the interaction of physical components such as muscle strength, range of motion, respiratory status, wheelchair dependence and age. The EK scale assesses ten functional categories (EK 1–10), each on a scale of 0=normal to 3= very impaired, contributing to an overall function score of 0 to 30. The EK scale has shown high inter- and intra-rater reliability (ICC-.98) and good construct validity [65].

Spine deformity Evaluations

For many NMD patients spine deformity should be evaluated at every clinic visit. Data obtained at the time of the first patient visit and thereafter should include the presence or absence of spine deformity, any interventions, and the patient's age at time of observation. Radiographs should be reviewed and the results for kyphosis and scoliosis recorded along the guidelines recommended by Carman et al [66], Fon et al. [67], and Gupta et al. [68].

Pulmonary Evaluations

Depending on the specific NMD diagnosis, pulmonary evaluations by a pulmonologist may be indicated. Pulmonary function tests (PFTs) include forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC, maximal voluntary ventilation (MVV), residual volume (RV), peak expiratory flow rate (PEFR), and peak cough flow. Measurements are made using a spirometer (e.g. KoKo spirometer and digidoser, nSpire Health, Inc.) and the pulmonary function data may be interpreted using the Crapo et al.[69] and Polgar et al.[70] normative reference set for 6–7 year old participants or the Hankinson et al.[71] normative reference set for ≥8 year old participants. Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) are helpful and are measured near RV and total lung capacity (TLC), respectively, following the technique described by Black and Hyatt [72] using a direct ready dial gauge force meter and ventilated T-tube assembly. Three technically satisfactory measurements should be obtained and the maximum reading recorded. Interpretation of MIP and MEP values can be based on Wilson et al.[73] and Domenech-Clar et al.[74] normative pediatric reference sets. Participants are evaluated in a seated position with support for the back and feet and they wear nose clips or have their

noses held closed by hand during testing. If necessary, cardboard mouthpiece adapters can be used to enable participants to make a full lip seal. PFTs should be done at least yearly and more frequently if clinical indications exist. If clinically indicated, arterial blood gas studies, pulse oximetry, and/or capnography (CO_2 monitoring) should be obtained. Formal sleep studies may be indicated depending on the NMD diagnosis and results of regular screening studies such as overnight pulse oximetry.

Cardiac Evaluations

Depending on the specific NMD diagnosis, cardiac evaluations by a cardiologists may be indicated. Regular assessments may include ECG, echocardiography, Holter monitoring, and Cardiac: MR Imaging. Standard 12-lead electrocardiograms (ECGs) should be obtained at 1-year intervals. In some diseases, particularly the myopathies with associated cardiomyopathy, echocardiograms are indicated.

Neuropsychological tests

Neuropsychologic measurements may be helpful in some of these diseases, particularly if there are educational and vocational problems. However, previous reports that used some of the standard measurement tools suggested that subtle physical impairments may have negatively affected the test results. Therefore, caution is advised in interpreting these tests. Tools such as the Category Test, Seashore Rhythm Test, and Speech-Perception Test should be used, if possible, because performance on these instruments is not dependent on motor function[75–77].

Patient-Reported Outcomes (PROs)

Consumers, clinical researchers, the Food and Drug Administration, and industry have increasingly recognized the importance of patient-reported outcome (PRO) measures in the determination of clinically meaningful outcomes and validation of clinical and surrogate endpoints for therapeutic trials [78]. There are regulatory requirements that registration studies must incorporate primary endpoints that objectively measure clinically meaningful “life-changing” events with significant impact on health and well-being. In addition, the FDA has strongly recommended inclusion of PRO measures such as health-related quality of life (HRQOL) assessments as an endpoints in all clinical trials [79, 80]. Both global measures of HRQOL and disease-specific NMD measures have been used in NMD populations.

Ongoing Management / Anticipatory Guidance

Once the diagnosis is confirmed, the patient and family should be thoroughly educated about the expected outcome and what problems may be encountered. The Neuromuscular specialist and /or physiatrist should then assess the patient’s and family goals and develop a medical management and rehabilitative program that matches those goals. Palliative care focuses on living well with optimized quality of life despite life expectancy.

Major advances in the understanding of the molecular basis of many NMDs has greatly enhanced diagnostic accuracy and provides the basis for novel therapeutic interventions. There have also been major pharmacologic advances in the treatment of some NMDs, particularly ALS and DMD. The physiatrist may become involved in the prescription of disease-altering medications for the various NMDs, and therefore should familiarize him/herself with the appropriate pharmacologic agents available. In addition, if not directly involved in research, the physiatrist should nonetheless encourage enrollment in experimental protocols, which not only furthers science but provides some hope for the patient. Education and employment are very important with respect to self-esteem, quality of life, and integration into the community and should be emphasized in people with slowly

progressive NMD. Patients should be referred to a support group. Support groups often are a great resource, not only for psychologic support but for problem-solving and recycling of equipment.

Given the many advances that have occurred in the management of people with NMD, many patients will survive through their childbearing years, possibly having children, and can expect to enjoy a good quality of life. The physiatrist can play a critical role during important life transitions and provide care which can maximize function and quality of life.

Summary

Although currently incurable, NMDs are not untreatable. The neuromuscular medicine, and physiatry specialists are key health care providers who work cooperatively with a multidisciplinary team to maximize health and functional capacities, inhibit or prevent complications, and provide access to resources which promote full integration into the community to optimize quality of life. Addressing the many complications of NMDs in a comprehensive and consistent way is also crucial for planning multicenter trials, as well as for improving care worldwide. The development and implementation of standardized care recommendations have been emphasized by government agencies, clinicians, scientists, academicians, volunteer health agencies, and advocacy organizations. The Neuromuscular specialists and physiatrists are well suited to working cooperatively to provide this type of multidisciplinary care and they can play a significant role in improving care for patients.

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Key Points

- Both neuromuscular medicine specialists and physiatrists are key health care providers who work cooperatively with a multidisciplinary team to provide coordinated care for persons with Neuromuscular diseases (NMDs).
- Ongoing input from different specialties is important as the specific assessments, and interventions which are necessary will change as the NMD progresses.
- Addressing the many complications of NMDs in a comprehensive and consistent way is also crucial for planning and determining eligibility for clinical trials, as well as for improving care worldwide.
- The development and implementation of standardized care recommendations for NMDs will lead to improved health, function, participation, and quality of life.

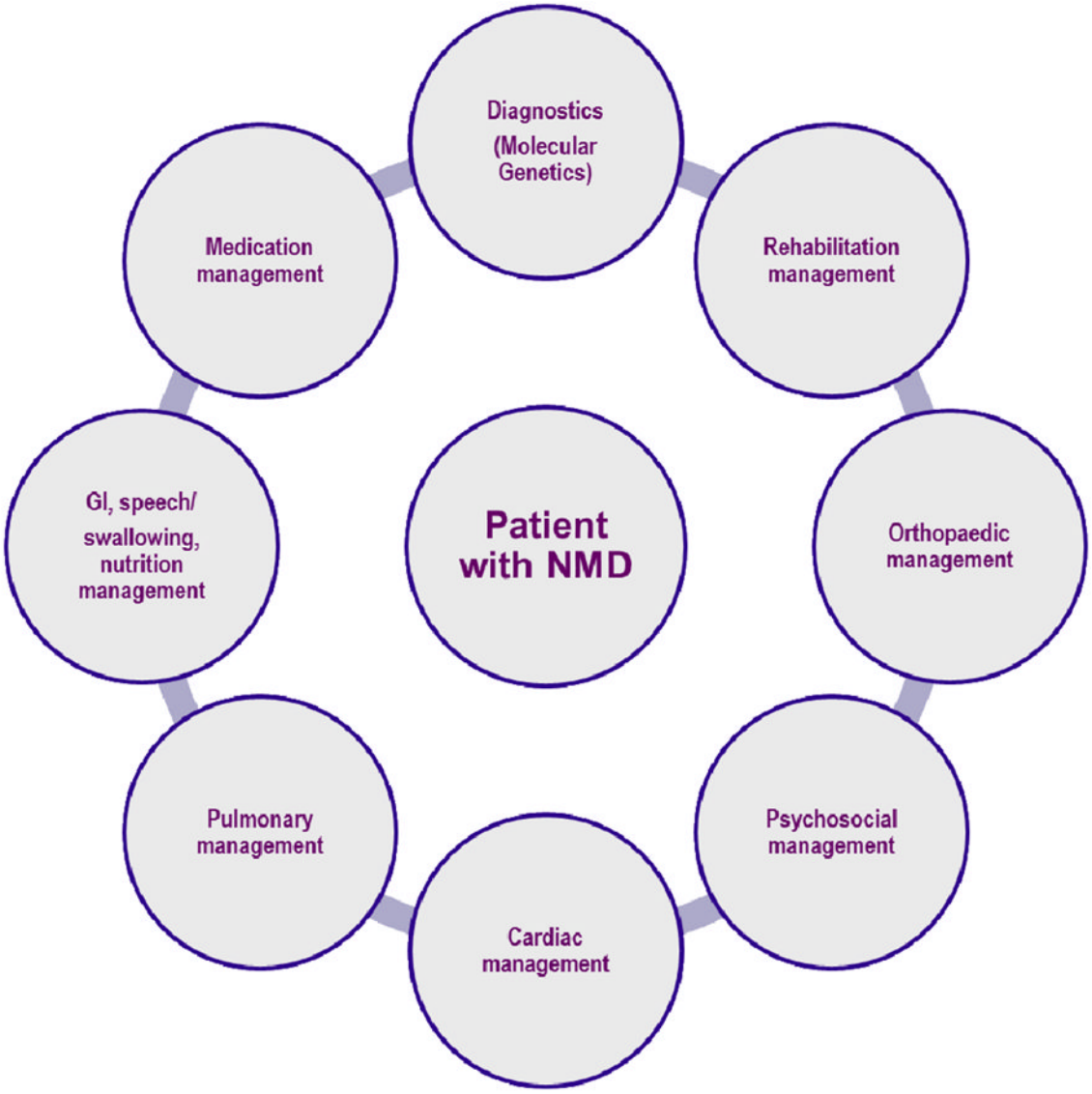

Figure 1. Interdisciplinary NMD Clinical Care Coordination (
Data from Bushby, K., et al., Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurology, 2010. 9(1): p. 77–93.)

Table 1

Selected Problems Impacting Health-Related Quality of Life in NMD (n = 1169)

How much difficulty do you have performing the following functions?	Moderate or Severe	Slight	Not a problem
Difficulty with muscle weakness.	72.4%	11.6%	6.0%
Difficulty getting exercise.	66.1%	17.5%	16.3%
Difficulty with fatigue.	70.8%	21.7%	7.6%
Difficulty controlling weight.	36.0%	27.9%	36.2%
Difficulty with sleeping.	36.2%	28.6%	35.1%
Difficulty with muscle contractures.	33.6%	29.9%	36.6%

How much does your health limit you in the following activities?	A lot	A little	Not at all
Vigorous activities such as running?	93%	3%	4%
Walking more than a mile?	84%	9%	7%
Walking several blocks?	73%	17%	10%
Walking one block?	54%	27%	18%

Table 2

Multidisciplinary Domains, Assessments, and Interventions for the NMD Team

Multidisciplinary Domains	Tools / Assessments	Interventions
Diagnostics (Neuromuscular medicine specialist, geneticist, pathologist)	Biomarkers (e.g. Creatine Kinase) Electrodiagnostics Molecular Genetics Muscle Biopsy	Genetic Counseling Family Support
Medication Management (Neuromuscular medicine specialist, neurodevelopmental pediatrician, physiatrist)	Clinical Evaluation Strength Function Range of Motion	Considerations Age of patient Stage of disease Risk factors for side-effects Available medications Choice of regimen Side-effect monitoring and and prophylaxis Dose alteration
Rehabilitation Management	ROM Strength Posture Function Alignment Gait	Stretching Positioning Splinting Orthoses Submaximum exercise / activity Seating Standing devices Adaptive equipment Assistive technology Strollers/scooters Manual / power wheelchairs
Orthopedic Management	Assessment of ROM Spinal assessment Spinal radiograph Bone age (left wrist and hand radiograph) Bone densitometry	Tendon surgery Osteotomies / arthrodesis Posterior spinal fusion
GI, speech/ swallowing, nutrition management	Upper and lower GI investigations Anthropometry	Diet control and supplementation Gastrostomy Pharmacological management of gastric reflux and constipation
Pulmonary Management	Spirometry Static Airway pressures (MIP/MEP) Peak cough Flow Pulse oximetry Capnography / End tidal CO_2 ABG Sleep Studies / Polysomnography	Volume recruitment Noninvasive Ventilation (via mask and nasal interfaces) Invasive Ventilation (via tracheostomy) Airway Clearance (Mechanical insufflator/Exsufflator, Theravest) Immunizations
Cardiac management	ECG Echo Holter Cardiac MRI	ACE inhibitors Angiotension Receptor Blockers β blockers Diuretcs Inotropes Other heart failure medication Antiarrhythmics
Psychosocial management	Coping Neurocognitive Speech and language Autism Social work	Psychotherapy Pharmacological interventions Social support Educational support Palliative / Supportive care

Table 3

Clinical Endpoints used in Duchenne Muscular Dystrophy Prospective Natural History Studies and Clinical Trails (ICF Framework[35])

Body Structure / Function	
• Molecular Diagnostics • Dystrophin Analysis by Muscle Biopsy (Immunohistochemistry) • Health Status / Review of Systems • Medications, Clinical Complications • Anthropometric measures (standing height, weight, ulnar lenth, tibial length, skinfolds) • Vital Signs • Body Composition (DEXA) • Body Composition (Bioelectrical impedance) • Magnetic Resonance Imaging • Magnetic Resonance Spectroscopy (Muscle) • Ultrasound Imaging (Muscle) • Bone Health (DEXA) • Passive Range of motion (Goniommetry) • Spine Deformity Evaluation	• Strength: Quantitative Grip strength • Strength: Quantitative Tip Pinch and Key Pinch strength • Strength: Isometric Strength with Hand-held devices • Strength: Isometric Strength with Fixed Devices • Strength: Isokinetic strength with fixed devices • Strength: Manual Muscle Testing (or MRC%) • Pulmonary fuction tests: FVC, FEV1, PEFR, Peak Cough Flow, MIP, MEP • Cardiac: ECG • Cardiac: Echocardiography • Cardiac: Holter Monitoring • Cardiac: MR Imaging • Cognitive and Neuropsychological Testing
Activities (Clinical Evaluator-Determined Scales)	
• Vignos Lower Extremity Functional Grade • Brooke Upper Extremity Functional Grade • Northstar Ambulatory Assesssment (NSAA) • French Motor Function Measure (MFM) • Bayley Scales of Infant Development	• Hammersmith Functional Motor Scale • Modified-Hammersmith Functional Motor Scale (Extended) • Gross Notor Function Measure (GMFM) • Egen Klassification Scale v. 2 (EK2)
Activities (Functional Tests with Timed Dimension)	
• Time to rise from the floor (supine to stand) • Time to climb four steps (beginning and ending standing with arms at sides) • Time to walk/run 10 meters or 30 feet (as fast as compatible with safety) • Time to stand from a chair (chair height should allow feet to touch floor) • Tine to propel a manual wheelchair 10 meters or 30 feet • Time to Put on a T-shirt • Time to cut out a 3″ × 3″ pre-marked square from a piece of paper with safety scissors (lines do not need to be followed precisely)	• 6-Minute Walk Test • Two-Minute Walk Test • 10-minute Walk Test with Energy Expenditure using COSMED K4B2 • Gait kinematics, kinetics with time-distance parameters • Stepwatch Step Activity Monitoring • ActiCal • 9-Hole Peg test • Jebsen Taylor Hand Function Test
Participation Measures	
• Pediatric Evaluation of Disability Inventory (PEDI) • Children's Assessment of Participation and Enjoyment (CAPE)	• Preferences for Activities of Children (PAC) • Assessment of Preschool Children's Participation (APCP)
Patient-Reported Outcome Measures (PROs)	

- Pediatric Quality of Life Questionnaire PedsQLTM) Generic Core Scale
- POSNA pediatric musculoskeletal functional health questionnaire / Pediatric Outcomes Data Collection Instrument (PODCI).
- PedsQL Neuromuscular Module
- PedsQL Multidime0sional Fatigue Scale
- NeuroQoL Patient-reported Quality of Life
- Life Satisfaction Scale (Life Satisfaction Scale for Adolescents)
- Individualised Neuromuscular QoL (InQoL)
- Child Behavioral Checklist (ASEBA)
- Canadian Occupational Performance Measure (COPM)
- Caregiver Burden Scale
- WHO Quality of Life – Bref
- SF-36
- Pittsburgh Sleep Quality Index

Table 4

MRC Grade Degree of Strength

5.	Normal strength.
5−	Barely detectable weakness.
4S	Same as 4 but stronger than reference muscle.
4	Muscle is weak but moves the joint against a combination of gravity and some resistance.
4W	Same as 4, but weaker than reference muscle.
3+	The muscle is capable of transient resistance but collapses abruptly. This degree of weakness is difficult to put into words, but it is a muscle that is able to move the joint against gravity and an additional small amount of resistance. It is not to be used for muscles capable of sustained resistance throughout their whole range of movement.
3	Muscle cannot move against resistance but moves the joint fully against gravity. With the exception of knee extensors, the joint must be moved through its full mechanical range against gravity. If a patient has contractures that limit movement of the joint, the mechanical range obviously will be to the point at which the contractures cause a significant resistance to the movement.
3−	Muscle moves the joint against gravity but not through the full extent of the mechanical range of the joint.
2	Muscle moves the joint when gravity is eliminated.
1	A flicker of movement is seen or felt in the muscle.
0	No movement.