Published in final edited form as:

J Child Neurol. 2012 March ; 27(3): 363–382. doi:10.1177/0883073812436605.

Consensus Statement on Standard of Care for Congenital Myopathies

Ching H. Wang, MD, PhD[1], **James J. Dowling, MD, PhD**[2], **Kathryn North, MD, FRACP**[3], **Mary K. Schroth, MD**[4], **Thomas Sejersen, MD, PhD**[5], **Frederic Shapiro, MD**[6], **Jonathan Bellini, BS**[1], **Hali Weiss, MD**[1], **Marc Guillet, PT**[7], **Kimberly Amburgey, MS**[2], **Susan Apkon, MD**[8], **Enrico Bertini, MD**[9], **Carsten Bonnemann, MD**[10], **Nigel Clarke, FRACP, PhD**[3], **Anne M. Connolly, MD**[11], **Brigitte Estournet-Mathiaud, MD**[12], **Dominic Fitzgerald, MD**[3], **Julaine M. Florence, DPT**[11], **Richard Gee, PT, MS**[1], **Juliana Gurgel-Giannetti, MD, PhD**[13], **Allan M. Glanzman, PT, DPT, PCS**[14], **Brittany Hofmeister, RD**[1], **Heinz Jungbluth, MD**[15], **Anastassios C. Koumbourlis, MD, MPH**[16], **Nigel G. Laing, PhD**[17], **Marion Main, MA, MCSP**[18], **Leslie A. Morrison, MD**[19], **Craig Munns, MD**[3], **Kristy Rose, PT**[3], **Pamela M. Schuler, MD**[20], **Caroline Sewry, PhD**[18], **Kari Storhaug, DDS, PhD**[21], **Mariz Vainzof, PhD**[22], and **Nanci Yuan, MD**[1]

[1]Stanford University School of Medicine, Stanford, CA, USA

[2]University of Michigan, Ann Arbor, MI, USA

[3]University of Sydney, Westmead, Australia

[4]University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

[5]Karolinska Institute, Stockholm, Sweden

[6]Harvard School of Medicine, Boston, MA, USA

[7]A Foundation Building Strength, Palo Alto, CA, USA

[8]Seattle Children's Hospital, Seattle, WA, USA

[9]Bambino Gesu' Children's Research Hospital, Rome, Italy

[10]National Institutes of Health, Bethesda, MD, USA

[11]Washington University School of Medicine, St Louis, MO, USA

Corresponding Author: Ching H. Wang, MD, PhD, Department of Neurology and Neurological Sciences, Division of Child Neurology, Stanford University Medical Center, 750 Welch Road, Suite 317, Palo Alto, CA 94304, ching.wang11@gmail.com.

Authors' Contributions

All authors were members of the International Committee for Standard of Care for Congenital Myopathies who also attended the International Conference on Standard of Care for Congenital Myopathies on May 27 to 29, 2010, at Stanford University. Dr Ching Wang, chairman of the committee, led the project and was the corresponding author for this article. Drs Dowling, North, Schroth, Sejersen, and Shapiro were leaders of the working groups who also composed the sections on the perspective care areas for this manuscript. Mr Bellini was the clinical coordinator of the project. Dr Weiss and Mr Guillet drafted the last section of this manuscript. The rest of the authors are listed in alphabetical order.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

This project was approved by Stanford University Institution Review Board.

[12]Hôpital Raymond Poincaré, Garches, France

[13]Federal University of Minas Gerais, Belo Horizonte, Brazil

[14]The Children's Hospital of Philadelphia, Philadelphia, PA, USA

[15]Evelina Children's Hospital, London, UK

[16]Children's National Medical Center, Washington, DC, USA

[17]University of Western Australia, Nedlands, Australia

[18]Dubowitz Neuromuscular Centre, London, UK

[19]University of New Mexico School of Medicine, Albuquerque, New Mexico

[20]University of Florida, Gainesville, FL, USA

[21]National Resource Centre for Oral Health in Rare Medical Conditions, Oslo Norway

[22]University of Sao Paulo, Sao Paulo, Brazil

Abstract

Recent progress in scientific research has facilitated accurate genetic and neuropathological diagnosis of congenital myopathies. However, given their relatively low incidence, congenital myopathies remain unfamiliar to the majority of care providers, and the levels of patient care are extremely variable. This consensus statement aims to provide care guidelines for congenital myopathies. The International Standard of Care Committee for Congenital Myopathies worked through frequent e-mail correspondences, periodic conference calls, 2 rounds of online surveys, and a 3-day workshop to achieve a consensus for diagnostic and clinical care recommendations. The committee includes 59 members from 10 medical disciplines. They are organized into 5 working groups: genetics/diagnosis, neurology, pulmonology, gastroenterology/nutrition/speech/oral care, and orthopedics/rehabilitation. In each care area the authors summarize the committee's recommendations for symptom assessments and therapeutic interventions. It is the committee's goal that through these recommendations, patients with congenital myopathies will receive optimal care and improve their disease outcome.

Keywords

standard of care; congenital myopathy; rod; myotubular; centronuclear; central core; cap; nemaline; zebra body; myosin storage

---

Congenital myopathies are a group of rare neuromuscular disorders that present with a wide spectrum of clinical severities. Recent advances in molecular genetics research have allowed accurate genetic diagnosis in many of these disorders. Similarly, advances in the field of muscle pathology have allowed more insights into the distinct pathological features of different congenital myopathies. However, given their low incidence, congenital myopathies are not well-known to most care providers. The multisystem involvement of congenital myopathies requires physicians from several disciplines to collaborate to provide optimal care for this group of patients. However, this care model has not been adopted by many

providers, and the care that these patients currently receive is quite variable. There is an urgent need for care guidelines to provide clinicians with diagnostic strategies and approaches to develop multidisciplinary care when they encounter patients with congenital myopathies.

In early 2009, a group of neuromuscular specialists decided to take on this task and worked to establish consensus guidelines for the care of these patients. The group worked through periodic conference calls, frequent e-mail communications, and an in-person 3-day workshop to develop 2 consensus statements: one addressing the diagnostic guidelines and one for the multidisciplinary clinical care guidelines. In the diagnostic guideline, the approach to the diagnostic assessment of congenital myopathies was presented. Emphasis was placed on the clinical, pathological, and genetic hallmarks of the individual myopathies, with a concentration on the differences in these features that enable distinction between congenital myopathy subtypes and allows accurate diagnosis. We list the classification of congenital myopathies in Table 1 as a reference for the scope of diseases we are studying. The congenital myopathies are currently classified on the basis of the major morphological features seen on muscle biopsy—that is, protein accumulations such as rods, cores, central nuclei, and selective hypotrophy of type 1 fibers. As evident from the table, each congenital myopathy can be caused by mutations in more than 1 gene, and mutations in the same gene can cause different pathological changes in muscle. Further discussion of diagnostic approach to congenital myopathies is described in a separate article that is in preparation for submission.

In this article addressing clinical care guidelines, we present the consensus recommendations for the care of patients with congenital myopathies, with a focus on guidelines applicable to all congenital myopathy subtypes. We also note the clinical features and care requirements specific and/or unique to individual myopathy subtypes. As with other pediatric neuromuscular disorders, the emphasis of care is on an integrated, multidisciplinary team approach. Optimally, such a team should include providers from neurology, genetics, pulmonology, orthopedics, rehabilitation, gastroenterology and nutrition, and oral care; therapy services should include occupational, physical, and speech therapies. In reference to specific recommendations, the Standard of Care Committee has stressed anticipatory guidance and points of care aimed at preventing or reducing secondary morbidities. These guidelines were formulated from a multistage approach that included a comprehensive literature review, a 2-part online survey, and an intensive in-person workshop. The specific methods used for establishing care guidelines are detailed in the following section.

Methods

The International Committee on Standard of Care for Congenital Myopathies

In February 2009, a group of clinicians who provide care for children with neuromuscular disorders met by telephone to discuss the current care issues in congenital myopathies. The core group of members decided to invite more colleagues to form the International Standard of Care Committee for Congenital Myopathies and to address the various care issues in this broad category of muscle diseases. A total of 59 experts in the field joined this committee.

The committee was divided into 5 working groups: diagnostics/genetics, neurology, pulmonology, orthopedics/physical therapy and rehabilitation, and gastroenterology/nutrition/speech/oral care. The group met by periodic conference calls and frequent e-mail correspondences to delineate the missions and goals and the timelines to achieve these goals. It was decided that the mission of the committee was to improve the lives of patients with congenital myopathies by providing consensus guidelines for clinical care for this group of patients. The goal was to publish 2 documents: one to address the diagnostic aspects of the disorder and the other to address the various clinical care issues. The documents should be easily accessible to care providers. To achieve consensus on the care recommendations, the group conducted 2 rounds of online surveys to gather opinions on various clinical care issues from the experts in different disciplines. The committee then met in a 3-day workshop in May 2010 to achieve consensus for these care recommendations.

Online Survey of Experts' Opinions on Standard of Care for Congenital Myopathies

The International Standard of Care Committee for Congenital Myopathies conducted 2 rounds of online surveys to poll the experts' opinions on the various care issues. A waiver status was obtained from Stanford University Institution Review Board. Data collected from these surveys provided a broad base for building the consensus for care recommendations. The survey questions were initially drafted by 2 group leaders from each working group. They were reviewed by all members within each working group and then submitted to the chair of the committee. All 5 sections of the survey questions were then assembled into one document and sent to the entire committee for answers. The first round survey used 66 open-ended questions that asked the respondents to list all appropriate answers for each care issue, with an intention to encompass a wide range of clinical practices in different care areas. All committee members were encouraged to answer the entire survey according to their current clinical practice. Forty-eight committee members answered the first round survey. Their answers were collected and tabulated and then distributed to the group leaders. The group leaders then counted the frequencies of each answers and collected the top 5 to 7 most frequent answers for each question. They then used these most frequent answers to construct a second round survey. The second round survey used the original 66 questions, but instead of providing open-ended answers the respondents were asked to rank order the answers listed under each question for their importance or appropriateness as a strategy to manage the clinical issue encountered. Each answer then received an average score representing the group's rating on its priority as a management strategy for the clinical question. Fifty-two committee members answered the second round survey. The results were collected and presented to participants of the International Standard of Care Workshop for Congenital Myopathies in May 2010.

International Standard of Care Workshop for Congenital Myopathies

The International Standard of Care Committee for Congenital Myopathies met in person in May 2010 at Stanford University to review the current care issues and to achieve consensus on care recommendations for patients with congenital myopathies. Thirty-five committee members from 8 countries attended this 3-day workshop. During the workshop, the working groups presented their review of literature and current state of sciences in their care areas. They also outlined care issues in their specialty areas. Several break-out sessions were held

during the conference for the working groups to review the care issues, examine the results of the online surveys, and achieve consensus on care recommendations in their specialty area. Group leaders were asked to summarize the group consensus and to present to the entire committee to receive comments from the entire committee. Areas for which consensus and no consensus for care recommendations were identified. Future directions of research in each area were discussed and recommended. The following sections include the clinical care recommendations from this committee. The diagnostic guidelines are presented in a separate article.

Consensus Care Guidelines for Congenital Myopathies

Neurological Care Guidelines

The neuromuscular specialist plays a central role in the diagnosis and management of congenital myopathies. Patients are usually seen in a multidisciplinary neuromuscular clinic with the presence of a pediatric neurologist. The recommendations for neurological management of patients with congenital myopathies are listed below.

Disclosure or Initial Interview After Diagnosis—The initial disclosure interview with the family is extremely important after the diagnosis of congenital myopathy in a child. This interview should take place as soon as a clinical diagnosis of congenital myopathy is made, even if a specific genetic diagnosis is not yet known. This disclosure interview may take place in the office but may also be in a separate conference room and should allow ample time for questions. Other family members including grandparents and mature siblings of the patient may be invited by the parents if desired.

The information given to the family should include 5 major areas: diagnosis, prognosis, genetic recurrence risk if known, treatment plan, and family support and resources. First, the neuromuscular specialist should name the specific pathological and/or genetic diagnosis if it is known. Second, the family should be given information about prognosis of the myopathy based on different relevant organ systems affected. In particular, the physician should educate the family about how weakness may affect movements, breathing, and eating. Different congenital myopathies have variable life expectancies and it is difficult to predict life span. Third, if a specific genetic diagnosis is known, recurrence risk of future pregnancies should be discussed according to the mode of transmission of the gene mutation. Even if the specific genetic diagnosis is not known, recurrence risk may still be discussed albeit with less certainty. A referral to genetic counseling is often helpful. Other associated medical risks such as malignant hyperthermia in patients with ryanodine receptor 1 *(RYR1)* mutations and the high frequency of respiratory involvement in those individuals with selenoprotein N *(SEPN1)* mutations must be emphasized.[1] A medical alert notice or bracelet detailing the risk for malignant hyperthermia is recommended in case of unexpected surgery or accident. Fourth, the physician needs to discuss prognosis and a specific treatment plan including general preventive health measures such as vaccinations and issues related to growth and development. The need for multidisciplinary team involvement should be stated. The family should understand that the neuromuscular specialist (in conjunction with the general practitioner) will help organize that care through appropriate referrals. Fifth, family

support and resources should be discussed, including advocacy groups, educational resources, and opportunities to participate in research projects.

Follow-Up Care—After the initial diagnosis, frequency of follow-up visits is determined by the age of the child, the severity of the disease, and the different organ systems involved. In patients without a specific pathologic or genetic diagnosis, the follow-up guidelines are essentially the same, that is, according to the age and clinical symptoms. In infants less than 12 months of age, follow-up every 3 to 4 months is recommended. In older children, follow-up every 6 to 12 months is standard. However, precise frequency of follow-up should always be determined on an individual basis, taking into account overall morbidity and specific symptoms. Ideally, this follow-up should occur in a multidisciplinary clinic.

At all follow-up visits, the neuromuscular specialist should anticipate and monitor for respiratory, speech, and swallowing difficulties. Cardiac signs and symptoms should be considered as a rare primary manifestation of specific congenital myopathies or, more commonly, secondary to respiratory failure (cor pulmonale). Orthopedic complications are common and include scoliosis and progressive joint contractures. These should be monitored at each visit. Monitoring growth (height and weight) is important to recognize early failure to thrive or early signs of obesity.

Anticipatory Guidance—High consensus was achieved for repeating anticipatory guidance advice at follow-up visits. This guidance should include advice concerning maintenance of healthy body weight, encouraging exercise, good nutrition with supplementary vitamin D, and prophylactic immunizations (especially in those congenital myopathies in which respiratory involvement is prominent). Preventive physiotherapy (motor and pulmonary) should be reviewed. The parents and/or patient should be reminded of the risk of malignant hyperthermia.

Roles of a Consultant Neurologist in the Inpatient Setting—In the event of hospitalization for a critical illness, the neuromuscular specialist should provide information to the medical team including the specific diagnosis. The neuromuscular specialist should also educate the primary team regarding specific clinical features, care needs, and prognosis of the congenital myopathy when known.

Diagnostic Reassessment—In the event that a child has clinical features of a congenital myopathy but does not have a specific histopathological and/or genetic diagnosis, the neuromuscular specialist should review the previous diagnostic workup and reassess the diagnosis at each follow-up visit. The diagnostic guidelines prepared by this committee, which will be published separately, provide an in-depth discussion of the differential diagnosis of congenital myopathies. Examples are congenital muscular dystrophies and congenital myasthenic syndromes.[2] If establishing a specific diagnosis is unsuccessful, a second biopsy should be considered. The follow-up diagnostic workup may be guided by new clinical signs and by muscle imaging patterns (muscle magnetic resonance imaging [MRI] or ultrasound) if available.

Specific Care Areas—Several areas of subspecialty management are fundamental to the care of patients with congenital myopathies. These include pulmonary care, orthopedic management, rehabilitation and physical therapy, occupational therapy and speech therapy, management of nutrition and gastrointestinal complications, and neuropsychological evaluation and management. These areas are discussed individually in later sections. Other care issues or special topics initially identified or managed by the pediatric neuromuscular specialist are discussed here.

Pain and fatigue: Even though congenital myopathies are a heterogeneous group of disorders, it is possible to identify common impairments that influence quality of life. Some of the commonest complaints are muscle weakness, reduced exercise endurance, and pain. Although a few systematic studies on chronic pain and fatigue have been conducted in a group of neuromuscular disorders,[3,4] there are no published data focused on these specific issues in congenital myopathies. The origin of pain in neuromuscular disorders is likely multifactorial, originating from the diseased skeletal muscle itself or secondary to joint contractures and reduced range of motion, hyperlaxity, osteopenia with or without fractures, or spine and other skeletal deformities. Recent research suggests that chronic pain may be a significant problem in many patients with neuromuscular disorders.[4–6] However, systematic studies on chronic pain in congenital myopathies are lacking and have been reported only in a few single patients.[7,8] Our survey revealed that myalgias occur frequently in congenital myopathies, particularly in patients harboring *RYR1* mutations. Management of myalgias and pain may include nonsteroidal anti-inflammatory drugs, gabapentin, and massage.

Fatigue and reduced endurance also appear to be frequent complaints in congenital myopathies. These symptoms often are accompanied by and worsened by exercise-induced myalgias. Exercise intolerance is best managed by activity modification and is greatly aided by the use of mobility devices including walkers, scooters, and wheelchairs. Rehabilitation assessment (with an emphasis on physical therapy) is recommended as an adjunct to the management of myalgias, fatigue, and reduced endurance.

Ocular involvement: Ophthalmoparesis with or without ptosis is common in patients with centronuclear myopathy of various genetic backgrounds.[9] Ocular involvement is also seen in myopathies due to recessive *RYR1* gene mutations.[10] Eye findings are exceedingly rare in nemaline myopathy.[11] Often patients do not perceive these abnormalities, although in certain patients they can be extremely debilitating. Surgical intervention is of uncertain benefit for these problems and should be considered only in extreme cases of ptosis in which vision is significantly impaired.[12] Patients are at risk for developing eye irritation and corneal abrasions because of incomplete lid closure in combination with ophthalmoplegia. Eye lubrication is recommended to prevent these complications. Patients with corneal abrasions should be referred for ophthalmological management.

Central nervous system involvement: Central nervous system involvement is rare in congenital myopathies. Significant cognitive impairment should prompt an exploration for causes not related to congenital myopathies or reconsideration of the primary diagnosis. One exception is the observed presence of hypoxic–ischemic encephalopathy in patients who experienced severe respiratory failure at birth, a situation not uncommon, for example, in

severe cases of X-linked myotubular myopathy.[13,14] Progressive dementia has been documented in 1 case of myotubular myopathy,[15] and mild cognitive impairment has also been reported in patients with centronuclear myopathy due to dynamin 2 *(DNM2)* gene mutations.[16]

Cardiac involvement: Cardiac involvement, in particular primary cardiomyopathies, is rare in congenital myopathies and has not yet been documented in genetically confirmed cases with mutations in the ryanodine receptor 1 *(RYR1)* and myotubularin 1 (*MTM1)* genes. However, a primary cardiomyopathy has been reported rarely in patients with actin α1 *(ACTA1)*,[17] dynamin 2 *(DNM2)*, and tropomyosin 2 *(TPM2)* (unpublished observations) mutations. Transient cardiac failure has been reported in nemaline myopathy, and electrocardiographic abnormalities of uncertain clinical significance are present in some nemaline cases.[11] Primary cardiomyopathies have been reported in genetically unresolved cases with histopathological features of multi-minicore disease,[18–22] centronuclear myopathy,[18–22] and congenital fiber type disproportion.[23] Secondary right ventricular impairment may occur where marked respiratory involvement is a feature, particularly in those with multi-minicore disease due to mutations in the *SEPN1* gene.[24,25]

With the exceptions outlined below, the consensus recommendation is for screening evaluation in asymptomatic patients by a cardiologist approximately every 2 years, particularly in those patients whose precise genetic diagnosis is uncertain. More frequent evaluations, as directed by a cardiologist, may be indicated in the setting of overt symptoms or electrocardiographic or echocardiographic abnormalities. In the absence of overt signs or symptoms, patients with *MTM1* and *RYR1* mutations likely do not require routine monitoring, as primary cardiac involvement has not been reported in these genetic backgrounds, although a potential caveat to this recommendation is the theoretical risk of cor pulmonale in *MTM1* or *RYR1* patients with severe respiratory disease.

Pregnancy: Pregnancy in patients with a congenital myopathy is a special challenge that has not yet been systematically studied. Patients may experience worsening of motor function and pulmonary function during pregnancy.[26–28] Specific subtypes for which diaphragmatic weakness tends to be a prominent feature are at particular risk during pregnancy. The potentially associated malignant hyperthermia risk needs to be taken into account when choosing anesthetics for operative delivery in patients harboring *RYR1* mutations. We recommend that all pregnancies be considered high risk and be monitored by obstetricians specializing in care of high-risk patients, with potential involvement by both pulmonary and cardiology services.

Specific Recommendations for Individual Congenital Myopathies—In addition to general recommendations applicable to the management of the congenital myopathies as a group, advice ought to be tailored to the needs of individual conditions with specific management requirements.

Marked bulbar involvements: Often out of proportion to the degree of overall muscle weakness, marked bulbar involvement is common in nemaline myopathy[11] and particularly in cases due to mutations in the nebulin *(NEB)* gene. This issue should be addressed by early

referral for speech and language assessment including more formal investigations where indicated. Although marked bulbar involvement is not usually a feature in central core disease due to dominant mutations in the skeletal muscle *RYR1* gene, this may be prominent in multi-minicore disease[24] and subgroups of centronuclear myopathy due to recessive mutations in the same gene.[29] Similarly, bulbar involvement may be a feature in severe cases of *DNM2*-related centronuclear myopathy but is not usually present in the milder forms of the disease.[30,31]

Respiratory involvement: Profound respiratory impairment requiring ventilatory support from birth is typical in X-linked myotubular myopathy due to *MTM1* mutations[32] and in severe cases of nemaline myopathy with *ACTA1* mutations.[33] Respiratory involvement of moderate severity may be observed in multi-minicore disease related to recessive *RYR1* mutations,[34] in centronuclear myopathy due to *DNM2* mutations affecting the pleckstrin homology domain,[30,31] and in centronuclear myopathy due to bridging integrator 1 *(BIN1)* mutations.[29,35] However, more systematic studies are required in these conditions and for rarer congenital myopathies. Respiratory involvement out of proportion to the overall limb girdle weakness is common in *SEPN1*-related multi-minicore disease[36,37] and nemaline myopathy due to *NEB* or *ACTA1* mutations[38] and in select patients with *TPM3* mutations.[39,40] Respiratory failure is least common in typical central core disease secondary to dominant heterozygous *RYR1* mutations and in late-onset centronuclear myopathy associated with *DNM2* middle domain mutations.[41–43]

Orthopedic manifestations: Orthopedic problems are frequently encountered in both dominant and recessive *RYR1*-related myopathies, with congenital dislocation of the hips a particularly common presenting feature.[1,42,44] Scoliosis with or without associated rigidity of the spine may develop in all forms of congenital myopathies but is particularly common in forms with marked axial weakness. These forms include especially those myopathies due to mutations in the *SEPN1* and *NEB1* genes.[36,37,45]

Potential association with malignant hyperthermia: Malignant hyperthermia is a pharmacogenetic disorder characterized by pathological hyperthermia, muscle rigidity, and hypermetabolism in response to triggering anesthetic agents.[46] These agents include volatile gases such as halothane, sevoflurane, and desflurane as well as depolarizing muscle relaxants like succinylcholine. Malignant hyperthermia is a medical emergency that is treated with dantrolene and additional supportive care measures. Malignant hyperthermia susceptibility is suspected in an individual with congenital myopathy when (a) there is a positive family history of malignant hyperthermia susceptibility, (b) there have been previous difficulties with anesthesia, and (c) the patient has a documented *RYR1* mutation. The in vitro contraction test, although not routinely performed, is the definitive diagnostic test for malignant hyperthermia susceptibility.

The risk of developing malignant hyperthermia is most highly associated with *RYR1*-related myopathies, particularly those with dominant or de novo mutations or with the King-Denborough syndrome.[1,42,47] The risk is much less clearly defined in cases of recessive *RYR1* mutations. Malignant hyperthermia susceptibility is also a feature of Native American myopathy, a rare congenital muscle disease reported in Lumbee Native Americans.[48] Little

evidence supports the presence of malignant hyperthermia susceptibility in other genetically defined congenital myopathies. However, the general recommendation is to avoid volatile anesthetics and depolarizing muscle relaxants in congenital myopathies when possible. Malignant hyperthermia susceptibility needs to be considered in the anesthetic management of cases where the genetic background is not yet known and/or histopathological features are nonspecific. There is also some evidence for a more general disturbance of temperature regulation in patients with *RYR1*-related myopathies such as excessive sweating and a predisposition to heatstroke.[49] Of note, prophylactic dantrolene is not recommended prior to anesthesia, even in cases where malignant hyperthermia susceptibility has been established.

Other features: Other subtype-specific features include the often intense exercise-induced myalgias seen in *RYR1*-related myopathies. Muscle pain may also be a presenting feature in *DNM2*-related centronuclear myopathy. Undescended testis is common in *RYR1*-related myopathies and males with X-linked myotubular myopathy. Bleeding diathesis and gastrointestinal complications have been reported in long-term survivors of X-linked myotubular myopathy.[50,51]

Progression—Dramatic progression is not typically associated with congenital myopathies. In fact, many patients make significant motor developmental progress after the neonatal period and maintain strength into adulthood. However, it is clear that these conditions are not static and that some degree of symptom worsening can occur late in the disease course. Thorough understanding of this aspect of disease is limited by the lack of natural history data; this is particularly true for congenital onset patients once they reach adulthood. Three specific areas of progression are particularly important to consider and monitor: ambulation, respiratory function, and scoliosis.

Ambulation: In general, extremity weakness is largely non-progressive. Patients who achieve the ability to walk usually do not lose this ability later in childhood. One notable exception is in late-onset *DNM2*-related centronuclear myopathy, in which the vast majority of patients have a progressive phase of extremity weakness that is associated with impairments in ambulation.[31] The potential for loss of ambulation in adulthood is uncertain but has been observed. Secondary factors that may negatively influence ambulation are joint contractures, scoliosis, limb fractures, and excessive weight gain.

Respiratory function: Many patients with congenital myopathies have some degree of respiratory insufficiency, most commonly seen as sleep disordered breathing. Some degree of intervention to prevent complications of respiratory insufficiency is common, and early involvement of pulmonary sub-specialists is recommended. Severe respiratory failure outside of the first year of life is uncommon unless present in infancy. Exceptions are patients with *SEPN1*, *TPM3*, *ACTA1*, *NEB*, and *DNM2* mutations,[11,31,36,52] in whom progressive respiratory failure may occur in the teen and adult years even if respiratory impairment was not prominent earlier in life. Patients with myotubular myopathy often require 24-hour ventilatory support throughout their lifetime.[32]

Scoliosis: Progressive scoliosis is not uncommon; spine curvature thus needs to be monitored closely and referral to orthopedic services initiated at the first signs of significant

progression. Patients with *SEPN1* mutations are at very high risk for developing scoliosis at the end of the first decade and in the second decade[36] of their lives. Respiratory function and spine curvature are not always correlated with extremity strength, and patients may experience worsening in these areas without obvious change in motor function.

Sporadic late-onset nemaline myopathy: This entity deserves special mention because it is both rapidly progressive and amenable to specific therapeutic intervention. Sporadic late-onset nemaline myopathy presents in adulthood with extremity and respiratory muscle weakness and subacute progression.[52,53] Its cause is unclear, and it has not been associated with specific gene mutations. Untreated patients may die from respiratory disease within 1 to 5 years. Successful treatment of sporadic late-onset nemaline myopathy has been reported with intravenous immunoglobulin (with or without additional immunosuppression)[53,54] and with melphalan plus stem cell transplantation.[55,56]

Prognosis—Survival into adulthood is likely in all congenital myopathies unless severe respiratory failure and profound weakness are present in infancy. The course of these disorders in adulthood is less well understood, and it is not clear whether life expectancy is ultimately affected. One exception is myotubular myopathy due to *MTM1* mutations, where a significant percentage of patients with infantile onset die in the first year or years of life.[32,50] Another exception involves patients with *ACTA1* mutations and severe neonatal presentation, as they often die in the first year of life.[33]

Pulmonary Care Guidelines

Background—The hallmark of congenital myopathies is generalized muscle weakness.[1,11,57–60] Muscle weakness may affect respiratory health both at birth and throughout life, and respiratory complications may present in either the acute or the chronic setting.[1,11,24,38,60–67] Respiratory complications are varied, however, and do not necessarily correlate with skeletal muscle function.[1,11,57–60] The factors influencing respiratory impairment include respiratory muscle weakness (especially diaphragm weakness), abnormal respiratory control of breathing, swallow and bulbar dysfunction, and failure to thrive resulting in restrictive lung disease, difficulty managing oral and respiratory secretions, and sleep disordered breathing.[1,11,24,38,60–67] Respiratory function can also be significantly compromised by factors such as intercurrent illness and progressive scoliosis. It is essential for medical care providers to be aware of possible respiratory involvement in patients with congenital myopathies of all ages and at all stages of disease. Respiratory failure may be the presenting respiratory complication.[62]

Literature Review—Given both the relative rarity and the heterogeneity of congenital myopathies, the medical literature on pulmonary involvement is limited. The largest available study reporting pulmonary involvement in congenital myopathies was published by Ryan et al[11] on 143 patients with nemaline myopathy. Respiratory insufficiency was the leading cause of death in 17 of 23 infants with the severe congenital form.[11] A large longitudinal study of congenital myopathies published by Akiyama and Nonaka[63] in 1996 found that 9% to 13% of patients had respiratory disease. In this study, 16% of patients had progressive deterioration in muscle strength and respiratory function after achieving

ambulation, with 14% mortality from respiratory or cardiac failure by 20 years of age. As discussed in the neurology subsection, severe respiratory complications, often out of proportion to extremity muscle involvement, have been reported in a subset of congenital myopathies (related to mutations in *MTM1, SEPN1, DNM2, NEB, TPM3, ACTA1* genes[1,11,24,38,57–60]). The breadth and extent of pulmonary involvement have been extensively examined in nemaline myopathy, X-linked myotubular myopathy, and *SEPN1*-related myopathy. Severe respiratory failure, often associated with death in the first year of life, is frequently observed in infants with severe congenital nemaline myopathy and nearly universally observed in infants with X-linked myotubular myopathy.[11,57–59] Surviving patients with these conditions typically require chronic ventilatory support. Additionally, patients with intermediate congenital and typical congenital nemaline myopathy classifications frequently have respiratory compromise (approximately 96% and 37%, respectively), with pulmonary dysfunction usually in proportion to the age and severity of overall clinical presentation. Significant respiratory dysfunction is much less common in the childhood-onset nemaline myopathy subgroup. Patients with *SEPN1*-related myopathies often have respiratory compromise discordant with their extremity weakness. In particular, one study reported respiratory impairment with a decreased vital capacity of 18% to 65% in 11 of 11 ambulant children with *SEPN1* mutations.[36]

Recommendations for Pulmonary Care—All patients with congenital myopathy should be considered at risk for respiratory insufficiency.[61,68–74] Respiratory complications, with the exception of some specific myopathy subtypes (see above), usually evolve gradually as a result of the progressive weakness of the respiratory muscles.[11,24,61–63] Gradual hypoventilation and atelectasis are among the most common complications, and they can remain undetected for a long time because of a lack of associated clinical symptoms.[11,24,61–63] Thus, it is imperative that affected patients have early and regular evaluations of their respiratory status in order to identify abnormalities before they become clinically evident.

General pulmonary screening studies: Pulmonary screening studies should be performed in all patients with congenital myopathy except those physically unable to perform the testing. The Standard of Care Committee highly recommends a minimum set of screening studies. These tests, which assess lung function and respiratory muscle strength, should be performed at least annually in patients who are considered low risk because of their genotype and/or lack of clinical symptoms. These tests should be performed more often (eg, every 6 months) in patients who are considered high risk and/or have recurrent respiratory symptoms. The tests include the following:

- Spirometry with maximal flow-volume curve for the assessment of lung volume (forced vital capacity) and airway function
- Maximal inspiratory pressure, maximal expiratory pressure, and peak cough flow for the evaluation of respiratory muscle strength
- Spot pulse oximetry for the detection of hypoxemia.

Screening study interpretation: Special consideration should be given to the interpretation of the results of pulmonary function tests. In the general population, the growth of the lungs closely follows the increase in height that serves as the basis for development of predicted normal reference values. However, standing height is not reflective of lung growth in patients with scoliosis and other skeletal abnormalities.[75] Alternatives to standing height, such as arm span, ulnar length, and knee–hip length, have been proposed given the difficulty of obtaining accurate measurements in a nonstanding individual with contractures. The committee recommends obtaining serial pulmonary function tests to assess patients with congenital myopathy relative to themselves, that is, in comparison with previous tests. The vital capacity of patients with muscle weakness varies significantly between positions relative to gravity. For example, the supine vital capacity can be significantly lower than the vital capacity measured in a sitting or an erect position. Therefore, in addition to measuring the vital capacity in a sitting position, clinicians should monitor the supine vital capacity, especially in patients with decreasing lung function. A supine vital capacity that is lower by more than 20% compared with the sitting vital capacity suggests significant diaphragm weakness, and the patient is at risk for nocturnal hypoventilation regardless of the presence or absence of symptoms during wakefulness.[68]

Assessment of nocturnal respiratory function: Because respiratory complications during sleep, including obstructive sleep apnea, hypoventilation hypoxemia, and hypercarbia, usually precede abnormalities during wakefulness and are not predictable based on skeletal muscle strength, the early and routine evaluation of patients during sleep is recommended.[11,61,68] Although an attended polysomnographic study is the most comprehensive study, providing information both on the mechanics of sleep and on gas exchange, it is not always readily available. Thus, the committee highly recommends that patients have, at a minimum, a screening evaluation with overnight oximetry for the detection of hypoxemia and capnography or end-tidal CO_2 or transcutaneous CO_2 for the detection of hypercarbia and the pH and PCO_2 as indicators of respiratory acidosis. If the latter modalities are not available, a venous blood gas should be considered for the measurement of serum bicarbonate as an indicator of chronic hypercarbia. Abnormalities detected with screening studies should be further evaluated with referral to a center for polysomnographic evaluation. The frequency of the evaluation will depend on whether the patients are considered to be at high risk based on their genotype, symptoms, and/or lung function. Patients with decreasing lung volume are at a higher risk for sleep-related abnormalities. Table 2 lists the recommended frequency for different pulmonary function tests.

Routine anticipatory respiratory care: Maintenance treatments in patients with congenital myopathies are similar to those used in patients with other conditions associated with respiratory muscle weakness. Because of the wide variability of congenital myopathy phenotypes, there is no single regimen applicable to all patients. Thus, the treatment plan should be adapted to the specific phenotype of the patient. However, the committee highly recommends the following for all patients:

- Administration of pneumococcal and influenza vaccinations in addition to routine vaccinations.

- Use of mechanical or manual assisted cough techniques including mechanical insufflation–exsufflation, air-stacking, and manual assisted cough when the patient's cough is ineffective. Impaired cough can independently contribute to recurrent chest infections and respiratory insufficiency by compromising clearance of airway secretions. Of note, it is highly recommended that patients and their caregivers familiarize themselves with these techniques during a period of clinical stability.
- Familiarity with secretion mobilization in addition to airway clearance techniques and use as indicated based on the patient's specific phenotype and the severity of respiratory muscle weakness. Individuals with severe respiratory muscle weakness may benefit from scheduled secretion mobilization and airway clearance 1 to 2 times daily even when they are clinically well. The type of secretion mobilization technique (manual or mechanical percussion, high-frequency chest wall oscillation, or intrapulmonary percussion ventilation) should be determined by the patients acceptance and tolerance of the technique.
- Although evidence in the literature is limited for the use of preventive insufflation to improve chest wall expansion and lung recruitment as well as growth, the committee recommends that in the setting of early respiratory muscle weakness, use of chest wall expansion to improve chest compliance is beneficial.
- Bronchodilators and mucolytics are not recommended but may be of benefit when clinically indicated during acute deterioration. Their efficacy has not been established.

Noninvasive ventilatory support: Noninvasive positive pressure ventilation is a recommended modality in the treatment of respiratory complications in neuromuscular diseases.[61,71–74,76,77] The use of bilevel positive airway pressure noninvasively is recommended to treat hypoventilation associated with congenital myopathy. Bilevel positive airway with a backup respiratory rate provides respiratory muscle rest while facilitating ventilation. Continuous positive airway pressure is not recommended for the usual respiratory complications of congenital myopathy and does not treat hypoventilation. Patients with congenital myopathies lack adequate inspiratory muscle strength during sleep to generate an adequate breath. Patients with chronic respiratory insufficiency, sleep disordered breathing based on sleep study results, recurrent respiratory infections, and chronic atelectasis are candidates for noninvasive positive pressure ventilation. The goal is to use noninvasive positive pressure ventilation at night to improve lung expansion, improve gas exchange, and provide respiratory muscle rest. Secretion mobilization and assisted

cough techniques should continue to be used as needed day and night. Progressive or acute respiratory insufficiency, for example, as a result of an acute respiratory infection, may require the addition of daytime noninvasive positive pressure ventilation to maintain adequate ventilation.

Invasive ventilation: Respiratory failure with significant hypoxemia and hypercarbia nonresponsive to noninvasive positive pressure ventilation requires intubation and mechanical ventilation. Invasive ventilator support may be required in the setting of acute respiratory failure associated with illness or may be associated with chronic respiratory insufficiency. It also is used in temporary settings such as operative procedures.

Tracheotomy: Tracheotomy can be considered when noninvasive positive pressure ventilation is required continuously 24 hours per day or if the patient has repeatedly failed extubation following invasive ventilation. The family should be involved in all discussions considering tracheotomy. In selected situations of continuous bilevel positive airway pressure, it may be beneficial to continue mechanical ventilation via a tracheotomy tube in order to optimize neurodevelopment and independence. In these settings, the performance of a tracheotomy is not an emergency.

Acute respiratory failure: Respiratory support should be instituted promptly. When possible, noninvasive positive pressure ventilation and intensive airway clearance should be used. Invasive ventilation should be used when noninvasive positive pressure ventilation fails or in cases of acute severe respiratory failure unless the patient and/or parents or legal guardians have explicitly expressed their opposition to this intervention. For example, during an acute illness, acute severe respiratory failure with hypercapnia and hypoxemia may be best managed with endotracheal intubation. When patients require invasive ventilation, efforts should be made to optimize secretion mobilization and airway clearance and extubate to noninvasive positive pressure ventilation as soon as their condition allows.

Chronic respiratory failure: Invasive ventilation for chronic respiratory failure may be necessary in some individuals with congenital myopathy. A particularly vulnerable time is during infancy, when neonates with severe congenital myopathy may have limited respiratory effort and thus require endotracheal intubation and mechanical ventilation. Chronic respiratory failure requiring invasive, 24-hour ventilator support outside of the neonatal period is relatively uncommon in congenital myopathies. The most important exceptions are X-linked myotubular myopathy and severe congenital nemaline myopathy.[11,57–59] In some situations, long-term ventilation may not be desired, and options for care should be discussed with the family and medical team. The topic of palliative care is discussed in detail in a recently published standard of care for congenital muscular dystrophies.[78]

Perioperative management: Airway management during operative procedures is a special challenge in patients with congenital myopathies. Patients frequently need ventilator support postoperatively. Anesthesia alone, even during a minor procedure, carries the risk of prolonged respiratory depression and thus the potential need for prolonged respiratory support. Noninvasive positive pressure ventilation is often required in the perioperative/

postsurgical period as a bridge to recovery from anesthesia. In addition, if additional respiratory support is anticipated postoperatively such as following spinal fusion procedures, consideration should be given to either initiating noninvasive positive pressure ventilation preoperatively or anticipating extubation to noninvasive positive pressure ventilation postoperatively.[79]

Additional Considerations

Respiratory illnesses: Because patients with muscle weakness have poor respiratory reserve, they may develop disproportionately severe symptoms even with relatively mild respiratory infections. Factors that negatively influence pulmonary status during an acute respiratory illness include weak cough and poor mobilization and clearance of airway secretions. Airway secretions are increased with intercurrent viral illness and can contribute to the development of mucus plugging and atelectasis. In addition, viral respiratory infections may predispose to a secondary bacterial infection. Therefore, it is recommended that during an acute illness with increased respiratory symptoms, a chest radiograph, spot pulse oximetry, and blood gas reading (venous or capillary) be obtained to detect the presence of pneumonia, atelectasis, acute hypoxemia, and/or hypercarbia. If possible, spirometry and measurement of peak cough flow should be considered.

Recommended interventions are based on the severity of respiratory muscle weakness and include frequent respiratory secretion clearance with assisted cough techniques, for example, CoughAssist device and/or manual cough assist as often as needed to facilitate cough. Antibiotics are often used prophylactically, as the consequences of bacterial pneumonia can be life-threatening for this population. Patients using noninvasive positive pressure ventilation may require increased use during the day as well as during sleep. Secretion mobilization techniques should be performed more frequently including manual or electric percussion or high-frequency chest wall oscillation or intrapulmonary percussive ventilation followed by using secretion clearance techniques (eg, CoughAssist).

Control of oral secretions: Patients with congenital myopathies frequently develop difficulty managing oral secretions in the neonatal and childhood periods because of excessive salivation and/or poor oral motor control. Excessive oral secretions can result in pulmonary complications such as aspiration and can have a significantly negative social impact. Therefore, control of oral secretions is essential to overall care of patients with congenital myopathies.

More detailed recommendations for control of excessive oral secretions are addressed later in the section on gastrointestinal/nutrition/oral care.

Orthopedics and Rehabilitation Care Guidelines

Orthopedic complications are frequently encountered in congenital myopathies.[1,9,11,36,37,42,80–84] They are particularly prominent in patients with *RYR1*-[82,83] and *SEPN1*-related[36,37] myopathies. The overall recommendations for this group of patients are to maximize function and independence through the following:

- Promotion of physical activity and avoidance of inactivity

- Prevention and correction of deformities
- Maintenance of bone health
- Management of pain
- Education and dissemination of information on therapy
- Provision of assistive technology to maximize function
- Access to appropriate specialized orthopedic management when necessary.

General Guidelines Related to Orthopedic and Rehabilitation Management

Exercise: To maintain and maximize muscle strength, we advise regular symmetrical endurance exercise, ideally concentric in character, and the inclusion of recreational activities in the exercise plan. Exercise is to be encouraged to maintain muscle function. There is no evidence that exercise is harmful in this group of diseases, as some believe is the case in the muscular dystrophies. Symmetrical endurance exercise regimens should be done on a regular basis. Although there is no direct evidence to specify frequency or intensity of exercise in congenital myopathies, consensus suggests (as in healthy children) a minimum recommended frequency of 2 to 3 times per week. Exercise-induced fatigue and muscle soreness should be avoided. If they are present at a particular level of activity, this should be used as a guide to modulate exercise intensity. High-impact sports should be avoided because of increased risk of injury.

Standing: Standing is strongly recommended even for extremely weak children and can be facilitated through upright or supine standing frames, parapodiums, and orthotics. Contracture management through stretching programs and orthotics will help to maintain the ability to stand. Standing will assist in contracture management and with the development of trunk, pelvic, and head control. Standing also serves as a precursor to ambulation and helps to promote self-esteem. Bone strength and development can be improved by standing. Caution is needed when positioning patients into standing frames, especially those with joint contractures and osteopenia. Patients can suffer pathological metaphyseal fractures of the femur or tibia, especially at the knee region, with relatively excessive tightening of supportive straps or pads.

Assisted ambulation and mobility: Promotion of independent mobility is essential to patients with congenital myopathies and is often accomplished using assisted ambulation or manual or power wheelchairs. Functional mobility should be maintained throughout life. Power wheelchairs can be provided to children as young as 2 years of age when appropriate. Seating systems for manual and power wheelchairs should provide effective support to maintain pelvic, trunk, and spinal balance and pressure relief. Lap belts must be provided for safety in all vehicles, whereas chest straps and head and neck supports may be advisable in some. Adapted vehicles and environmental modifications may be needed when power wheelchairs are provided. When ready for driving, patients will need adapted driver education programs.

Joint range of motion: Recommendations for maintaining joint range of motion include passive and active-assisted stretching, static and progressive splinting (orthotics), and serial casting. Orthoses are used for improved postural control and to minimize contracture formation. Orthotics can be used to maximize independent mobility and in the context of a static standing program. Truncal bracing can be used to stabilize the spine in either sitting or standing positions. Botulinum toxin (Botox) is contraindicated in skeletal muscle for children with primary muscle disease for any indication. Botox causes muscle paralysis, and by the time it wears off in 3 to 6 months, the disuse atrophy in muscle superimposed on the primary muscle disease markedly delays rehabilitation or may render the patient nonambulatory.

Safety considerations related to ambulation: Safety and prevention of falls are primary considerations for both the patient and care providers. Use of lifts for transfers is encouraged. Environmental modifications for home, school, and work include ramps, rails, shower chairs, stair glides, and lifts (or hoists). Assistive devices that increase independence include mobile arm supports, bath aids, reachers, and canine assistants. To allow full access to the school curriculum, educational and teaching assistants may be required.

Scoliosis Management—Scoliosis (lateral curvature of the spine) is very common in the congenital myopathies, and early detection and management are essential. Worsening deformity negatively affects pulmonary and cardiac function, is often cosmetically unacceptable, makes seating difficult owing to associated pelvic obliquity and truncal deformity, can worsen the ability to walk, and frequently becomes painful. Referral to a pediatric orthopedic surgeon is warranted when scoliosis is detected.

Nonambulatory children without the ability to sit by 18 to 24 months of age can benefit from a soft spinal orthosis to assist with sitting balance. Such devices are often used for short intervals in the morning and late afternoon but are not necessary for recumbent or nocturnal use. Use of these orthoses is generally temporary since most children develop independent sitting balance.

A spinal examination by clinical observation should be done at every visit with the patient in sitting or standing positions. In nonambulatory children, sitting baseline radiographs in anterior–posterior and lateral projections are taken at the first sign of clinical scoliosis and every 6 months if the curve is worsening. The lateral film also allows for detection of kyphosis. A spinal orthotic is warranted for curves between 20° and 40° in the sitting position. Orthoses must strike a balance between stabilizing the spine, correcting the deformity, maintaining comfort, not negatively affecting respiration, and allowing for oral and G-tube nutrition. Many types of braces have been developed and are often specific to different institutions and different countries.[85–87] They are not necessary for recumbent or nocturnal use. Progressive curves beyond 50° prompt consideration of spinal surgery. Growing rods are indicated in some children less than 10 years of age to allow for correction of deformity and internal stabilization while growth of the spine continues. Spinal systems with 2 rods are currently used, but this technique is relatively early in development and complications can occur, although many favorable results are seen.[85,88] When the child is at or close to skeletal maturity, the growing rods are removed or incorporated into a full

posterior spinal fusion from the upper thoracic region into the pelvis. Many surgeons still prefer to use spinal orthoses to stabilize scoliotic curves even greater than 50° in the first decade of life and then perform definitive spinal fusion early in the second decade when most or all of spinal growth is completed. If the deformity remains flexible, decreasing significantly when the patient is supine or in brace, this approach can still lead to good results. If the deformity becomes rigid, delay of surgery can compromise the long-term value of spinal fusion since significant correction of deformity may not be achievable even with surgery. The timing for definitive spinal fusion is classically based on Tanner staging, Risser staging, and bone age determination on wrist and hand radiographs rather than chronological age alone. In severe neuromuscular disorders, patients often undergo fusion at 11 to 13 years of age.

In ambulatory children, standing baseline radiographs are taken with initial clinical curve detection and then annually. There is consideration of orthotic treatments for curves 20° to 40° if ambulatory function is not disturbed by bracing. Growing rods are considered in children less than 10 years of age for curves greater than 40 . Posterior spinal fusion is done for patients 12 years and older for curves greater than 50°. Curve correction extends from the upper thoracic region into the lower lumbar region and avoids fusion to the pelvis to preserve ambulation. Spinal fusion surgery may need to be deferred until the child becomes nonambulatory if it appears likely to interfere with or cause loss of ambulation.

In children too weak or malnourished for surgery, or in accordance with family or patient preference, spinal support can be continued after skeletal maturation with brace or wheelchair modifications. Of note, unlike the situation in healthy children with idiopathic scoliosis, neuromuscular scoliosis deformity can continue to worsen after skeletal maturity.

Additional Specific Orthopedic Management Issues

Congenital hip subluxation or dislocation: Hip subluxation or dislocation at birth is particularly common with central core (*RYR1*-related) myopathies but can occur in any variant. Owing to this high incidence, hip ultrasound is warranted in the early postnatal period along with careful clinical hip examination. When present, these hip disorders are treated, in most centers, with flexion–abduction splinting (Pavlik harness), similar to management in the otherwise healthy child. This tends to reposition the femoral head deeply into the acetabulum and stabilize it there sufficiently well for capsular tightening and cartilage and bone remodeling to hasten normal hip development. Patients with central core myopathy, however, are prone to develop hip contractures either associated with hip dysplasia at birth or developing or worsening with several weeks of immobilization in the fixed position. Results are not as favorable as in healthy children, but improved to normal hip position is preferable to untreated persistent dislocation or sub-luxation that proceeds to dislocation. Owing to the incidence of contractures, immobilization greater than 10 to 12 weeks should be avoided. If contractures occur, there may be the need for lengthy physical therapy to regain motion after repositioning of the hip or, on occasion, surgical musculotendinous releases. The majority of those patients with congenital myopathy who develop hip subluxation and dislocation generally do so with time, however, over a period of several years. This leads to the consideration that dislocatable or subluxatable hips at birth

represent a variant of developmental dysplasia of the hip superimposed on but separate from the congenital myopathy. This view is supported by the high number of breech presentations reported in central core myopathy patients and the early ligamentous laxity that accompanies most myopathies, both of which predispose to hip malposition. Patients can benefit from the Pavlik harness splinting, especially since the eventual prognosis of the myopathy in any patient is difficult to determine in the newborn. The high level of reducibility in these patients predisposes to better results the earlier the hip diagnosis is made, that is, in the neonatal period or first few weeks of life. Persisting displacement after 1 year of age may warrant more invasive surgical procedures (open reduction, osteotomies) dependent on the severity of the child's myopathy.

Hip subluxation or dislocation in nonambulatory children: Hip subluxation or dislocation developing with time in the nonambulatory child can be managed as follows: the children are observed with clinical hip assessments at each visit. There is no consensus of opinion as to the essential need for keeping hips located in all nonambulatory children in the absence of pain or significant clinical symptoms. Many children with myopathies have unilateral or bilateral hip dislocations and remain asymptomatic throughout life. Unilateral hip dislocation may warrant operative correction as it can worsen sitting balance and increase the likelihood of lumbar scoliosis. If severe or continually troublesome pain develops, major surgical correction may be considered. This should involve not only adductor and iliopsoas tendon releases but also proximal femoral varus-shortening derotation osteotomy to reduce the femoral head into the acetabulum and often an acetabular redirection or augmentation procedure to increase femoral head coverage and diminish the likelihood of recurrence.

Hip disease in ambulatory children: This is managed with the following considerations. Surgery is rarely considered in ambulatory patients with proximal hip muscle weakness and hip subluxation or dislocation because hip relocation surgery may significantly compromise ambulation by further hip abductor and flexor muscles. If surgery becomes necessary for intractable pain, the patient and family must recognize the likelihood of worsening gait and even loss of ambulation.

Knee flexion contractures: Surgery is rarely indicated for knee flexion contractures, especially in nonambulatory patients. Treatment is warranted, however, with stretching, night splints, or serial casts to minimize the extent of the problem. Worsening knee contractures beyond 15° to 25° in nonambulatory patients that prevent them from using a stander or in ambulatory patients that prevent them from continuing to walk may warrant surgical correction. Medial hamstring tendon lengthening or (rarely) bone surgery to hyperextend the distal femur can be considered, although precautions must be taken to prevent posterior neurovascular stretching.

Foot and ankle deformities: For newborn club feet, treatment is warranted similar to that done in the healthy child with club feet. This includes serial casting, percutaneous heel cord lengthening, and nighttime splinting. If the child is clinically stable, the casting treatment can begin in the newborn nursery or newborn intensive care unit.

The older neuromuscular patient with acquired club foot may require tendo-Achilles or gastrocsoleus muscle lengthening, tendon transfers (tibialis anterior tendon transfer), and calcaneal osteotomies for foot correction.

Surgical and Postsurgical Management

Anesthetic consideration and concern for malignant hyperthermia: Malignant hyperthermia is always a concern in myopathy patients undergoing general anesthesia. Virtually all cases in the past have been associated with use of muscle relaxants such as succinylcholine and inhalational agents such as halothane.[89–91] Malignant hyperthermia is a pharmacogenetic disorder in which volatile (halogenated inhalation) anesthetics trigger a sustained release of Ca^{2+} from the sarcoplasmic reticulum that lead to muscle rigidity, hypermetabolism (hyperthermia), and rhabdomyolysis and death.[90] The term “anesthesia-induced muscle injury” is used by some to encompass malignant hyperthermia, acute rhabdomyolysis, and hyperkalemic cardiac arrest. Malignant hyperthermia risk is highly specific for association with *RYR1*-related myopathies, but cases have been recorded in other variants of congenital myopathy.

Rather than attempting to determine or predict the likelihood of malignant hyperthermia with any specific type of congenital myopathy or specific gene defect, it is safest for anesthesiologists to consider any patient with a neuromuscular disorder to potentially have malignant hyperthermia. Anesthesiologists should use clean technique and avoid succinylcholine and inhalational agents (other than nitrous oxide) by using alternative intravenous agents with known high safety profiles. The term *clean technique* refers to using only anesthesia machines and equipment specifically cleaned immediately prior to operation on patients with neuromuscular disorders so as to remove all traces of anesthetic agents used for other patients in previous procedures. Additional precautions include extensive monitoring of cardiopulmonary parameters, availability of dantrolene, capnography to measure CO_2 concentration, and intensive care unit support. Dantrolene sodium is a direct-acting skeletal muscle relaxant. It should be present on the anesthesia cart for any patient with a neuromuscular disorder undergoing anesthesia. In many centers dantrolene is always present as part of the anesthesia setup for all surgical procedures. Although there is a universal agreement that succinylcholine (a depolarizing neuromuscular blocking agent) is not indicated for neuromuscular disorders, some anesthesiologists in specialty hospitals point to the value of volatile anesthetics and potential disadvantages of alternative techniques for disorders not clearly associated with malignant hyperthermia.[90] Concern exists, however, that the congenital myopathies are sufficiently rare that statistical certainty of safety using inhalational agents remains difficult if not impossible to determine. In addition, many patients with a suspected myopathy undergo surgery without a known histopathological or genetic diagnosis. If symptoms of malignant hyperthermia occur intraoperatively, the surgery is stopped, all anesthetic agents are immediately discontinued, increased oxygen is given, and dantrolene sodium by intravenous injection is started at a dose of 1 mg/kg to a maximum level of 10 mg/kg.

Lower extremity fractures and surgery: It is essential to make extensive efforts to maintain ambulation during fracture healing and after corrective lower extremity surgery.

Prolonged disuse of muscle by limb immobilization without walking leads to increased atrophy and either greatly prolongs rehabilitation or in some instances leads to full loss of ambulation, even if the bone or soft tissue deformity is corrected. Internal fixation may be warranted in unstable lower extremity fractures, such as use of an intramedullary rod for the femur in a 7-year-old boy. If casts or braces are used for treatment, these should be designed to enable continuing ambulation during healing. Such modifications include lightweight casts and articulated orthoses. After tendon lengthening or tendon transfer surgery, return to ambulation with walkers or crutch assists within 1 to 2 days and throughout rehabilitation is advised.

Upper extremity contractures: Upper extremity management involves maintaining range of motion at shoulder, elbow, wrist, and hand. Wrist and hand splints are particularly helpful. Occupational therapists should be consulted for help with activities of daily living and for school functioning. Elbow splints can be used to diminish flexion contractures. Surgery is rarely indicated for elbow flexion contractures. Anterior releases at the elbow joint with biceps lengthening run the risk of weakening elbow flexion, which worsens function. In addition, stretching of the neurovascular bundle and early recurrence of deformity limit the value of surgery.

Maintenance and Management of Bone Health—Children with reduced mobility are at increased risk of osteopenia and pathological fracture. As such, interventions to maintain bone health are essential in children with congenital myopathies. Muscle interaction with bone by mobility, physical activity, and even by standing maximizes normal bone development. Vitamin D should be supplemented at 400 IU daily in all children, and serum 25-hydroxyvitamin D levels should be measured annually to ensure normal blood levels. Calcium intake should be maintained at the recommended daily intake through diet or supplementation. Pubertal assessment (Tanner staging) should be undertaken from age 11 years to monitor the pubertal progression. A fracture history should be included in routine visits and inquiries made as to bone pain.

More intensive bone health evaluation should be undertaken in children who sustain a pathological fracture (low-impact long bone or vertebral) or 2 or more traumatic fractures, experience bone pain, or demonstrate severe osteopenia on plain radiographs or when reduced bone strength may have resulted in orthopedic instrumentation failure. Further assessments include bone density evaluation by dual energy x-ray absorptiometry or quantitative computed tomography. These studies should be performed and interpreted in pediatric facilities with sufficient expertise and experience. A lateral thoracolumbar spine radiograph should be performed to look for vertebral compression fractures. Additional causes of secondary osteopenia such as pubertal delay, celiac disease, and thyroid disorders should be investigated and treated. Once coexistent medical causes of osteopenia have been excluded and dental assessment undertaken, bisphosphonate therapy should be considered. This therapy should only be prescribed by a physician experienced with its use.

Gastrointestinal, Nutritional, and Oral Care Guidelines

Introduction and Literature Review—Infants and children with congenital myopathies often have feeding and swallowing impairments that can affect many aspects of their general health, including growth, pulmonary function, oral health, and energy and activity level. The care and management recommendations of the Standard of Care Committee are based on the existing medical literature, extrapolation from data of other neuromuscular diseases, online survey results, and expert opinion.

There is a paucity of medical literature describing specific gastrointestinal, nutritional, and oral care issues for children with congenital myopathies. Therefore, one must additionally consider literature from other similar neuromuscular diseases such as myotonic dystrophy and spinal muscular atrophy. The most comprehensive review specific to feeding issues in children with congenital myopathy relates to nemaline myopathy, with which poor growth is a very common problem.[92] Feeding issues are commonly observed in the first year of life of children with nemaline myopathy, but they tend to improve with increasing age.[11] Feeding difficulty was observed in 17 of 19 children evaluated, with the majority of them presenting in infancy with a weak suck. Alternative feeding with gastrostomy tube was frequently needed. Improvement in growth and decrease in recurrent respiratory problems were common after gastrostomy tube placement.

Results of Online Survey on Feeding and Nutrition Care Issue—Areas of concern identified from the survey included weak suck, feeding and swallowing problems, failure to thrive, excessive secretions, aspiration, drooling, and problems with gastroesophageal reflux and constipation.

Methods of growth assessment most frequently mentioned were height and weight as well as dietary assessment carried out frequently in the first years of life. A multidisciplinary team was recommended to provide infants and children with a comprehensive evaluation and treatment.

Craniofacial issues identified in the survey included lower facial weakness, poor oral hygiene, dental care, malocclusion, high arched palate, and jaw contractures.

General Recommendations

Swallowing and nutrition: Orofacial and bulbar weakness, a distinctive feature of congenital myopathies, may result in a weak suck and swallowing dysfunction at birth in the severely affected neonate. The infant may present with drooling, prolonged feeding times, failure to gain weight, aspiration, and gastroesophageal reflux. The older child may present with deceleration of linear growth including height and weight and recurrent respiratory infections.

Measurements of growth should be obtained at every clinic visit or at least every 3 months in the infant and should include height and weight. Surrogate measurements for the child who is unable to stand include arm span or ulnar length.[93] Assessment of growth trends will provide the physician and dietician with critical information to make appropriate recommendations. Dietary information is optimally collected by a dietician at each visit to

evaluate caloric and micronutrient status. Yearly assessment of calcium and vitamin D levels should be obtained (see also the section on bone health).

The general assessment of an infant or child should include a clinical feeding evaluation by a specialized therapist. This assessment may include an oral motor examination focusing on strength of the oral musculature, visual inspection of the oral cavity structures, and a trial of liquids and food. A video fluoroscopic swallow study is recommended when the clinical examination identifies potential swallowing problems.[94] Absence of a cough during the clinical evaluation should not preclude the video fluoroscopic swallow study, as silent aspiration may be occurring without any overt signs or symptoms. Use of a chest radiograph may help identify lung changes related to chronic aspiration. Nasoendoscopic evaluation of swallow may be helpful when available but is not considered a standard evaluation tool in many institutions.

A multidisciplinary team approach to feeding and swallowing issues in children with congenital myopathy is critical to ensure appropriate evaluation and treatment. The team should include a pediatrician or neonatologist, a pediatric neurologist, a nutritionist or dietician, and a therapist who is an expert in feeding issues in this population.[76] Typically, a speech–language pathologist or occupational therapist has the most expertise. If placement of a gastrostomy tube is warranted, a surgeon or gastroenterologist should be consulted for placement. Endoscopic or laparoscopic approaches should be considered to decrease morbidity and pain. It is recommended that a pulmonologist be consulted when feeding difficulties are observed, as acute and chronic aspiration may lead to short- and long-term pulmonary issues. It is critical to involve the community physician upon discharge to ensure appropriate follow-up.

Management for swallowing impairments in an infant may include positioning of the infant, thickened feeds, caloric enrichment, selection of nipples and bottles, and breast nipple shield to assist the infant with latching on to the breast.[95,96] Oral motor stimulation and training have been recommended, but evidence of effectiveness is mixed. Use of a nasogastric tube should be considered if the above techniques prove ineffective or the infant is not able to meet the caloric needs. If supplemental feeds are provided by a nasogastric or gastrostomy tube, oral stimulation should continue to avoid future oral aversion. A nasogastric tube is not recommended for long-term use. The decision to move from a nasogastric to a gastrostomy tube should be made when there is very slow progress toward the child meeting his or her caloric needs orally. Gastrostomy tube placement should be strongly considered in a child with a very severe myopathy in the newborn period.[97] Placement of nasojejunal or gastrojejunal tube may also be helpful in the presence of gastroesophageal reflux. Suctioning of the oral cavity may be necessary when an infant is unable to swallow secretions.

Close observation of the nutritional status of the older child is important to ensure appropriate growth. Prolonged mealtimes caused by weak chewing and swallowing may lead to insufficient food intake, weight loss, and recurrent respiratory infections. A gastrostomy tube is recommended when the child is unable to meet caloric needs orally. However, excessive weight gain in children with muscle weakness can also be problematic, leading to increased difficulty with ambulation or, for those who are wheelchair dependent, more

difficulty with transfers. Routine weight checks during clinic visits will allow the providers to identify excessive weight gain and the need to reduce calories.

Gastrointestinal motility: Gastroesophageal reflux is a frequently encountered problem[98] in children with myopathies. Symptoms suggesting gastroesophageal reflux include chest or upper abdominal pain, vomiting, aspiration, and recurrent respiratory infections. These signs of gastroesophageal reflux warrant further assessment and management. Obtaining a detailed history is of primary importance for this assessment. Impedance manometry and pH studies can give additional information in the evaluation of gastroesophageal reflux. However, there is a poor correlation between pH analysis results and occurrence of gastroesophageal reflux. Medical treatment includes proton pump inhibitors, H_2 blockers, and antacids. Nonpharmacological treatments can include thickening of the infant's formula, feeding in an upright position, and positioning the infant or child with the head of the bed slightly elevated. In some cases, antireflux surgery has been shown to improve symptoms.[98]

Gastrointestinal dysmotility, including delayed gastric emptying and constipation, is another common problem with multifactorial causes. Abdominal radiograph can be helpful in demonstrating evidence and magnitude of constipation. Treatment includes ensuring sufficient fluid intake, positioning and mobilization, and the use of stool softeners and laxatives. Some physicians also use prokinetic drugs such as erythromycin.

Excessive oral secretions (drooling): Excessive oral secretion is a common problem that can be a major issue for children with congenital myopathies. This is often due to bulbar and facial weakness, resulting in difficulties with lip closure and swallowing sputum. Different treatment regimes, in addition to suctioning, have been suggested, but there is no consensus on recommendations for the problem of drooling. Lip strengthening exercises (eg, oral screen or wind instrument) have been effective in a few cases. Botulinum toxin injections and salivary gland ligation are not recommended for this group of patients. Anticholinergic drugs administered systemically (eg, scopolamine, hyoscine) may be effective but should be used with care as they may result in thickened secretions leading to more difficulty with airway clearance and constipation. Drooling is clearly an area in need of further research to find appropriate treatment. Such further studies may include an alternative approach for using anticholinergics such as administering atropine topically. A recent small study found encouraging evidence that L-tyrosine supplementation could decrease sialorrhea in children with nemaline myopathy.[99]

Speech and communication: Oral communication can be affected by difficulty in articulation and limited facial expression. The difficulties with speech and articulation are due to weakness of oral motor muscles, weak voice or hypophonia, difficulties with breath control, hypernasality, and abnormal oral structures.[92,100] The presence of a tracheostomy can also affect communication ability. Problems with communication should prompt a referral to a speech and language pathologist. Other professionals may be consulted for alternative and augmentative communication. Expertise from oral surgeon and ear-nose-throat specialists may be needed. Specific treatments that can be suggested include speech therapy to provide strategies to improve intelligibility such as articulation and breath training and oral motor therapy to normalize oral sensory function and prevent development of oral

aversion. Alternative and augmentative communication training may include use of signing, sound amplification, and other assistive communicative devices. In case of hypernasality, a speech prosthesis may be considered. In selected cases, surgical intervention by pharyngoplasty has been documented to have a beneficial effect on speech articulation. A specialty dentist can be consulted if a palatal lift is judged to be beneficial. In selected cases, surgical intervention by pharyngoplasty has been documented to have a beneficial effect on speech articulation.

Oral and dental care: Orofacial problems, including malocclusion, facial deformities as a result of noninvasive ventilation, high arch palate, and poor oral hygiene and dental care, are very common findings in children with congenital myopathy.[101,102] Jaw contractures have been observed in older individuals. Referral to a pediatric dentist is recommended by 1 year of age for initial anticipatory guidance. Parents should be instructed to brush a child's teeth twice daily from the first tooth eruption. In children who have intraoral or extraoral hypersensitivity, parents may find brushing teeth challenging; in such cases, a pediatric dentist can help with desensitization techniques. Primary teeth should be treated when necessary to avoid infection and unnecessary feeding problems.

Routine dental check-ups are recommended every 6 months by a regular dentist in consultation with a pediatric dentist. Referral to an orthodontist for an assessment of malocclusion and/or a high arch palate should be made by age 6 or 8 years. Treatment planning needs to take into account the severity and progression of the neuromuscular disease in consultation with other specialists. Extensive orthodontic treatment in children with very weak facial muscles is not recommended given the high recurrence risk.[103,104] Surgical treatment of severe malocclusion should not be considered given the high risk of serious complications from intubation and anesthesia. To avoid unnecessary dental problems, adolescents and adults should continue to see a dentist on a regular basis.[105,106] Use of assistive devices to support independent oral hygiene should be considered and can be provided by an occupational therapist in conjunction with a dentist.

Transition to Adult Care

Children with congenital myopathies have special health care needs that require planning for health care transitions in adulthood. Successful transition requires an integrated and coordinated care plan involving adult caregivers, patients, and both pediatric and adult medical providers. Discussions with adolescent patients must include transition to future adult providers, future adult health care needs, changes in health insurance, and encouraging the adolescent patient to take responsibility for his or her own care.[107,108]

Future Research Directions

The International Standard of Care Committee for Congenital Myopathies, after evaluation of the existing medical literature and extensive internal discussions, identified several areas of need in terms of the diagnostic evaluation and clinical care of the patient with congenital myopathies. Foremost among them is the lack of meaningful pharmacological interventions for congenital myopathy patients. In fact, no prospective clinical trial for therapeutic intervention has been conducted for this group of disorders. The other major area requiring

future investigation relates to the natural history of these disorders. Comprehensive natural history studies are lacking for essentially all congenital myopathies, which hinders the ability to provide the most comprehensive care recommendations throughout the life span of the patient and also presents a barrier to clinical trial readiness and development. The committee strongly recommends the development of a patient registry, in the form of a general myopathy registry or as a subtype specific registry, to facilitate these and other studies.

Additional specific areas identified by the committee are as follows.

Genetics and Diagnostics—The most important recent advances in congenital myopathies have been made in genetics and diagnostics. Subjects identified for future study in this area include:

- Better diagnostic tools related to nebulin gene mutations for nemaline myopathy
- Improved and more cost-effective gene sequencing analysis
- Use of muscle imaging techniques such as MRI or ultrasound to assist in diagnosis of specific subtypes of congenital myopathies.

Neurology—The neurology subgroup focused on the need for translational research, with an emphasis on the generation and use of vertebrate models of the specific congenital myopathies, for the development of new therapeutic approaches. Advances in our understanding of disease progression and natural history, as mentioned above, are clearly essential for the promotion of new therapies.

- Establishment and comprehensive evaluation of vertebrate models for each genetic subtype of congenital myopathy
- Establishment of patient registries for all congenital myopathies
- Initiation of comprehensive natural history studies

Pulmonology—Given the limited numbers of patients with congenital myopathy, studies for further investigation will require multicenter design. Areas of investigation to consider include:

- Identification of the incidence of sleep disordered breathing relative to gene mutation and/or type of myopathy
- Identification of respiratory parameters that predict respiratory deterioration
- Evaluation of palivizumab (respiratory syncytial virus prophylaxis) effectiveness in congenital myopathies

- Evaluation of whether respiratory muscle training and pulmonary inspiratory exercise affect respiratory motor strength and the development of respiratory compromise
- Evaluation of the impact of CoughAssist or other passive positive pressure techniques on chest wall expansion.

Orthopedics and Rehabilitation—Much needs to be done to better understand the optimal orthopedic and rehabilitation management of children with congenital myopathies. Areas of potential research topics recommended by the committee include:

- Identification of optimal characteristics of exercise programs—strength versus endurance, duration, intensity, and frequency—to improve function and mobility
- Natural history studies of bone health to provide data from which intervention studies can be based, for example, exercise, whole body vibration, and bisphosphonate
- Disease-specific natural history studies to allow planning for therapies and to provide anticipatory guidance
- Identification of impairment-based causes of functional limitations to allow focused therapeutic interventions
- Investigation into the need for surgical correction of hip dysplasia in nonambulatory myopathy patients.

Summary

This review represents the consensus recommendations for the standard of care for congenital myopathies. The recommendations were formulated by a group of clinicians and scientists from several disciplines including genetics, neurology, neuropathology, pulmonology, orthopaedics, gastroenterology, nutrition, rehabilitation medicine, physical therapy, occupational and speech therapy, and oral medicine. The consensus recommendations are based on an extensive literature review, a 2-stage online survey, and a comprehensive in-person workshop. This is the first such document to outline the clinical recommendations for this group of disorders. It is the hope of the committee that these recommendations will lead to improved care for congenital myopathies. Measuring the influence of this work on improving the quality of lives and improving disease outcomes of these patients will be the next focus of our committee.

Acknowledgments

Members of the International Standard of Care Committee for Congenital Myopathies also include Annie Aloysius, MRCSLT, HPC, London, United Kingdom; Allen Beggs, PhD, Boston, Massachusetts; Valerie Biancalana, MD, PhD, Strasbourg, France; David Birnkrant, MD, Cleveland, Ohio; Kate Bushby, MD, Newcastle, United Kingdom; Ana Ferreiro, MD, PhD, Paris, France; Hans Goebel, MD, Mainz, Germany; Siegfried Labeit, MD, Mannheim, Germany; David Little, FRACS, PhD, Westmead, Australia; James Kemp, MD, St. Louis, Missouri; Dennis Matthews, MD, Aurora, Colorado; Francesco Muntoni, MD, PhD, London, United Kingdom; Carmen Navarro, MD, PhD, Vigo, Spain; Howard Panitch, MD, Philadelphia, Pennsylvania; Katarina Pelin, PhD, Helsinki, Finland; Susana Quijano-Roy, MD, PhD, Garches, France; Maria Teresa Santiago, MD, Schneider Children’s Hospital,

Great Neck, New York; Anita Simonds, MD, London, United Kingdom; Helga Cristina Almeida da Silva, MD, PhD, Sao Paulo, Brazil; Lawrence Rinsky, MD, Stanford, California; Norma Romero, MD, PhD, Paris, France; Peter Schochet, MD, Plano, Texas; Carina Wallgren-Pettersson, MD, PhD, Helsinki, Finland and Colin Wallis, MD, London, United Kingdom.

Funding

The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This project is supported by grants from A Foundation Building Strength (www.buil-dingstrength.org) and TREAT-NMD (www.treat-nmd.edu).

References

1. Jungbluth H. Multi-minicore disease. Orphanet J Rare Dis. 2007; 2:31. [PubMed: 17631035]
2. Kinali M, Beeson D, Pitt MC, et al. Congenital myasthenic syndromes in childhood: diagnostic and management challenges. J Neuroimmunol. 2008; 201–202:6–12.
3. Feasson L, Camdessanche JP, El Mandhi L, Calmels P, Millet GY. Fatigue and neuromuscular diseases. Ann Readapt Med Phys. 2006; 49(6):289–300. 375–284. [PubMed: 16780988]
4. Abresch RT, Carter GT, Jensen MP, Kilmer DD. Assessment of pain and health-related quality of life in slowly progressive neuromuscular disease. Am J Hosp Palliat Care. 2002; 19(1):39–48. [PubMed: 12173612]
5. Engel JM, Kartin D, Carter GT, Jensen MP, Jaffe KM. Pain in youths with neuromuscular disease. Am J Hosp Palliat Care. 2009; 26(5):405–412. [PubMed: 19820205]
6. Bushby KM, Pollitt C, Johnson MA, Rogers MT, Chinnery PF. Muscle pain as a prominent feature of facioscapulohumeral muscular dystrophy (FSHD): four illustrative case reports. Neuromuscul Disord. 1998; 8(8):574–579. [PubMed: 10093064]
7. Sobreira C, Marques W Jr, Barreira AA. Myalgia as the revealing symptom of multicore disease and fibre type disproportion myopathy. J Neurol Neurosurg Psychiatry. 2003; 74(9):1317–1319. [PubMed: 12933945]
8. Ginanneschi F, Mondelli M, Malandrini A, Gambelli S, Dotti MT, Federico A. Nemaline myopathy: description of an adult onset case. J Submicrosc Cytol Pathol. 2002; 34(1):105–108. [PubMed: 11989852]
9. Jungbluth H, Wallgren-Pettersson C, Laporte J. Centronuclear (myotubular) myopathy. Orphanet J Rare Dis. 2008; 3:26. [PubMed: 18817572]
10. Jungbluth H, Zhou H, Hartley L, et al. Minicore myopathy with ophthalmoplegia caused by mutations in the ryanodine receptor type 1 gene. Neurology. 2005; 65(12):1930–1935. [PubMed: 16380615]
11. Ryan MM, Schnell C, Strickland CD, et al. Nemaline myopathy: a clinical study of 143 cases. Ann Neurol. 2001; 50(3):312–320. [PubMed: 11558787]
12. Wong VA, Beckingsale PS, Oley CA, Sullivan TJ. Management of myogenic ptosis. Ophthalmology. 2002; 109(5):1023–1031. [PubMed: 11986113]
13. Heckmatt JZ, Sewry CA, Hodes D, Dubowitz V. Congenital centronuclear (myotubular) myopathy: a clinical, pathological and genetic study in eight children. Brain. 1985; 108(pt 4):941–964. [PubMed: 4075080]
14. Barth PG, Van Wijngaarden GK, Bethlem J. X-linked myotubular myopathy with fatal neonatal asphyxia. Neurology. 1975; 25(6):531–536. [PubMed: 1168872]
15. McCrea HJ, Kretz C, Laporte J, Ment LR. Dementia in a child with myotubular myopathy. Pediatr Neurol. 2009; 40(6):483–485. [PubMed: 19433289]
16. Echaniz-Laguna A, Nicot AS, Carre S, et al. Subtle central and peripheral nervous system abnormalities in a family with centronuclear myopathy and a novel dynamin 2 gene mutation. Neuromuscul Disord. 2007; 17(11-12):955–959. [PubMed: 17825552]
17. D'Amico A, Graziano C, Pacileo G, et al. Fatal hypertrophic cardiomyopathy and nemaline myopathy associated with ACTA1 K336E mutation. Neuromuscul Disord. 2006; 16(9–10):548–552. [PubMed: 16945537]

18. Willemsen MA, van Oort AM, ter Laak HJ, Sengers RC, Gabreels FJ. Multicore myopathy with restrictive cardiomyopathy. Acta Paediatr. 1997; 86(11):1271–1274. [PubMed: 9401528]
19. Ohkubo M, Ino T, Shimazaki S, Yabuto K, Okada R, Sato T. Multicore myopathy associated with multiple pterygium syndrome and hypertrophic cardiomyopathy. Pediatr Cardiol. 1996; 17(1):53–56. [PubMed: 8778704]
20. Bertini E, Bosman C, Bevilacqua M, et al. Cardiomyopathy and multicore myopathy with accumulation of intermediate filaments. Eur J Pediatr. 1990; 149(12):856–858. [PubMed: 2226571]
21. Magliocco AM, Mitchell LB, Brownell AK, Lester WM. Dilated cardiomyopathy in multicore myopathy. Am J Cardiol. 1989; 63(1):150–151. [PubMed: 2909155]
22. Shuaib A, Martin JM, Mitchell LB, Brownell AK. Multicore myopathy: not always a benign entity. Can J Neurol Sci. 1988; 15(1):10–14. [PubMed: 3345455]
23. Banwell BL, Becker LE, Jay V, Taylor GP, Vajsar J. Cardiac manifestations of congenital fiber-type disproportion myopathy. J Child Neurol. 1999; 14(2):83–87. [PubMed: 10073429]
24. Jungbluth H, Sewry C, Brown SC, et al. Minicore myopathy in children: a clinical and histopathological study of 19 cases. Neuromuscul Disord. 2000; 10(4–5):264–273. [PubMed: 10838253]
25. Ferreiro A, Estournet B, Chateau D, et al. Multi-minicore disease—searching for boundaries: phenotype analysis of 38 cases. Ann Neurol. 2000; 48(5):745–757. [PubMed: 11079538]
26. Eskandar OS, Eckford SD. Pregnancy in a patient with nemaline myopathy. Obstet Gynecol. 2007; 109(2 pt 2):501–504. [PubMed: 17267873]
27. Rudnik-Schoneborn S, Glauner B, Rohrig D, Zerres K. Obstetric aspects in women with facioscapulohumeral muscular dystrophy, limb-girdle muscular dystrophy, and congenital myopathies. Arch Neurol. 1997; 54(7):888–894. [PubMed: 9236578]
28. Wallgren-Pettersson C, Hiilesmaa VK, Paatero H. Pregnancy and delivery in congenital nemaline myopathy. Acta Obstet Gynecol Scand. 1995; 74(8):659–661. [PubMed: 7660780]
29. Wilmshurst JM, Lillis S, Zhou H, et al. RYR1 mutations are a common cause of congenital myopathies with central nuclei. Ann Neurol. 2010; 68(5):717–726. [PubMed: 20839240]
30. Bitoun M, Bevilacqua JA, Prudhon B, et al. Dynamin 2 mutations cause sporadic centronuclear myopathy with neonatal onset. Ann Neurol. 2007; 62(6):666–670. [PubMed: 17932957]
31. Susman RD, Quijano-Roy S, Yang N, et al. Expanding the clinical, pathological and MRI phenotype of DNM2-related centronuclear myopathy. Neuromuscul Disord. 2010; 20(4):229–237. [PubMed: 20227276]
32. McEntagart M, Parsons G, Buj-Bello A, et al. Genotype-phenotype correlations in X-linked myotubular myopathy. Neuromuscul Disord. 2002; 12(10):939–946. [PubMed: 12467749]
33. Sparrow JC, Nowak KJ, Durling HJ, et al. Muscle disease caused by mutations in the skeletal muscle alpha-actin gene (ACTA1). Neuromuscul Disord. 2003; 13(7–8):519–531. [PubMed: 12921789]
34. Jungbluth H, Muller CR, Halliger-Keller B, et al. Autosomal recessive inheritance of RYR1 mutations in a congenital myopathy with cores. Neurology. 2002; 59(2):284–287. [PubMed: 12136074]
35. Nicot AS, Toussaint A, Tosch V, et al. Mutations in amphiphysin 2 (BIN1) disrupt interaction with dynamin 2 and cause autosomal recessive centronuclear myopathy. Nat Genet. 2007; 39(9):1134–1139. [PubMed: 17676042]
36. Schara U, Kress W, Bonnemann CG, et al. The phenotype and long-term follow-up in 11 patients with juvenile selenoprotein N1-related myopathy. Eur J Paediatr Neurol. 2008; 12(3):224–230. [PubMed: 17951086]
37. Ferreiro A, Quijano-Roy S, Pichereau C, et al. Mutations of the selenoprotein N gene, which is implicated in rigid spine muscular dystrophy, cause the classical phenotype of multiminicore disease: reassessing the nosology of early-onset myopathies. Am J Hum Genet. 2002; 71(4):739–749. [PubMed: 12192640]
38. Jungbluth H, Sewry CA, Brown SC, et al. Mild phenotype of nemaline myopathy with sleep hypoventilation due to a mutation in the skeletal muscle alpha-actin (ACTA1) gene. Neuromuscul Disord. 2001; 11(1):35–40. [PubMed: 11166164]

39. Waddell LB, Kreissl M, Kornberg A, et al. Evidence for a dominant negative disease mechanism in cap myopathy due to TPM3. Neuromuscul Disord. 2010; 20(7):464–466. [PubMed: 20554445]
40. Kiphuth IC, Krause S, Huttner HB, Dekomien G, Struffert T, Schroder R. Autosomal dominant nemaline myopathy caused by a novel alpha-tropomyosin 3 mutation. J Neurol. 2010; 257(4):658–660. [PubMed: 20012312]
41. Jeub M, Bitoun M, Guicheney P, et al. Dynamin 2-related centronuclear myopathy: clinical, histological and genetic aspects of further patients and review of the literature. Clin Neuropathol. Nov; 2008 27(6):430–438. [PubMed: 19130742]
42. Jungbluth H. Central core disease. Orphanet J Rare Dis. 2007; 2:25. [PubMed: 17504518]
43. Quinlivan RM, Muller CR, Davis M, et al. Central core disease: clinical, pathological, and genetic features. Arch Dis Child. 2003; 88(12):1051–1055. [PubMed: 14670767]
44. Gamble JG, Rinsky LA, Lee JH. Orthopaedic aspects of central core disease. J Bone Joint Surg Am. 1988; 70(7):1061–1066. [PubMed: 3403575]
45. Laing NG, Wallgren-Pettersson C. 161st ENMC International Workshop on nemaline myopathy and related disorders, Newcastle upon Tyne, 2008. Neuromuscul Disord. 2009; 19(4):300–305. [PubMed: 19264483]
46. Rosenberg H, Davis M, James D, Pollock N, Stowell K. Malignant hyperthermia. Orphanet J Rare Dis. 2007; 2:21. [PubMed: 17456235]
47. Dowling JJ, Lillis S, Amburgey K, et al. King-Denborough syndrome with and without mutations in the skeletal muscle ryanodine receptor (RYR1) gene. Neuromuscul Disord. 2011; 21(6):420–427. [PubMed: 21514828]
48. Stamm DS, Aylsworth AS, Stajich JM, et al. Native American myopathy: congenital myopathy with cleft palate, skeletal anomalies, and susceptibility to malignant hyperthermia. Am J Med Genet A. 2008; 146A(14):1832–1841. [PubMed: 18553514]
49. Carpenter D, Robinson RL, Quinnell RJ, et al. Genetic variation in RYR1 and malignant hyperthermia phenotypes. Br J Anaesth. 2009; 103(4):538–548. [PubMed: 19648156]
50. Herman GE, Kopacz K, Zhao W, Mills PL, Metzenberg A, Das S. Characterization of mutations in fifty North American patients with X-linked myotubular myopathy. Hum Mutat. 2002; 19(2):114–121. [PubMed: 11793470]
51. Herman GE, Finegold M, Zhao W, de Gouyon B, Metzenberg A. Medical complications in long-term survivors with X-linked myotubular myopathy. J Pediatr. 1999; 134(2):206–214. [PubMed: 9931531]
52. Clarke NF, Kolski H, Dye DE, et al. Mutations in TPM3 are a common cause of congenital fiber type disproportion. Ann Neurol. 2008; 63(3):329–337. [PubMed: 18300303]
53. Chahin N, Selcen D, Engel AG. Sporadic late onset nemaline myopathy. Neurology. 2005; 65(8): 1158–1164. [PubMed: 16148261]
54. Milone M, Katz A, Amato AA, et al. Sporadic late onset nemaline myopathy responsive to IVIg and immunotherapy. Muscle Nerve. 2010; 41(2):272–276. [PubMed: 19852026]
55. Novy J, Rosselet A, Spertini O, Lobrinus JA, Pabst T, Kuntzer T. Chemotherapy is successful in sporadic late onset nemaline myopathy (SLONM) with monoclonal gammopathy. Muscle Nerve. 2010; 41(2):286–287. [PubMed: 19918772]
56. Voermans NC, Minnema M, Lammens M, et al. Sporadic late-onset nemaline myopathy effectively treated by melphalan and stem cell transplant. Neurology. 2008; 71(7):532–534. [PubMed: 18565829]
57. Wallgren-Pettersson C. Nemaline and myotubular myopathies. Semin Pediatr Neurol. 2002; 9(2): 132–144. [PubMed: 12138997]
58. Sewry CA. Pathological defects in congenital myopathies. J Muscle Res Cell Motil. 2008; 29(6–8): 231–238. [PubMed: 19115049]
59. North K. What's new in congenital myopathies? Neuromuscul Disord. 2008; 18(6):433–442. [PubMed: 18482838]
60. Kudou M, Kobayashi Y, Yamashita K, Kita H, Yasuba H, Hamada K. [Two cases of nemaline myopathy diagnosed after episodes of respiratory failure]. Nihon Kokyuki Gakkai Zasshi. 2006; 44(6):474–478. [PubMed: 16841721]

61. Khan Y, Heckmatt JZ, Dubowitz V. Sleep studies and supportive ventilatory treatment in patients with congenital muscle disorders. Arch Dis Child. 1996; 74(3):195–200. [PubMed: 8787421]
62. Rowe PW, Eagle M, Pollitt C, Bullock RE, Bushby KM. Multicore myopathy: respiratory failure and paraspinal muscle contractures are important complications. Dev Med Child Neurol. 2000; 42(5):340–343. [PubMed: 10855655]
63. Akiyama C, Nonaka I. A follow-up study of congenital non-progressive myopathies. Brain Dev. 1996; 18(5):404–408. [PubMed: 8891237]
64. Cook BJ, Berkowitz RG. Tracheostomy in children with nemaline core myopathy. Int J Pediatr Otorhinolaryngol. 2005; 69(2):263–266. [PubMed: 15656962]
65. Danhaive O, Lozzi S, D'Amico A, et al. Neonatal-onset nemaline myopathy mimicking congenital diaphragmatic hernia. J Pediatr Surg. 2007; 42(7):E19–E22.
66. Sasaki M, Takeda M, Kobayashi K, Nonaka I. Respiratory failure in nemaline myopathy. Pediatr Neurol. 1997; 16(4):344–346. [PubMed: 9258972]
67. Schweitzer C, Danet V, Polu E, Marchal F, Monin P. Nemaline myopathy and early respiratory failure. Eur J Pediatr. 2003; 162(3):216–217. [PubMed: 12655434]
68. Wallgren-Pettersson C, Bushby K, Mellies U, Simonds A. 117th ENMC workshop: ventilatory support in congenital neuromuscular disorders— congenital myopathies, congenital muscular dystrophies, congenital myotonic dystrophy and SMA (II) 4–6 April 2003, Naarden, The Netherlands. Neuromuscul Disord. 2004; 14(1):56–69. [PubMed: 14659414]
69. Simonds AK. Recent advances in respiratory care for neuromuscular disease. Chest. 2006; 130(6): 1879–1886. [PubMed: 17167012]
70. Bach JR. Mechanical insufflation-exsufflation. Comparison of peak expiratory flows with manually assisted and unassisted coughing techniques. Chest. 1993; 104(5):1553–1562. [PubMed: 8222823]
71. Shneerson JM, Simonds AK. Noninvasive ventilation for chest wall and neuromuscular disorders. Eur Respir J. 2002; 20(2):480–487. [PubMed: 12212984]
72. Ward S, Chatwin M, Heather S, Simonds AK. Randomised controlled trial of non-invasive ventilation (NIV) for nocturnal hypoventilation in neuromuscular and chest wall disease patients with daytime normocapnia. Thorax. 2005; 60(12):1019–1024. [PubMed: 16299118]
73. Young HK, Lowe A, Fitzgerald DA, et al. Outcome of noninvasive ventilation in children with neuromuscular disease. Neurology. 2007; 68(3):198–201. [PubMed: 17224573]
74. Arens R, Muzumdar H. Sleep, sleep disordered breathing, and nocturnal hypoventilation in children with neuromuscular diseases. Paediatr Respir Rev. 2010; 11(1):24–30. [PubMed: 20113988]
75. Linderholm H, Lindgren U. Prediction of spirometric values in patients with scoliosis. Acta Orthop Scand. 1978; 49(5):469–474. [PubMed: 707060]
76. Wang CH, Finkel RS, Bertini ES, et al. Consensus statement for standard of care in spinal muscular atrophy. J Child Neurol. 2007; 22(8):1027–1049. [PubMed: 17761659]
77. Finder JD, Birnkrant D, Carl J, et al. Respiratory care of the patient with Duchenne muscular dystrophy: ATS consensus statement. Am J Respir Crit Care Med. 2004; 170(4):456–465. [PubMed: 15302625]
78. Wang CH, Bonnemann CG, Rutkowski A, et al. Consensus statement on standard of care for congenital muscular dystrophies. J Child Neurol. 2010; 25(12):1559–1581. [PubMed: 21078917]
79. Birnkrant DJ, Panitch HB, Benditt JO, et al. American College of Chest Physicians consensus statement on the respiratory and related management of patients with Duchenne muscular dystrophy undergoing anesthesia or sedation. Chest. 2007; 132(6):1977–1986. [PubMed: 18079231]
80. Sanoudou D, Beggs AH. Clinical and genetic heterogeneity in nemaline myopathy—a disease of skeletal muscle thin filaments. Trends Mol Med. 2001; 7(8):362–368. [PubMed: 11516997]
81. Shuaib A, Paasuke RT, Brownell KW. Central core disease. Clinical features in 13 patients. Medicine (Baltimore). 1987; 66(5):389–396. [PubMed: 3626847]
82. Rueffert H, Olthoff D, Deutrich C, Schober R, Froster UG. A new mutation in the skeletal ryanodine receptor gene (RYR1) is potentially causative of malignant hyperthermia, central core

disease, and severe skeletal malformation. Am J Med Genet A. 2004; 124A(3):248–254. [PubMed: 14708096]

83. Wu S, Ibarra MC, Malicdan MC, et al. Central core disease is due to RYR1 mutations in more than 90% of patients. Brain. 2006; 129(pt 6):1470–1480. [PubMed: 16621918]
84. Pierson CR, Tomczak K, Agrawal P, Moghadaszadeh B, Beggs AH. X-linked myotubular and centronuclear myopathies. J Neuropathol Exp Neurol. 2005; 64(7):555–564. [PubMed: 16042307]
85. Akbarnia BA. Management themes in early onset scoliosis. J Bone Joint Surg Am. 2007; 89(suppl 1):42–54. [PubMed: 17272422]
86. Duval-Beaupere G, Poiffaut A, Bouvier CL, Garibal JC, Assicot J. [Molded plexidur corrective corsets in the treatment of paralytic scolioses: evaluation after 7 years usage]. Acta Orthop Belg. 1975; 41(6):652–659. [PubMed: 1241834]
87. Morillon S, Thumerelle C, Cuisset JM, Santos C, Matran R, Deschildre A. [Effect of thoracic bracing on lung function in children with neuromuscular disease]. Ann Readapt Med Phys. 2007; 50(8):645–650. [PubMed: 17854942]
88. Bess S, Akbarnia BA, Thompson GH, et al. Complications of growing-rod treatment for early-onset scoliosis: analysis of one hundred and forty patients. J Bone Joint Surg Am. 2010; 92(15): 2533–2543. [PubMed: 20889912]
89. Campagna JA, Miller KW, Forman SA. Mechanisms of actions of inhaled anesthetics. N Engl J Med. 2003; 348(21):2110–2124. [PubMed: 12761368]
90. Klingler W, Rueffert H, Lehmann-Horn F, Girard T, Hopkins PM. Core myopathies and risk of malignant hyperthermia. Anesth Analg. 2009; 109(4):1167–1173. [PubMed: 19762745]
91. Davis PJ, Brandom BW. The association of malignant hyperthermia and unusual disease: when you're hot you're hot or maybe not. Anesth Analg. 2009; 109(4):1001–1003. [PubMed: 19762721]
92. Bagnall AA-MA, Manzur A. Feeding and speech difficulties in typical congenital neamline myopathy. Advances in Speech-Language Pathology. 2006; 8:7–16.
93. Miller F, Koreska J. Height measurement of patients with neuromuscular disease and contractures. Dev Med Child Neurol. 1992; 34(1):55–60. [PubMed: 1544515]
94. Newman LA, Keckley C, Petersen MC, Hamner A. Swallowing function and medical diagnoses in infants suspected of dysphagia. Pediatrics. 2001; 108(6):E106. [PubMed: 11731633]
95. Glass RP, Wolf LS. A global perspective on feeding assessment in the neonatal intensive care unit. Am J Occup Ther. 1994; 48(6):514–526. [PubMed: 8067372]
96. Willig TN, Paulus J, Lacau Saint Guily J, Beon C, Navarro J. Swallowing problems in neuromuscular disorders. Arch Phys Med Rehabil. 1994; 75(11):1175–1181. [PubMed: 7979925]
97. Ramelli GP, Aloysius A, King C, Davis T, Muntoni F. Gastrostomy placement in paediatric patients with neuromuscular disorders: indications and outcome. Dev Med Child Neurol. 2007; 49(5):367–371. [PubMed: 17489811]
98. Berezin S, Newman LJ, Schwarz SM, Spiro AJ. Gastroesophageal reflux associated with nemaline myopathy of infancy. Pediatrics. 1988; 81(1):111–115. [PubMed: 3336576]
99. Ryan MM, Sy C, Rudge S, et al. Dietary L-tyrosine supplementation in nemaline myopathy. J Child Neurol. 2008; 23(6):609–613. [PubMed: 18079309]
100. Bagnall AA-MA, Manzur AY. Feeding and speech difficulties in typical congenital neamline myopathy. Advances in Speech-Language Pathology. 2006; 8(1):7–16.
101. Morel-Verdebout C, Botteron S, Kiliaridis S. Dentofacial characteristics of growing patients with Duchenne muscular dystrophy: a morphological study. Eur J Orthod. 2007; 29(5):500–507. [PubMed: 17974540]
102. Ueki K, Nakagawa K, Yamamoto E. Bite force and maxillofacial morphology in patients with Duchenne-type muscular dystrophy. J Oral Maxillofac Surg. 2007; 65(1):34–39. [PubMed: 17174761]
103. Sjogreen L, Engvall M, Ekstrom AB, Lohmander A, Kiliaridis S, Tulinius M. Orofacial dysfunction in children and adolescents with myotonic dystrophy. Dev Med Child Neurol. 2007; 49(1):18–22. [PubMed: 17209971]

104. Engvall M, Sjogreen L, Kjellberg H, Robertson A, Sundell S, Kiliaridis S. Oral health in children and adolescents with myotonic dystrophy. Eur J Oral Sci. 2007; 115(3):192–197. [PubMed: 17587294]

105. Mielnik-Blaszczak M, Malgorzata B. Duchenne muscular dystrophy—a dental healthcare program. Spec Care Dentist. Jan; 2007 27(1):23–25. [PubMed: 17388226]

106. Balasubramaniam R, Sollecito TP, Stoopler ET. Oral health considerations in muscular dystrophies. Spec Care Dentist. 2008; 28(6):243–253. [PubMed: 19068065]

107. Yoshioka M, Tsuji M, Kawamoto M, Kouhara N. [Care continuity for patients with myopathy during transition of childhood to adulthood]. Nippon Rinsho. 2010; 68(1):53–56.

108. Lotstein DS, Ghandour R, Cash A, McGuire E, Strickland B, Newacheck P. Planning for health care transitions: results from the 2005–2006 National Survey of Children With Special Health Care Needs. Pediatrics. 2009; 123(1):e145–e152. [PubMed: 19117836]

Table 1

Classification of Congenital Myopathies

Disorder	Inheritance	Protein (gene)/Locus
Congenital myopathies associated with protein accumulations		
Nemaline myopathy	AD, AR	α-tropomyosin$_{SLOW}$ (*TPM3*)
	AR	nebulin *(NEB)*
	AD, AR	skeletal α-actin *(ACTA1)*
	AD	β-tropomyosin *(TPM2)*
	AR	troponin T *(TNNT1)*
	AR	cofilin *(CLF2)*
Cap disease (variant of nemaline myopathy)	AD	β-tropomyosin *(TPM2)*
	AD	α-tropomyosin$_{SLOW}$ (*TPM3*)
	AD	skeletal α-actin *(ACTA1)*
Zebra body myopathy (variant of nemaline myopathy)	AD	skeletal α-actin *(ACTA1)*
Myosin storage myopathy (hyaline body)	AD	slow/β-cardiac myosin heavy chain (*MYH7*)
Congenital myopathies associated with cores		
Central core disease	AD, AR	ryanodine receptor *(RYR1)*
Multi-minicore disease	AD, AR	ryanodine receptor *(RYR1)*
Including congenital myopathy with cores (both central and minicores)	AR	selenoprotein N *(SEPN1)*
	AD	skeletal α-actin *(ACTA1)*
Congenital myopathies associated with cores and rods		
Core-rod myopathy	AD, AR	ryanodine receptor *(RYR1)*
	AD	kelch repeat and BTB (POZ) domain containing 13 *(KBTBD13)*
	AR	nebulin (NEB)
Congenital myopathies associated with centralized nuclei		
Myotubular myopathy	X-linked	myotubularin *(MTM1)*
Centronuclear myopathy	AD	dynamin 2 *(DNM2)*
	AR	amphiphysin 2 *(BIN1)*
	AR	ryanodine receptor *(RYR1)*
Congenital myopathies associated only with small type 1 fibers		
Congenital fiber type disproportion	AD	skeletal α-actin *(ACTA1)*
	AD	α-tropomyosin$_{SLOW}$ *(TPM3)*
	AR	selenoprotein N *(SEPN1)*
	AD	β-tropomyosin *(TPM2)*
	X-linked	Xp22.13 to Xq22.1

Abbreviations: AD, autosomal dominant; AR, autosomal recessive. Adapted from North KN. What's new in congenital myopathies? *Neuromusc Disord.* 2008;18(6):433–442.

Table 2

Recommended Frequency of Pulmonary Function Tests for Congenital Myopathies

Test	Frequency
Highly recommended	
Spirometry sitting[a]	6–12 mo
Maximal inspiratory pressure, maximal expiratory pressure	6–12 mo
Peak cough flow	6–12 mo
Overnight oximetry with measurement of CO_2 (CBG, transcutaneous CO_2, end-tidal CO_2)	Annually, if polysomnography not available
Recommended	
Spirometry supine in addition to sitting	6–12 mo
Comprehensive pulmonary function tests including lung volumes	Annually
Oximetry spot check and/or venous bicarbonate	6–12 mo
Attended polysomnography	1–2 y if stable, sooner if change in baseline status

[a]Spirometry is indicated for children older than 5 years.